

# Tolerability and Efficacy of Vortioxetine Versus SSRIs in Elderly With Major Depression. Study Protocol of the VESPA Study: A Pragmatic, Multicentre, Open-Label, Parallel-Group, Superiority, Randomized Trial

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## Study protocol

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# Abstract

**Introduction.** Depression is a highly prevalent condition in the elderly, with a vast impact on quality of life, life expectancy, and medical outcomes. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed agents in this condition and, although generally safe, tolerability issues cannot be overlooked. Vortioxetine is an antidepressant with a novel mechanism of action. Based on available studies, it may have a promising tolerability profile in the elderly, as it does not adversely affect psychomotor or cognitive performance, and does not alter cardiovascular and endocrine parameters. The present study aims to assess the tolerability profile of vortioxetine in comparison with the SSRIs considered as a single group in elderly participants with depression. The rate of participants withdrawing from treatment due to adverse events after six months of follow-up will be the primary outcome.

**Methods and analysis.** This is a pragmatic, multicentre, open-label, parallel-group, superiority, randomized trial funded by the Italian Medicines Agency (AIFA - Agenzia Italiana del Farmaco ). Thirteen Italian Community Psychiatric Services will consecutively enrol elderly participants suffering from an episode of major depression over a period of 12 months. Participants will be assessed at baseline and after 1, 3 and 6 months of follow-up. At each time point, the following validated rating scales will be administered: Montgomery–Åsberg Depression Rating Scale (MADRS), Antidepressant Side-Effect Checklist (ASEC), EuroQual 5 Dimensions (EQ-5D), Short Blessed Test (SBT), and Charlson Age-Comorbidity Index (CACI). Outcome assessors and the statistician will be masked to treatment allocation. A total of 358 participants (179 in each group) will be enrolled.

**Ethics and dissemination.** This study will fully adhere to the ICH E6 Guideline for Good Clinical Practice. Participants' data will be managed and safeguarded according to the European Data Protection Regulation 2016/679. An external Ethical Advisory Board will help guarantee high ethical standards.

**Trial registration number.** EudraCT number: 2018-001444-66; Clinicaltrials.gov: NCT03779789, first submitted on December 12, 2018 and first posted on December 19 th trial status: protocol version 1.5; 09/06/2018. Recruitment started on February 2019 and it is ongoing. It is expected to end approximately on September 30 th 2021.

## Introduction

### Background and rationale

Depression is among the most disabling conditions worldwide [1]. It occurs in about 4% of elderly in the community [2] and in up to 49% of persons admitted to nursing homes and hospitals [3 4]. In elderly people, depression is associated with poor quality of life, reduced life expectancy, high risk of suicide [5], cognitive decline and dementia [6], reduced adherence to medical treatments and, therefore, poorer medical outcomes [7].

Current guidelines recommend pharmacological treatment in case of moderate-to-severe depression [8]. Although different medications can be used in people with depression, the first-line is typically represented by antidepressants. Traditionally, the theory of a “chemical imbalance” (and particularly the reduction of serotonin levels in some areas of the central nervous system) was claimed to explain the pharmacological mechanism of these drugs. However, there is growing evidence on multiple therapeutic targets of antidepressants, including neurotrophic actions, modulation of genetic, immunity and inflammatory processes. Selective serotonin reuptake inhibitor (SSRIs) are a class of antidepressants with the simplest pharmacological profile, and are generally chosen as first-line treatment considering a good balance between efficacy and safety in the general population according to data from randomized trials [9]. However, in the elderly there is debate around benefits and harms of antidepressants. Older adults may be particularly vulnerable to adverse events due to frailties associated with the aging process [10], medical comorbidities, multiple treatments, and high risk of pharmacological interactions [11 12]. SSRIs are generally considered the safest option in older adults [13] and are therefore recommended by most guidelines as first-choice treatment [8 14]. However, SSRIs are not without risks in the elderly, particularly hyponatraemia, postural hypotension, falls, gastrointestinal bleeding, and sexual dysfunctions are most common side effects [15 16]. Other antidepressants, such as tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and mirtazapine are associated with a similar or higher risk of a number of adverse events, including sedation, confusion, urinary retention, cardiovascular and gastrointestinal issues [16], and are generally avoided in these patients. Moreover, the magnitude of beneficial effects of antidepressants in late-life depression has been questioned [17], making it hard for clinicians to accurately balance benefits and risks.

Vortioxetine is a novel antidepressant, licensed for the treatment of depression in 2013 by FDA and EMA [18 19]. Vortioxetine is an antagonist to 5-HT<sub>3</sub>, 5-HT<sub>1D</sub> and 5-HT<sub>7</sub> receptors, a partial agonist to the 5-HT<sub>1B</sub> receptor and a 5-HT<sub>1A</sub> receptor agonist [20] [21]. Its mechanism of action is not fully understood yet, but it is likely to be related with both a direct modulation of the serotonergic receptor activity and an inhibition of the serotonin transporter. Despite similarities with SSRIs, its pharmacological profile is claimed to be novel, particularly because of its stronger binding to the 5-HT<sub>1B</sub> receptor as compared to other SSRIs [22], and because of promising results in animal models, showing antipsychotic, antidepressant, and pro-cognitive activities (enhanced memory, cognition, and executive functions) [23]. It is classified among “other antidepressants” by the World Health Organization (WHO) ATC/DDD Index 2018 [24]. Vortioxetine has similar pharmacokinetic properties in young and older adults [18], and existing data suggest it should not adversely affect psychomotor or cognitive performance, wakefulness, body weight, and electrocardiogram parameters [25 26]. Further, possible beneficial effects on cognition emerged from three randomized trials in participants with cognitive impairment [27]. A recent Cochrane systematic review, which included 15 randomized trials (7746 participants), showed vortioxetine to be effective compared to placebo, while no significant differences emerged between vortioxetine and SNRIs as a class, in terms of both efficacy and tolerability [28]. The review did not include any study comparing vortioxetine with the SSRIs, but a recent network meta-analysis showed that vortioxetine is well tolerated and effective when indirectly compared to SSRIs [9 29]. Moreover, in two recent randomized trials,

vortioxetine did not show significant differences on both mood and cognitive performance when compared to paroxetine [30] and escitalopram [31], respectively. The only available trial conducted in the elderly reported vortioxetine as more effective than placebo in terms of responders, i.e. participants with  $\geq 50\%$  reduction in the Hamilton Depression Scale-24 total score in 8 weeks (301 participants, relative risk 1.49, 95% CI 1.14 to 1.95), while no differences emerged in terms of tolerability [32].

## **Objectives**

The study will assess if, under real-world clinical circumstances, vortioxetine is better tolerated as compared with the SSRIs considered as a group in elderly participants with depression. In addition to tolerability, as secondary outcomes the study will assess acceptability, overall mortality, self-harm and suicide, adverse events, improvement of depressive symptoms, quality of life, and cognitive performance.

## **Methods And Analysis**

This protocol has been reported accordingly to the SPIRIT statements requirements. The complete SPIRIT checklist is available as an additional file and in the table at the end of the manuscript (additional file1).

### **Trial design**

The VESPA (Vortioxetine in the Elderly vs SSRIs: A Pragmatic Assessment) study is a randomized, parallel-group, multicentre, open-label, pragmatic, superiority trial. Over a 12-month recruitment period, psychiatrists from thirteen Italian Psychiatric Services will consecutively enrol in- and outpatients aged 65 or more suffering from an episode of major depression and requiring treatment with an antidepressant. A threshold of 65 year was selected because this age is generally accepted as a transition into older age [33] and is broadly accepted as a standard in existing randomized trials [29]. The study was designed in accordance with the principles of pragmatism, which aim to assess interventions under real-life circumstances by recruiting participants in ordinary care settings and employing outcomes with high practical value for clinicians [34].

Participants will be randomly allocated to vortioxetine or to one of the SSRIs. Apart from treatment allocation, clinicians and participants will be free of increasing or decreasing the dose according to clinical status and circumstances, as well as of stopping or continuing treatment as clinically indicated. Similarly, the use of concomitant medications during the study will be allowed according to clinical status and circumstances. Routine care outside the trial will continue as usual. During the study, participants will

be seen as often as clinically indicated with no extra visits required for the trial. The only requirement will be follow-up visits at one, three, and six months of follow-up (Figure 1). Visits will be conducted at usual care facilities in each centre.

**Figure 1. Study flow-chart.** Legend: RF=recruitment form; FUF=follow-up form; MADRS=Montgomery–Åsberg Depression Rating Scale; UKU=Udvalg for Kliniske Undersogelser Side Effect Rating Scale; EQ-5D=EuroQual 5 Dimensions

As a consequence of these pragmatic characteristics oriented to resemble clinical practice as much as possible, both participants and clinicians will not be blind to pharmacological treatments provided during the trial. Blinding will be applied to outcome assessors and statisticians performing the analyses. The study has been designed according to the principles described in the CONSORT statement (extended version for pragmatic trials) [35] and in agreement with the SPIRIT 2013 statement [36] (see Appendix 1). The study is financially supported by the Italian Medicines Agency (AIFA - *Agenzia Italiana del Farmaco*) and has already been approved by the Ethics Committee for Clinical Research of Verona and Rovigo (*Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo*) (prot. n. 61211 of the 19/09/2018; Protocol version n. 1.5 of the 09/06/2018).

### **Assessment of pragmatism**

To quantify the level of pragmatism of our study, we employed the pragmatic–explanatory continuum indicator summary-2 (PRECIS-2) [37]. This is a validated tool, developed to help investigators make design decisions consistent with the intended purpose of their trial. It explores nine domains (eligibility criteria, recruitment, setting, organisation, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, and primary analysis), for each of which a score from 1 (very explanatory) to 5 (very pragmatic) is provided. The result is graphically summarized in Figure 2.

### **Figure 2. Pragmatism wheel according to the PRECIS-2 tool**

Reasons for the scoring are reported in Table 1. A routine use of the PRECIS-2 tool when submitting RCT protocols to funders, research ethics committees and peer-reviewed journals, has been growingly recommended, considering that not all RCTs self-labelled as "pragmatic" or "naturalistic" are actually

pragmatic. This process can also help understand the extent to which trial results may be relevant to real-world practice [38].

**Table 1. Scoring of PRECIS-2 tool.** PRECIS 5-point Likert Scale score: (1) Very Explanatory; (2) Rather Explanatory; (3) Equally Pragmatic/Explanatory; (4) Rather Pragmatic; (5) Very Pragmatic.

Items	Score	Rationale
<p><b>Eligibility</b> - to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care</p>	4	<p>Target population: Elderly with depression. Inclusion criteria are wide. No exclusion criteria will be applied in terms of setting of recruitment, severity of depression, past use of psychotropic drugs, current use of benzodiazepines, number and severity of medical comorbidities, and multiple pharmacotherapy. Diagnosis are based on clinical judgment (considering DSM-5 criteria as a reference), as it is in usual practice..</p>
<p><b>Recruitment</b> - how much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients?</p>	5	<p>Participants will be recruited without extra efforts. They will be recruited during usual appointments and/or visits.</p>
<p><b>Setting</b> - how different is the setting of the trial and the usual care setting?</p>	4	<p>The study is multicenter, based in more than 10 psychiatric centers of the National Health System in Italy with a University center.</p>
<p><b>Organisation</b> - how different are the resources, provider expertise and the organisation of care delivery in the intervention arm of the trial and those available in usual care?</p>	4	<p>We will use usual staff and resources, but some extra resources will be necessary to hire researchers for the study. Visits will be conducted at usual care facilities in each centre.</p>
<p><b>Flexibility (delivery)</b> - how different is the flexibility in how the intervention is delivered and the flexibility likely in usual care?</p>	5	<p>The intervention is flexible, similar to usual care.</p>

<b>Flexibility (adherence)</b> - how different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care?	4	No extra measures. Participants will be free to assume the intervention or drop it, but drugs will be prescribed and given to the participants during visits. This is different from usual care (patients have a prescription and go to the pharmacy to buy drugs).
<b>Follow-up</b> - how different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care?	4	The primary outcome will be assessed after 1, 3 and 6 months, as it is usually done in everyday practice. Six months represent a clinically sound time frame for assessing the overall tolerability of medications, including both acute, short-term and medium-long-term effects. Visits could be slightly longer than usual to assess all the scales and long-term effects and adverse events could occur after 6 months.
<b>Primary outcome</b> - to what extent is the trial's primary outcome relevant to participants?	5	Primary outcome is relevant to participants and policy makers.
<b>Primary analysis</b> - to what extent are all data included in the analysis of the primary outcome?	5	The Intention to Treat (ITT) population will consist of all randomized participants. This ITT population will be used for the analysis of both primary and secondary outcomes. Missing values in rating scales will be imputed using the Last Observation Carried forward (LOCF) approach.

### Eligibility criteria and study setting

The following inclusion criteria will be applied:

1. The participant is 65 years old or above;
2. The participant is willing to participate by signing an informed consent form;
3. The participant is suffering from an episode of major depression, according to the clinical judgment of recruiting psychiatrists, considering DSM-5 criteria as a reference standard;
4. Treatment with an antidepressant is appropriate, based on clinical judgment;

5. In case the participant is receiving pharmacological treatment, there is clinical agreement between investigator and participant to discontinue any of the following concomitant drugs: antidepressant, second generation antipsychotic, or lithium. All other concomitant medications are allowed;
6. Uncertainty about which trial treatment would be best for the participant.

Participants will be excluded in case of:

1. Dementia, of any type and stage, as formally diagnosed by a specialist (geriatrician, neurologist, or others);
2. Diagnosis of schizophrenia or bipolar disorder;
3. Clinical conditions or treatments that contraindicate the use of oral vortioxetine or SSRIs, according to clinical/medical judgment (for example conditions or treatments that increase risk of bleeding, seizures, serotonergic syndrome, hyponatraemia, etc.).

All medications will be prescribed according to routine clinical practice and current guidelines [8, 14], in compliance with the Summary of Product Characteristics (SPC) registered in the AIFA databank (<https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/home>). Patients with a current depressive episode already receiving an antidepressant treatment that proved to be ineffective and/or poorly tolerable, and could benefit from the switch to vortioxetine or an SSRI, will be eligible for the study.

No exclusion criteria will be applied in terms of setting of recruitment, severity of depression, past use of psychotropic drugs, current use of benzodiazepines (as long as SPC indications are respected), number and severity of medical comorbidities, and multiple pharmacotherapy. Such criteria will select participants similar to those who require antidepressant treatment under usual care, including patients with multiple medical comorbidities. The recruitment will be pragmatic, as participants will be consecutively enrolled among those attending inpatient and outpatient community services and fulfilling the study inclusion criteria. Both people with new-onset or pre-existing major depression will be eligible. Therefore, people with no antidepressant treatment at baseline, as well as those already in treatment but needing a switch of medications on clinical grounds, will be eligible. There will not be overt recruitment effort, that can lead to the recruitment of participants that do not resemble usual care. Also, allowing different recruitment settings, having multiple sites of recruitment, and selecting patients similar to those who are treated in every day clinical practice, will increase the generalizability of trial results. To control

for a potential risk of excessive heterogeneity between centres, the randomization will be stratified by centre. All recruiters will take part to training meetings on recruitment procedures, including timing, how to administer rating scales, and how to provide synthetic yet exhaustive information to the patients. This is intended to minimize heterogeneous recruiting practices in different centres, which might reflect in different characteristics of patients recruited. We will keep track of the number of patients invited but refusing to participate. According to these features, the PRECIS-2 “setting” domain has been evaluated as pragmatic.

### **Interventions**

Participantss will be randomized to either vortioxetine or one of the SSRIs. Doctors will be free to choose which SSRIs is more appropriate among those marketed in Italy and commonly used in clinical practice in the elderly (sertraline, citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine). A flexible dosing schedule, within the licensed dose range and in line with the summary of product characteristics (SPC), will be suggested (Table 2) in order to resemble clinical practice as much as possible. All medications will be prescribed and switched accordingly to current guidelines.

### **Table 2. Treatments and dosing schedule**

Medication	Licensed dose range in the elderly	Notes from the registered Summary of Product Characteristics
vortioxetine	5 – 20 mg/day	The minimum effective dose of 5 mg vortioxetine once daily should always be used as an initial dose for participants aged $\geq 65$ years. Caution should be exerted when prescribing to elderly participants at doses above 10 mg vortioxetine once daily.
sertraline	50 – 200 mg/day	Caution is required in the elderly, because these patients may be at greater risk of hyponatraemia.
paroxetine	20 – 40 mg/day	In the elderly, increased plasma concentrations of paroxetine have been reported, however within the range observed in younger subjects. The treatment should start at the same doses used in adults.
citalopram	10 – 20 mg/day	In the elderly, half of the dose range prescribed in adults is required.
escitalopram	5 – 10 mg/day	In the elderly, half of the dose range prescribed in adults is required.
fluoxetine	20 – 60 mg/day	Caution is required when the dose is increased in the elderly, and generally the daily dose should not be above 40 mg/day. The maximum recommended dose is 60 mg/day.
fluvoxamine	100 – 300 mg/day	In elderly participants, titration should be slower and the dosage should always be established with caution.

Formulation choice (tablets versus drops) will be made by clinicians and participants following every day practice, and no measures will be implemented to optimise treatment adherence.

According to the PRECIS-2 “flexibility-delivery” and “flexibility-adherence” domains, treatment delivery has been rated as pragmatic, although a full score of 5 could not be reached as we were formally required to follow the EU pharmacovigilance regulation [39 40].

## Outcomes

The number of participants withdrawing from allocated treatment due to adverse events at the end of the study (6 months) will represent the primary outcome. This measure may be considered a pragmatic proxy of tolerability [41] as it occurs when adverse events actually reach an unbearable burden, as perceived by patients and/or relatives and/or carers and/or clinicians. Antidepressant treatment will be considered withdrawn due to adverse effects when the drug is stopped for more than two consecutive weeks following the occurrence of any adverse event, based on clinical judgment and/or as reported by participants. Participants will be additionally evaluated after also one, three and six months from randomization, collecting relevant clinical information and assessing scales, as showed in table 3. The information on the primary outcome, as well as on any co-medication taken by the participant, will be collected using a predefined follow-up form. Side effects responsible for treatment withdrawal, and their severity, will be recorded the follow-up form and an *ad hoc* form for Severe Adverse Events (SAE).

Secondary outcomes were chosen taking into account particular clinical characteristics of depression in the elderly (i.e. higher risk of committing suicide and higher likelihood of comorbid medical conditions) [42 43] and the peculiar characteristics of vortioxetine (i.e. potential pro-cognitive effects) [23].

Secondary outcomes will include:

1. acceptability: withdrawals from allocated treatment due to any cause (this outcome measure will include withdrawals for side-effects plus withdrawals for any other issues). Acceptability is generally considered a pragmatic measure of the balance between efficacy and tolerability of treatments [44];
2. overall mortality;
3. any episode of deliberate self-harm;
4. suicide mortality;
5. adverse events, measured as the mean change in scores at the Antidepressant Side-Effect Checklist (ASEC) [45] at each time point. ASEC is a validated rating scale measuring the occurrence and severity of 21 antidepressant adverse events;
6. response to treatment, defined as a reduction of at least 50% of the baseline score of the Montgomery–Åsberg Depression Rating Scale (MADRS) [46 47] at each time point. MADRS is a validated, ten-item questionnaire for assessing the severity of depression. Usually, scores from 0 to 6

- indicate absence of depression; 7 to 9 mild depression; 20 to 34 moderate depression; more than 34 severe depression. This rating scale is a reliable tool for assessing depression in elderly patients[48];
7. efficacy, measured as mean change scores at MADRS at each time point;
  8. quality of life, measured as mean change scores of the self-administered scale EQ-5D,[49], at each time point. EQ-5D explores five areas, including mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and assesses the overall subjective perception of health with an analogic scale. EQ-5D is a reliable tool for assessing quality of life in the elderly[50];
  9. cognitive performance, measured as mean change scores of the Short Blessed Scale (SBT) [51],at each time point. SBT is a validated, six-item weighted instrument, originally designed to identify dementia, which assesses orientation, registration, and attention.

Rating scales to assess the secondary outcomes will be administered by blind assessors at one, three and six months after randomization. In addition, the Charlson Age-Comorbidity Index (CACI) [52] will be employed. This is a validated rating scale used to evaluate the degree of medical comorbidity, and to predict the 10-year survival in participants with multiple comorbidities. All study tools and phases are shown in Table 3.

### **Table 3. Study timeline and tools**

<b>Procedures and tools</b>	<b>T0 Enrolment phase (duration: 12 months)</b>	<b>T1 (1 month)</b>	<b>T2 (3 months)</b>	<b>T3 (6 months)</b>
Review of criteria for inclusion in the study	X			
Informed consent document signed	X			
Randomization (allocation to treatment and number assigned)	X			
Recruitment Form	X			
ASEC		X	X	X
MADRS	X	X	X	X
EQ-5D	X	X	X	X
CACI	X	X	X	X
SBT	X	X	X	X
Follow-up form		X	X	X
Severe Adverse Event (SAE) Form		☒ ☒ any time ☒ ☒		

## Safety

The VESPA study will operatively employ the definitions endorsed by the EC Directive 2001/20/EC,[53]. As soon as a severe adverse event occurs, an *ad hoc* form for Severe Adverse Events (SAE) will be filled in and forwarded to the coordinating centre (University of Verona), in accordance with the EU regulation about pharmacovigilance in clinical research [39]. If, for any reasons, the disadvantages of participation will appear to be significantly greater than foreseen, the Principal Investigator (CB) of the site will inform trial participants and the bodies providing ethical oversight.

Considering that the study medications are already in the Italian market, and considering that they will be prescribed for licensed indications without altering clinical practice, the VESPA study has not appointed an ad hoc data safety and monitoring committee.

## Randomization and assignment of interventions

Participants will be randomly assigned to vortioxetine or SSRIs with an allocation ratio of 1:1. A centralized web-based randomization procedure will be employed to guarantee the concealment of allocation. The trial biostatistician will prepare the sequence of treatments randomly permuted in blocks of constant size. The site investigators will not know the block size. Allocation will be stratified by recruiting centre. By using the web-based application RedCap [54], investigators will be able to screen participants for inclusion, administer instruments maintaining the blindness to treatment allocation, and randomize them.

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### **Data collection and management**

At baseline, before randomization, and after one, three and six months, a number of socio-demographic and clinical information will be collected, along with the administration of the above-mentioned validated rating scales (MADRS, EQ-5D, CACI, SBT, ASEC). All data on other medications will be registered at every visit. The ASEC scale will be administered only during follow-up.

All study data will be collected with RedCap and digitally stored by the *Istituto di Ricerche Farmacologiche Mario Negri IRCCS*, a not-for-profit biomedical research organization based in Milan (Italy), where also the statistical analysis will be performed. RedCap will allow an immediate data validation at the moment of data collection. Moreover, a set of electronic and manual edit checks will be performed. The local coordinator of each recruiting centre will store and safely preserve hard copy documents (signed informed consent and self-administered questionnaires) for at least 7 years after the end of the study, according to the Italian law. At the end of the study the full dataset will be made available upon motivated request as a spreadsheet file in an online repository (e.g. Dryad Digital Repository). This is in line with FAIR principles [55], aimed at enhancing the accessibility and reutilization of novel research data.

The accuracy and completeness of data collection will be monitored by site visits. At least one visit for each recruiting centre is planned. Furthermore, auditing will be also carried out remotely, as the data manager of the study will be able to regularly check the trial dataset through the web application RedCap.

### **Sample size**

Considering the differential rate of withdrawals due to adverse events between SSRIs and vortioxetine on the basis of a meta-analysis of antidepressants for older people [13] and of three clinical trials of

vortioxetine in older patients with depression [26 32 56] we expect the vortioxetine group to show a clinically significant advantage by reducing this rate from about 17% [13] to about 5% [26 32 56]. A sample size of 276 participants (138 in each group) achieves 90% power to detect a difference of 12% between the two withdrawal proportions in favour of vortioxetine. The test statistics will be the two-sided Z test with pooled variance. The significance level of the test is targeted at 5%. On the basis of the above-mentioned studies, we can assume that about 23% of the participants could be lost within 6 months (the mean of the total dropout rates of vortioxetine and SSRI studies in the elderly). Therefore 358 participants (179 in each group) will be enrolled in order to obtain at least 276 evaluable participants. The sample size calculation was performed according to the methodology described by Pocock [57].

## **Statistical Analysis**

According to the pragmatic principle of intention-to-treat (ITT), efforts will be made to follow each participant until the end of the study. The ITT population will consist of all randomized participants, and will be used for the analysis of both primary and secondary outcomes. The absolute risk of the primary outcome will be calculated on the ITT population. Participants with missing primary outcome data will be allocated to the worst outcome. When possible, in addition to the primary analysis, appropriate statistical methods will adjust for the potential confounding effect of prognostic factors (sex, age, living condition, severity of comorbid medical conditions, previous psychiatric history, MADRS score at baseline). Missing rating scales scores will be imputed using the Last Observation Carried forward (LOCF) approach: ratings will be carried forward from the last available assessment to the 6-month follow-up assessment. As a secondary analysis, missing scores will be imputed following a multiple imputation approach [58].

In order to check the results of the ITT approach, though for confirmatory purposes only, the primary outcome will also be analysed using a per-protocol (PP) approach. According to the PP approach, analysis will be restricted to participants with primary outcome assessment available at six-months. Participants withdrawing for reasons not related to adverse effects will be excluded from the analysis. The proportion of participants withdrawing from the study due to adverse events within 6 months of follow-up will be compared between the two groups of treatment using a logistic regression with centre (random variable) as a covariate. A multivariable analysis (secondary analysis) will be performed through

a Poisson regression model with a robust error variance, given that this procedure allows to estimate relative risks directly [59].

For dichotomous secondary outcomes, the proportion of participants withdrawing from the study due to adverse events within 6 months will be compared between the two groups of treatment using a logistic regression with centre (random variable) as a covariate. When possible, a multivariable analysis will be performed through a Poisson regression model with a robust error variance. For continuous secondary outcomes, the 6-month estimate will be compared between the two groups of treatment with an analysis of covariance with baseline value as an additional covariate, or with Mann-Whitney test on changes, according to the variable's distribution. Some outcomes will be studied using linear mixed models taking into account all assessments to evaluate the rate of change with shorter repeated evaluations and no need of missing imputation. Further, score changes in subscales will be evaluated in order to detect possible specific treatment-related side-effects.

A Cox proportional hazard model will be used to explore time to treatment withdrawal due to adverse events (secondary analysis). The proportional hazard assumption of the effects will be tested. A Cox proportional-hazards model was chosen as it is a regression model commonly used for investigating the association between the survival time of patients (dropping out for side-effects) and one or more predictor variables (being allocated to vortioxetine or control SSRI).

Adverse events will be tabulated. Nominal value for statistical significance will be set at 0.05, two-tailed. A specific Statistical Analysis Protocol will be produced and made publicly available before the inclusion of the last participant. All analyses will be performed using STATA [60], release 15 or higher.

## ETHICS AND DISSEMINATION

This study will be conducted according to globally accepted standards of good clinical practice, as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996, in agreement with the Declaration of Helsinki [61] and in keeping with local regulations. The recruiting investigators will obtain informed consent. All participants will be informed about the study procedures and aims, both verbally and by written documentation. The subject's consent will be confirmed by the personally dated signature of the

subject and by the personally dated signature of the person conducting the informed consent discussion. Participants can withdraw from the study at any time without further explanation or any negative consequences. Participants' data will be managed and safeguarded in accordance with the European Data Protection Regulation 2016/679 [62]. The highly pragmatic design will minimize the time deduction to ordinary clinical practice. An Ethics Advisory Board (EAB) will indirectly supervise the processes of recruitment, informed consent procedures, and data management (protection and privacy), taking into due account the vulnerability of the population. Once the final report will be available, the study results will be extensively disseminated to the international scientific community in the form of peer-reviewed journal articles, giving preference to open-access journals.

The study is financially supported by the AIFA and has already been approved by the Ethics Committee for Clinical Research of Verona and Rovigo (*Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo*) (prot. n. 61211 of the 19/09/2018; Protocol version n. 1.5 of the 09/06/2018).

## Discussion

The design of this study aims at achieving a high level of pragmatism. This approach will allow to minimize the risk of selection bias (particularly relevant when assessing frail populations such as the elderly, often excluded from experimental research), to resemble routine clinical procedures as much as possible, and therefore to maximize the external validity and generalizability of results [63]. Firstly, participants will be enrolled on the basis of the need for an antidepressant prescription because of a depressive episode. Although the diagnostic reference standard is represented by DSM-5 criteria, in line with routine clinical practice, no formal diagnostic assessment will be performed, in order to recruit patients as similar as possible to those treated in the real world. No limitations to the recruitment setting will be applied. Rating scales will be easy to administer and of relatively short duration, in order not to substantially alter clinical practice. Secondly, a web-based application will allow to simplify the process of recruitment, randomization, and collection of socio-demographic and clinical data, minimizing the time deducted from ordinary clinical practice. Thirdly, the comparison group will consist of participants receiving any of the SSRIs. We made this choice in order to avoid the possibility of selection bias, that is to avoid the systematic exclusion of participants who did not benefit from a specific SSRI in the past. Furthermore, flexible dosing schedule will be employed, according to clinical judgment, within the recommended therapeutic range.

Some limitations need to be outlined. Firstly, according to the current pharmacovigilance regulation of the European Union, medication boxes must be labelled and dispensed by the hospital pharmacy. This deviates from ordinary practice and may have an impact on adherence to medications, since participants will not have to go and buy medications to their local pharmacies, but the medications needed until the next visit will be distributed to them after each visit. Secondly, in order to avoid the potential confounding

effect of other psychotropic drugs, to be included in the trial patients have to discontinue any other antidepressant or second generation antipsychotic before random allocation, but after random allocation any concomitant medication will be allowed. Again, this choice aims at resembling everyday practice, as elderly patients are sometimes prescribed low doses of second generation antipsychotics or antidepressant (e.g. mirtazapine, amitriptyline, trazodone) for insomnia or for other symptoms (e.g. cachexia, cephalalgia, etc.).

Thirdly, the open-label design might be associated with a risk of performance bias. Theoretically, it may be possible that clinicians, being aware of the treatments received by participants, perform differently according to the allocated treatment arms, based on personal subjective judgments. For example, they may provide vortioxetine, or the control SSRI, at excessively low or high doses, altering this way the likelihood of dropping out from treatment because of side-effects or lack of efficacy. Although we cannot completely rule out this possibility, we note the following. First, as both treatment arms involve active antidepressants, it seems unlikely that doctors involved in the study, working in very diverse settings across Italy, share similar a-priori opinions and, based on these opinions, systematically favour or disfavour either vortioxetine or the control SSRIs. Second, any dose changes and any use of concomitant medicines, as well as any provision of additional non-pharmacological treatments, will be recorded, which is important to investigate if, apart from the study medications, the two groups were treated similarly. Third, blinded assessors will independently assess the presence and severity of adverse events using the ASEC, and this will allow an internal quality check of the accuracy of the primary outcome.

Considering the overall psychological, medical and economic burden of depression in the elderly, and the few available pharmacological alternatives for treating this population group, the results of this study are likely to have a positive impact on everyday clinical practice. Furthermore, considering the pragmatic nature of the study, we expect that results will be immediately applicable to ordinary practice without requiring any specific training or implementation strategies. If the hypothesis of a better tolerability of vortioxetine is confirmed, this drug may become a reference first-line drug for the treatment of depression in the elderly. This, besides improving the overall psychological well-being and quality of life of elderly people with depression, might at the same time reduce hospitalizations for medical adverse events (such as falls, bleeding, hyponatraemia, QTc alterations), poor medical outcomes, and related health care costs. If, on the other hand, vortioxetine is not better tolerated than SSRIs, its place in the treatment of the elderly will be clearer, and the VESPA study results will be used to better inform clinical and policy practice.

Additionally, this study may have regulatory implications, considering that, currently, according to the EMA, “caution is advised when treating participants  $\geq 65$  years of age with doses higher than 10 mg vortioxetine once daily for which data are limited” [19 21]. We expect that this statement may be reformulated in view of the study results: if vortioxetine is better tolerated than the SSRIs, by mentioning its favourable tolerability profile; if vortioxetine is less tolerated than the SSRIs, by further reinforcing the cautionary statement.

## List Of Abbreviations

selective serotonin reuptake inhibitor (SSRIs), Randomized controlled trial (RCT), tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), Food and Drug Administration (FDA), European Medicine Agency (EMA), World Health Organization (WHO), Vortioxetine in the Elderly vs SSRIs: A Pragmatic Assessment (VESPA), Italian Medicines Agency (AIFA - *Agenzia Italiana del Farmaco*), Pragmatic-explanatory continuum indicator summary-2 (PRECIS-2), Summary of Product Characteristics (SPC), Severe Adverse Events (SAE), Antidepressant Side-Effect Checklist (ASEC), Montgomery-Åsberg Depression Rating Scale (MADRS), Short Blessed Scale (SBT), Charlson Age-Comorbidity Index (CACI), Intention-to-treat (ITT), Last Observation Carried forward (LOCF), per-protocol (PP), Ethics Advisory Board (EAB).

## Declaration

**Trial Status:** protocol version 1.5; 09/06/2018. Recruitment started on February 2019 and it is ongoing. It is expected to end approximately on September 30<sup>th</sup> 2021.

### Ethics approval and consent to participate

The protocol (version 1.5; 09/06/2018) has already been approved by the Ethics Committee for Clinical Research of Verona and Rovigo (approval reference number: Prot n. 61211 19/09/2018). All participants will sign a written informed consent form.

### Availability of data and materials

At the end of the study the full dataset will be made available upon motivated request as a spreadsheet file in an online repository (e.g. Dryad Digital Repository). This is in line with FAIR principles [55], aimed at enhancing the accessibility and reutilization of novel research data

### Competing interests

The authors have no competing interests to disclose.

### Funding

The study is funded by AIFA within the 2016 call for Independent Research on Drugs (*Bando AIFA per la Ricerca Indipendente 2016*); code: 2016-0234923. The study sponsor will have no role in study design; in the collection, management, analysis, and interpretation of data; in writing the report; and in the decision to submit the report for publication. The study sponsor has no ultimate authority over any of the listed activities.

### Consent to publication

N/A. Not applicable.

### Authors' contributions

All authors listed have made substantial contributions to the design of the study; contributed to draft and revising the manuscript, approving the final version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Designed the study: GO, CB, AB, BDA, MT; drafted the manuscript: GO, CB, AB, BDA, MT, CG; development and implementation on the online tool for data collection: IM; contributed to the design of the study and its in-field implementation via plenary meetings, revised and approved the manuscript: CG, AA, EA, CA, MA, FB, MB, PB, CC, GC, RC, SC, CCr, ADA, PDF, CDN, LG, LGr, GM, MN, DP, MP, AR, RR, LT, GT, EZ, FA, MR.

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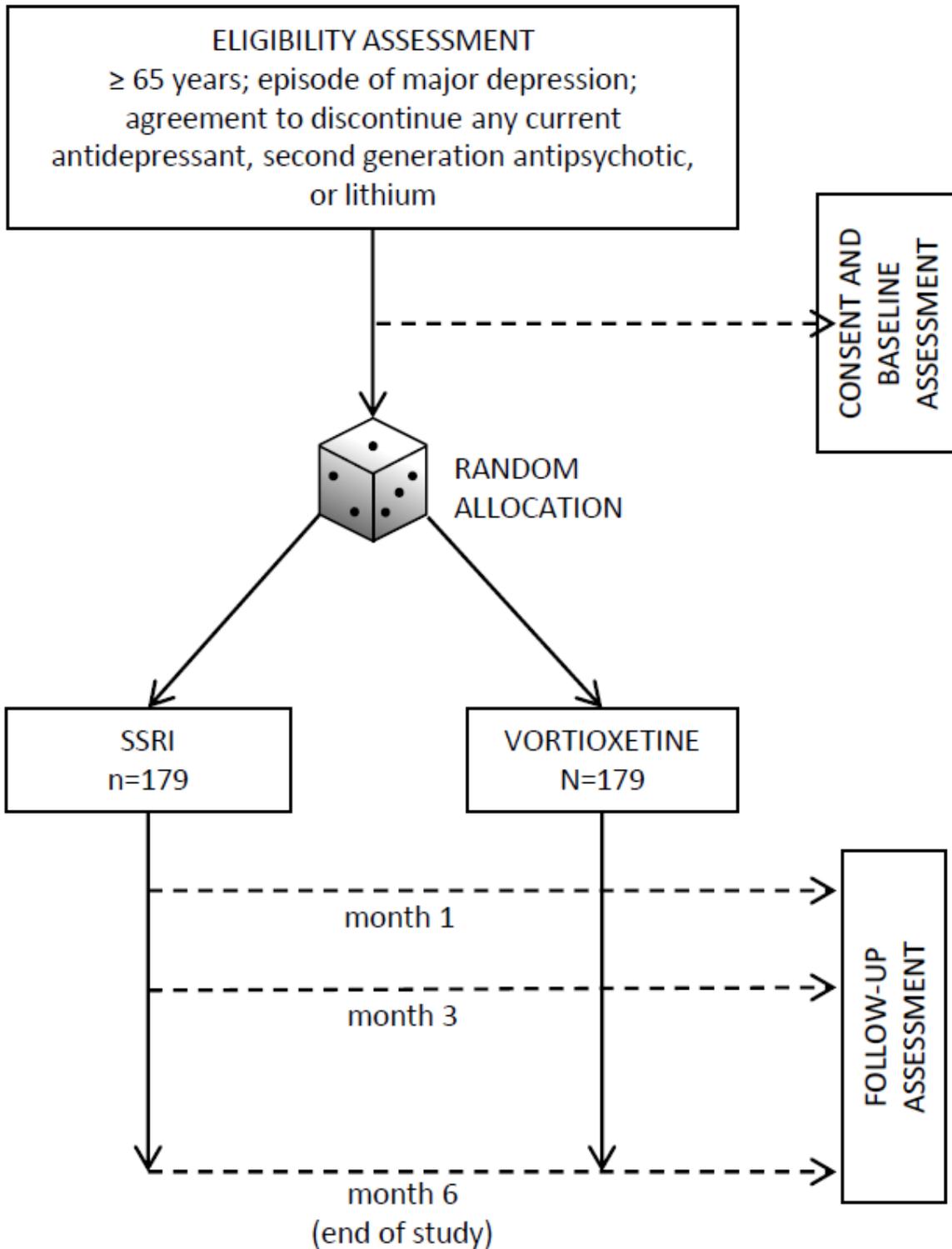
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## Table 4

Due to technical limitations, Table 4 is provided in the Supplementary Files.

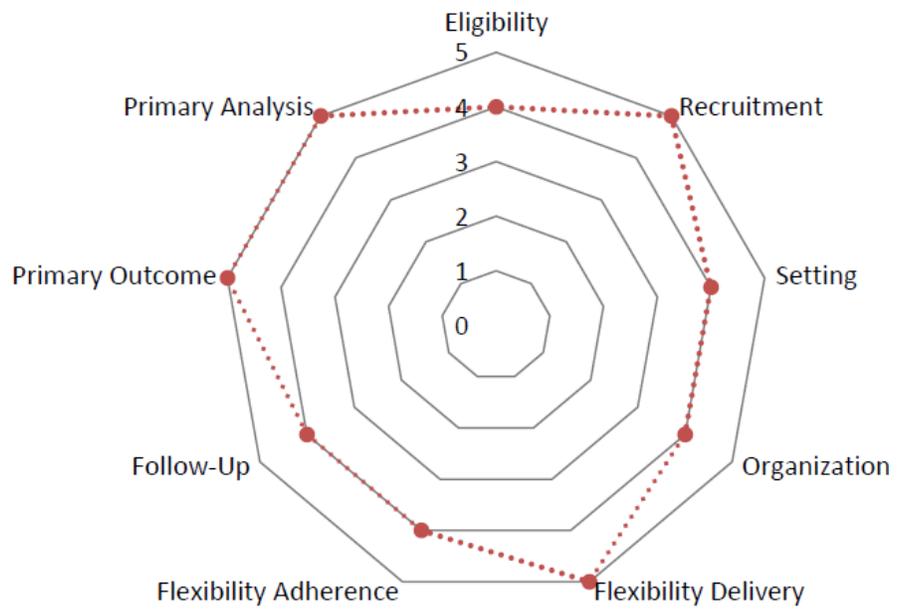
## Figures



**Figure 1**

Study flow-chart. Legend: RF=recruitment form; FUF=follow-up form; MADRS=Montgomery–Åsberg Depression Rating Scale; UKU=Udvalg for Kliniske Undersogelser Side Effect Rating Scale; EQ-5D=EuroQual 5 Dimensions

Eligibility	4
Recruitment	5
Setting	4
Organization	4
Flexibility Delivery	5
Flexibility Adherence	4
Follow-Up	4
Primary Outcome	5
Primary Analysis	5



**Figure 2**

Pragmatism wheel according to the PRECIS-2 tool

## Supplementary Files

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- [Additionalfile1.doc](#)
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