Real World Testing of an Artificial Intelligence-enabled App as an Early Intervention and Support Tool in the Mental Health Referral Care Pathway

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1 STUDY INFORMATION

1.1 Full/Long Title of the Study

Real world testing of an artificial intelligence-enabled app as an early intervention and support tool in the mental health referral care pathway

1.2 Short Study Title / Acronym

Clinical investigation of **Wysa**

1.3 Protocol Version Number(s) and Date(s)

0.1	Initial draft	25 October 2021
0.2	Circulation drafts	05 November 2021
0.3	Revisions following investigator review	26 November 2021
0.4	Minor revisions	01 December 2021
0.5	UoP Sponsor Review	02 December 2021
0.6	Minor drafting amendments	12 January 2022
0.7	Drafting amendments	7 February 2022
0.8	Amendments following Sponsor/faculty review	21 February 2022
0.9	Faculty approved version for HRA/REC review	19 March 2022
1.0	Amendments following REC Provisional Opinion	22 May 2022
1.1	Minor amendments following MHRA review	29 September 2022

1.4 Research Reference Numbers

IRAS Number:	310377
SPONSORS Number:	AM1000411, 3173
NIHR Award Number:	AI_AWARD02176

2 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's procedures, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:		
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Name (please print): ……		
Position: ……		
Chief Investigator:		
Signature: ……		Date: ……/……/……
Name: (please print): Professor Rohit Shankar		

3 KEY STUDY CONTACTS

Table 1. Key Study Contacts

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4 ABBREVIATIONS AND KEY TERMS

Table 2. Abbreviations

Abbreviation / Key Term	**Full Phrase / Definition**
A&E	Accident and Emergency (Emergency department)
AI	Artificial Intelligence
API	Application Programming Interface
CEO	Chief Executive Officer
CNWL	Central North West London (NHS Foundation Trust)
CONSORT	Consolidated Standards of Reporting Trials
DPA 2018	Data Protection Act 2018
EBCD workshops	Experience-based co-design workshops
EC	European Commission
EQ-5D-5L	EuroQoL 5 Dimensions
FREIC	Faculty Research Ethics and Integrity Committees
GAD-7	General Anxiety Disorder questionnaire
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
IAPT	Improving Access to Psychological Therapies
ICMJE	International Committee of Medical Journal Editors
ICO	Information Commissioner's Office
IRAS	Integrated Research Application System
MeSH	Medical Subject Headings
NASSS	Non-adoption, Abandonment, Scale-up, Spread, and Sustainability framework
NHS	National Health Service
NIHR	National Institute for Health Research
PERC	Patient Experience Research Centre
PHQ-9	Patient Health Questionnaire

PPI	Patient and Public Involvement
RCT	Randomised controlled trial
REC	Research Ethics Committee
SF-12	Short Form 12 health survey
SPIRIT-AI	Standard Protocol Items: Recommendations for Interventional Trials - Artificial Intelligence
SW AHSN	South West Academic Health Science Network
SWIFT	Structured What-IF Technique (prospective hazards analysis method)
TFA	Theoretical Framework of Acceptability
Wysa	Wysa Limited (Company Number: 11220172)

5 STUDY SUMMARY

Table 3. Study Summary

Study Title	Real world testing of an artificial intelligence-enabled app as an early intervention and support tool in the mental health referral care pathway
Short title	Clinical investigation of Wysa
Study Design	The study proposed is a non-blinded randomised controlled trial and mixed-methods evaluation to inform the impact of Wysa on depression and/or anxiety symptoms and user engagement and perceptions.
Study Participants	The target population of the will include individuals over the age of 18 years who are referred, or self-refer, to Improving Access to Psychological Therapies programme (IAPT) for mental health support.
Planned Size of Sample	The planned sample size is 480 individuals from the three provider sites of the London Community Living Well Service (run by the CNWL NHS Foundation Trust).
Follow up duration	The study implementation and follow-up period will last for nine months, with the primary outcome being measured at three months post-randomisation.
Planned Study Period	The study will last 17 months which includes five months of evaluation refinement, ethical approval, technical integration and testing, A further nine months of implementation and follow-up, ending with three months of post-evaluation analysis and preparation for dissemination.
Research Question/Aim(s)	The study aim is to establish real-world evidence of the Wysa impact on mental health outcomes (depression and/or anxiety symptoms) in individuals waiting for treatment through the NHS standard mental health care pathway. The main research question of the study is: how does an Artificial Intelligence (AI)-enabled self-help and triage app impact the mental well-being of patients who have been referred to the IAPT service for mental health support?

5.1 Funding and Support in Kind

Table 4. Funding Information

FUNDER	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
National Institute for Health Research (NIHR) and NHSX Charlotte Westbrook Programme Management Office Grange House, 15 Church Street Twickenham TW1 3NL charlotte.westbrook@nhs.net	£997,986.00

5.2 Role of Study Sponsor and Funder

This study is funded by an NIHR Artificial Intelligence in Health and Care Award granted to Wysa. Wysa distributes on behalf of NIHR funding to the University of Plymouth, the Institute of Cancer Research, and Dr Becky Inkster for this study execution. This funding arrangement is governed by a collaboration agreement which defines the University of Plymouth as being responsible for the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results in collaboration with the academic collaboration including the Institute of Cancer Research. Whilst Wysa has contributed and reviewed the study design and will support the trial in providing technology support, the academic collaboration, led by the University of Plymouth, is solely responsible for the study execution and dissemination of results to assure an independent assessment of Wysa technology. The academic collaboration maintains a free and independent unrestricted right of publication of the study's findings as to avoid any conflict of interest.

5.3 Roles and Responsibilities of Study Management Committees/Groups and Individuals

A study steering board composed of the Chief Investigator, Principal Investigators, Co-Investigators, a member of the public, Wysa's CEO and Clinical Lead, and an external researcher (from the study) will meet every two months to review progress against the protocol to provide study governance and oversight. Reports shall be distributed for review by the study team for action. An independent Data Governance Advisory Board will be formed to help further steer the project.

Wysa will appoint a Patient and Public Involvement (PPI) committee. With input from the Imperial College Patient Experience Research Centre (PERC) and the South West Academic Health Science Network (SW AHSN) and based on NIHR Involve guidance, a term of reference, confidentiality agreement and a background assessment form to Wysa to structure the aims of the PPI group. Membership of this Wysa PPI group is voluntary but requires members to be committed to attend meetings and to respond to emails/correspondence. The initial term of membership is for the duration of the study from early in the preparation phase (app. Dec 2021 / Jan 2022). Further details about PPI are included in the study protocol (see section 9.4).

5.4 Protocol Contributors

The sponsor, **the University of Plymouth**, controls the final decision regarding any aspect of the study.

Professor Rohit Shankar: Prof Shankar will be the Chief Investigator, will oversee the clinical investigation to ensure it follows the approved ethics and protocol, and will arrange suitable on call arrangements for any emergencies or decision-making around safeguarding.

Professor Ciere Costelloe: Prof Costelloe oversaw the drafting of the study protocol and statistical methods. She will lead the quantitative evaluation.

Dr Edward Meinert: Dr Meinert oversaw the drafting of the study protocol and coordinated revisions. He will lead the mixed-methods evaluation and the preparation of study findings for dissemination.

Miss Emma Selby: Miss Selby conceived of the study topic, contributed to the study design, and is the NIHR grant holder on behalf of Wysa in her role as Clinical Lead.

Dr Becky Inkster: Dr Inkster contributed to the study design and drafting and revising the study protocol.

Ms Madison Milne-Ives: Ms Milne-Ives contributed to drafting and revising the study protocol.

Dr Felix Achana: Dr Achana contributed to the design of the cost-effectiveness evaluation.

5.5 Keywords

Artificial Intelligence (MeSH), Mental Health (MeSH), Telemedicine (MeSH)

6 STUDY FLOW CHART

This project will conduct a real-world evaluation of Wysa as an early intervention tool introduced into the mental health referral pathway for adult IAPT service. There is currently an average wait time for IAPT between referral and treatment start of 8+ weeks with 95% of people starting treatment within 18 weeks [1]. Wysa will be made available to patients upon referral to IAPT. The control group will continue with service as usual whilst the test group will interact with Wysa while waiting for treatment.

Wysa will remain available to patients throughout their progression through the standard clinical pathway. Patients will be provided with information about the study at their initial referral point and will be contacted by our research assistants to collect informed consent and provide the product link. This will enable Wysa to offer immediate support tools and monitoring. While patients are waiting for treatment, Wysa will serve as a screening support tool for flagging assessment needs to the clinical team. After patients have received treatment, Wysa can be used as an extended monitoring tool. This is in line with the IAPT manual 2018's future goal [2] of using an app to prompt patients to fill in key outcome measures at regular intervals during the follow-up year, providing patients with easy access to their relapse prevention plan, alerting the service if relapse has occurred, and facilitating the scheduling of booster sessions. Figure 1 demonstrates the current clinical IAPT pathway with the proposed study procedures in blue.

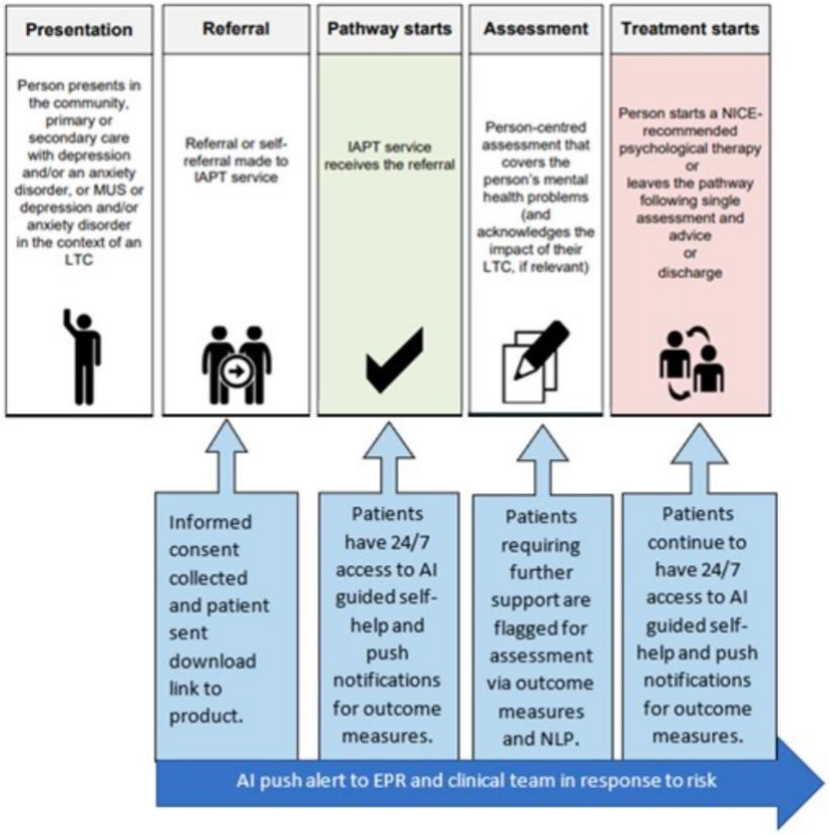

Figure 1. Current clinical pathway for adult IAPT referral and proposed study procedures (blue) (adapted from [2])

Based on the artificial intelligence (AI) recommendations generated by Wysa, patients may be passed to the IAPT for a full assessment using a combination of outcome measure scores and language used within the tool. A copy of the patients' responses to outcome measures will be

automatically pushed into their electronic patient record through the Mayden clinical information system and an automated email will be sent to the referrals coordinator to flag the need for onward referral.

Wysa will have two pathways to crisis alert and response. The first pathway is for patients to trigger the crisis response pathway by pressing a manual override button on the app. The second pathway is for the app to trigger the crisis response because of an individual's response to an outcome measure or the language used in free conversation with the AI. Because this pathway can be triggered by the app's natural language processing, the AI regularly checks in with the patient to ensure they are understanding them correctly.

When Wysa or the user triggers the crisis response pathway, users will be provided with a stepped crisis plan including grounding exercises, local crisis helplines, or a recommendation to attend A&E where there is significant injury or risk to life. Data will be collected indicating the number of false positives identified by the AI. Coinciding with this, the app pushes an update to the patient's linked electronic patient record through Mayden and sends an alert email to the 'Clinician of the Day' at each trust for human follow up.

Figure 2. High-level study Gantt chart

7 INTRODUCTION

7.1 Background

Mental health concerns can have significant negative impacts on health, well-being, and economies [3]. There is a growing recognition of the importance of mental health, which is reflected across the UK and international health sectors. Mental health concerns are projected to be the global leading cause of mortality and morbidity by 2030 [4]. Globally, depression and anxiety are estimated to cost US$1 trillion each year [5]. However, the impact of mental health conditions is not limited to those who have official diagnoses. It is estimated that 1-in-6 people will have experienced a common mental health concern in the past week below the threshold of a diagnosable mental health concern [6].

Mental health conditions can have wide ranging negative impacts on individuals' lives and well-being. For instance, depression and anxiety disorders can lead to a range of adverse psychological, social, and employment outcomes [7]. Mental health conditions also affect physical health; anxiety, depression, and substance abuse disorders have been associated with an increased risk of non-communicable diseases such as diabetes, cancer, and cardiovascular diseases [8–10]. Prolonged and severe mental illness is associated with reduced life expectancy; with people at risk of dying an average of 15 years sooner than those without severe mental illness. The cause of death in such cases is often avoidable, with two thirds of the deaths caused by heart disease and cancer, often because of excess smoking [11].

Common mental health concerns frequently go unsupported; an estimated 75% of people who would benefit from support for common mental health concerns do not receive it, resulting in approximately costs of £105.2 billion a year to the UK economy [12,13]. Lack of support at an early stage can lead to poorer physical health outcomes and the development of unhealthy coping strategies such as alcohol consumption or poorer diet choices [14]. Of those people with recognised mental health conditions, negative experiences with mental health services are commonly reported [15,16]. Nearly half of survey respondents (44%) who had received NHS therapies in 2019 reported that they had to wait too long to access them [15,16] and in 2017, half of the respondents reported only being offered pharmaceutical treatment [17]. Long wait times to access mental health services can have significant health and economic impacts; a recent study by the Royal College of Psychiatrists found that 38% of people waiting for treatment reach out to crisis services and 11% go to A&E [18].

The economic cost of mental health conditions can occur from sick days, reduced quality of life, and reduction in productivity [3,4]. Depression, anxiety, or stress are some of the most common reasons for lost workdays [19]. Symptoms of common mental health conditions like depression and anxiety have increased since before the Covid-19 pandemic, referrals to mental health services decreased, and the number of people presenting in crisis increased [20]. It is estimated that the economic cost for the UK due to poor mental health is greater than NHS spending on mental health services [21]. Reducing the impact of common mental illness will increase our national income and productivity.

In 2008, a programme for IAPT was launched by the NHS [22]. The number of referrals demonstrates the demand for mental health services in the UK; over 1.5 million referrals to adult IAPT services were made in 2018/2019 [23]. Over a quarter of these patients (n=441,775) were discharged without face-to-face contact following a telephone referral and another quarter (n=440,344) were discharged with a workbook [23]. With each contact costing an average of approximately £100 [24],

the total cost to the NHS was over £90 million. This figure does not include additional care needs or A&E attendances for those individuals who were unable to wait up to 12 weeks for assessment.

The NHS Long Term Plan aims to promote digitally enabled care, improve access to mental health support for 1.9 million people, and support NHS Trusts at meeting their referral waitlist key performance indicators (KPIs) [25]. Wysa's solution is well-placed to support these goals by providing a digital early intervention approach that can be implemented at the point of self-referral, reducing the need for inappropriate assessments and escalating cases based on clinical outcome measures as needed. This is also aligned with NHSx's missions, particularly the aims to use digital technology to improve health and care productivity and empower people to access information and services to manage their own health [26], and the Industrial Strategy's grand challenge of embedding AI to improve productivity in the UK [27].

7.2 Rationale

A key issue with the current mental health service provision is lack of accessibility. Our solution enables immediate service provision at the point of referral, to mitigate the impact of long wait times to access mental health services. Onboarding processes at the point of referral to IAPT involve collecting routine outcome measures (aligned to existing service referral measures). Users are asked to provide information and goals to personalise the guided self-help or escalation recommendations. These are provided using a combination of AI-enabled self help tools, natural language processing and conversation engines. Our Application Programming Interface (API) through the Mayden Prism system then pushes data directly into the iaptus electronic patient records and automates safety alerts.

Our preliminary work suggests that implementing Wysa's self help tools at the onboarding stage will result in improved outcomes for the service user, whilst automations in the referral process will result in less assessments that are then screened out of the service and a more comprehensive risk identification whilst awaiting assessment [28]. This is based upon our previous findings from our 2018 study showing a significant decrease in depressive symptoms in users of Wysa versus non users [28].

7.2.1 Benefits for patients and public

IAPT services used a stepped care model, with Steps 2-4 reflecting increasing intervention beyond the GP level; Step 2 is conducted by psychological wellbeing practitioners to manage mild to moderate mental health conditions, while Steps 3 and 4 involve CBT therapists and other specialised treatments for more severe or complex conditions [29]. Whilst computerised Cognitive Behavioural Therapy and guided self-help are recognised treatment options for step two low intensity support in IAPT, they are often offered later in the referral pathway resulting in a higher assessment cost and poorer user experience. The use of Wysa could help to improve patient experience of, and outcomes from, their use of mental health services, for example, by reducing their wait time to access evidence-based advice. Delivering timely and convenient evidence-based support could empower users to make choices about their health and coping strategies. The use of standard outcome measures also enables the app to escalate those patients in need of step three or higher intensity interventions. This solution also has the potential to reduce inequalities in service provision (e.g., those who might otherwise remain untreated [30] and is especially important for individuals from high risk groups (such as LGBTQ+ or Black and minority ethnic groups) who are least likely to receive support [31,32]).

7.2.2 Benefits for NHS and service provision

Wysa has the potential to benefit service provision by providing a more efficient care pathway. By providing mental health support and user outcome measures at the point of referral, rather than when patients are assessed and offered treatment, Wysa can help to identify users who have a more urgent need for treatment and escalate their care. Some users might find that Wysa sufficiently meets their needs for mental health support, which would reduce the number of patients who need to be assessed and treated in the standard care pathway and reduce the waiting times for patients who do need further care. Timely support provision and early identification of deteriorating mental health could enable earlier interventions before the patient's condition becomes more costly to their well-being and to the healthcare system.

7.3.3 Benefits for environment

Implementing automated support at an early intervention stage has the potential to reduce the number of face-to-face assessments both at the point of referral to the IAPT pathway and at the point of full assessment. This reduction could potentially contribute to a reduction in the demand for travel to attend appointments whilst also reducing the demand of building spaces, contributing to the NHS's Net Zero Carbon goal [33]. Early interventions also have the potential to prevent further ill health, which increases operational efficiency and reduces emissions [33]. If Wysa is proven effective and widely adopted, its early provision of self-help resources could help to prevent worsening mental health and identify people most at risk so that they can be treated before reaching a crisis. Evidence will be gathered as part of this project's health economic assessment to examine this hypothesis.

7.3 Theoretical Frameworks

Two frameworks will form the theoretical basis for the study:

1. Long-term adoption and suitability to further trials will be evaluated using the Non-Adoption, Abandonment and Challenges to the Scale-up, Spread and Suitability (NASSS) framework [34].This framework is important to include because interventions can only add value if they are successfully adopted and used. This framework emphasises the consideration of the multiple levels - individuals and systems - that influence adoption and non-adoption.
2. The Theoretical Framework of Acceptability (TFA) will be used to structure the semi-structured interview guide [35]. This framework was chosen because it was developed specifically for health interventions, captures a multi-faceted view of acceptability (with seven components), and emphasises the importance of considering different time points when evaluating acceptability.

7.4 Research Question

The main research question of the study is: how does an AI-enabled self-help and triage app impact the mental well-being of patients who have been referred to the IAPT service for mental health support?

7.5 Aims and Objectives

The primary aim of this project is to establish real-world efficacy that patient use of Wysa while waiting for treatment through the NHS mental health care pathway positively impacts well-being by comparing system users with standard services users.

The secondary aims of this project are:

1. To examine the feasibility of using Wysa to identify users at high risk of a mental health crisis and escalate them to further care;
2. To examine levels of user engagement with Wysa;
3. To evaluate patient acceptability of an autonomous early intervention supporting mental health services;
4. To complete a full health economic assessment of using Wysa for autonomous early intervention and triaging support;
5. To assess the potential for sustainable adoption of Wysa in mental healthcare pathways.

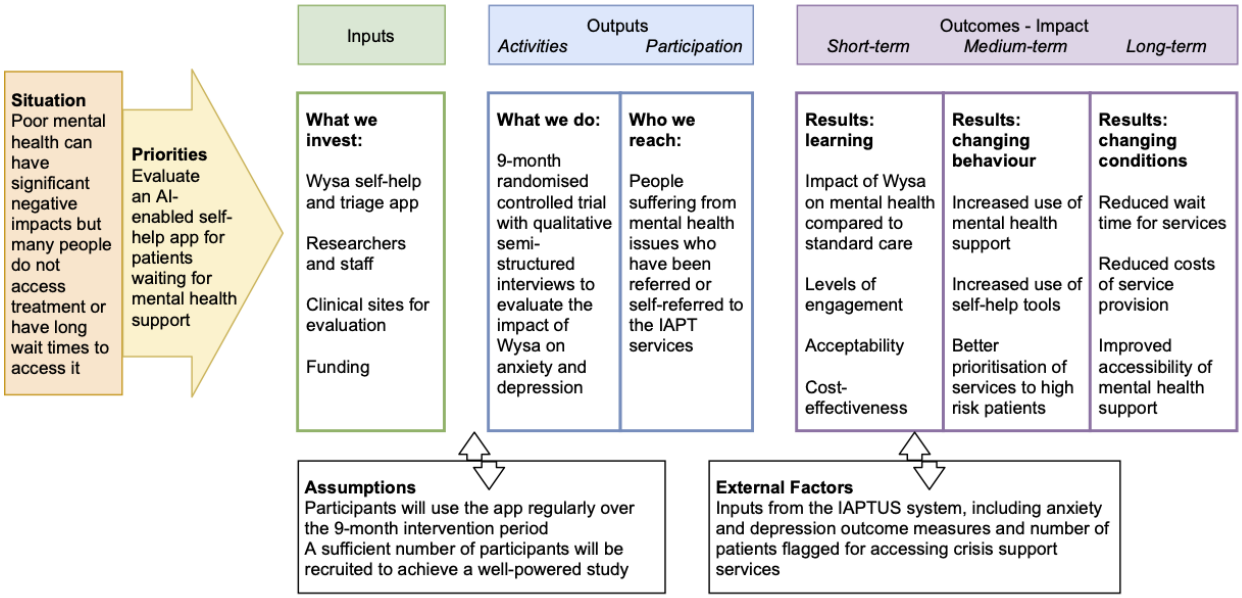

Figure 3. Wisconsin logic diagram

8 METHODS

8.1 Trial Design

This study will use an efficacy non-blinded randomised controlled trial (RCT) and mixed methods (process evaluation) design. Quantitative methods will be used to evaluate Wysa's efficacy at improving mental health outcomes as well as to examine engagement. Quantitative and qualitative methods, specifically semi-structured interviews, will also be used to gather a more in-depth understanding of users' engagement with Wysa and their feedback regarding its acceptability (see Figure 4 for an overview).

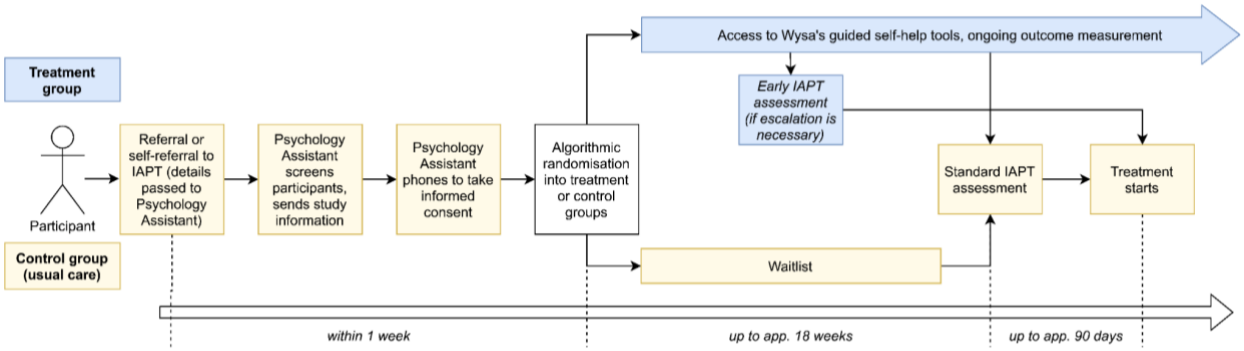

Figure 4. Participant flow diagram

8.1.1 Timeline

The study will last 17 months: 5 months of evaluation refinement and technical integration and testing, 9 months of implementation and follow-up, and 3 months of post-evaluation analysis and preparation for dissemination.

8.2 Study Context

8.2.1 Participants

The target population of the study will include adult patients who are referred, or self-refer, to IAPT for mental health support.

8.2.2 Setting

Participants will be recruited from the Central North West London NHS Foundation Trust but the intervention (Wysa) is accessible to users through a mobile app available on Apple and Android smartphones.

8.2.3 Intervention(s)

Wysa is a guided self-help and triaging tool delivered to patients via an app or widget. It uses Natural Language Processing to understand individuals' written inputs but not to generate responses. Wysa makes use of a wide range of clinically underpinned modules whilst gamification, clinical outcome measures and AI promotes engagement, improving efficacy and triage and reducing the cost of scale.

Wysa is delivered as a standalone system which patients download directly onto their personal device. Upon self-referral or professional referral to IAPT services the individual is automatically sent

a download link via sms or email. Once downloaded, data from within the app, including outcome measures, tools used and crisis alerts are automatically pushed to the electronic patient record iaptus using the Mayden Prism software. When considering the application of AI to mental wellbeing, the ability to feel listened to is the most influential factor in patient satisfaction and response. Users need to feel able to share their thoughts with the AI and our user testimonials show that the anonymous nature of this text-based interaction is imperative to them, even though they know they are communicating with an AI. Wysa has benefited from over 6 million conversations around the world to build up a complex listening algorithm, rules engine and content library. Clinical safety is applied to our rules engine and Content library to ensure that we regularly test for appropriateness, empathy, and presence of triggers in cases of misdirection. Each of Wysa's AI models is validated on at least 10,000 records that are manually tagged and not a part of the training set. Overall, Wysa has 100 million conversations to draw upon, with over 2 million users globally, which helps us overcome the cold-start problem that most AI faces.

Wysa can be used as a native app through android or IOS or as a web widget.

8.2.4 Comparator(s)

The intervention will be compared against a waitlist group. This comparator was selected to compare Wysa to the current standard of care for patients waiting for standard IAPT assessment and treatment.

8.2.5 Outcomes

8.2.5.1 Primary Outcomes

The primary analysis will be the comparison of depression severity between users of the app and patients in the standard clinical pathway (see Table 5). The primary outcome will be measured at baseline and three months post randomisation. In line with the national recommendations laid out by the IAPT Manual, we will be using Wysa's AI automation to encourage users to complete the Patient Health Questionnaire (PHQ-9 [36]) and General Anxiety Disorder (GAD-7 [37]) routine outcome measures [2]. Depression severity was chosen as the primary outcome because the PHQ-9, a depression symptom measure, is recommended for use in all patients presenting to IAPT services [2].

Table 5. Primary Outcome Measurement

Primary Outcome	**Outcome Measure**
Depression severity	● Score on the PHQ-9 [36]

8.2.5.2 Secondary Outcomes

There will be several secondary outcome measures to assess Wysa's ability to improve anxiety severity and identify people who need urgent support, engagement, and the acceptability and cost-effectiveness of the app (see Table 6). The secondary outcomes will also be measured at baseline and 3 months post randomisation.

Anxiety severity

As the GAD-7 [37], which measures anxiety symptoms, is recommended for the 6 most common presentations, it will also be used as an outcome measure for the study and will be presented to patients through the app in the same way as the PHQ-9 [36]. The remaining measures used by IAPT

are linked to specialist presentations of pre-existing conditions which would be excluded as participants from the study due to non-eligibility to IAPT standard pathway.

Crisis identification

Wysa's ability to identify users who are at high risk of a crisis and who need to be provided with additional support will be measured by comparing the number of patients that Wysa flags for escalation with the number of patients in the control group who contact the NHS Trust's crisis helpline or attend A&E. This data will be collected from iaptus, a cloud-based electronic patient record for managing psychological therapy services [38], which flags patients on the waitlist who access these crisis services.

Engagement

User engagement with Wysa will be assessed using a combination of complementary measures. Examining time spent using a digital health intervention is not by itself a reliable measure of effective engagement, as it cannot differentiate between users who spend a long time on the app because they're positively engaged compared to those who are frustrated and struggling to use it [39]. Therefore, objective measures of app usage will be supplemented with an assessment of uptake and dropout rates and a qualitative exploration of subjective user experience and engagement behaviour.

Acceptability

Wysa's acceptability will be examined through qualitative semi-structured interviews in a subset of participants. These interviews will provide a means of collecting in-depth data about participants' experiences with Wysa, what they liked and disliked, and why.

Health-related quality of life

Two questionnaires will be used to assess health-related quality of life: the EQ-5D-5L [40] and the Short Form 12 (SF-12) health survey [41]. The EQ-5D-5L provides a descriptive self-assessment of health in 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [40]. It is commonly used as a quality of life measure to conduct cost effectiveness analyses [42]. The EQ-5D-5L has a greater emphasis on physical than mental health, but has demonstrated the ability to capture changing anxiety severity [43]. The SF-12 survey is a reliable measure of functional health and is well-suited for this study, as it includes mental health items and has been shown to be acceptable for use as a screening tool for depressive disorders [44].

Cost-effectiveness

To conduct a health economic analysis, the study will collect data on health and social care service use, medication use and treatment costs, the implementation costs of Wysa, out of pocket medical expenses borne by patient and carers and productivity related costs such as work absence / time off work due illness. This data will be combined with the quality-of-life indicators to produce an assessment of the costs of adopting Wysa from the perspective of both the UK health and social care services and the wider society [45]. This analysis will also produce a budget impact model for each site that will be used to provide a final overall implementation strategy for more rapid adoption at other NHS sites and dissemination across the AHSN network in partnership with the new Integrated Care Systems. The team will also incorporate the environmental sustainability calculation in line with the Greener NHS agenda.

Table 6. Secondary Outcome Measurement

Secondary Outcome	Outcome Measure
Anxiety severity	● Score on the GAD-7 [37]
Crisis identification	● Number of users identified by the app for escalation of care compared to the number of patients in the control group who access A&E or out-of-hours services while waiting for treatment
Engagement	● Uptake rates ● Dropout / 'did not attend' rates ● App usage data ● Qualitative feedback from semi-structured interviews
Acceptability	● Qualitative feedback from semi-structured interviews ● Automated review questions periodically requested during general use of the tool
Health-related quality of life	● EQ-5D-5L [40] ● Short Form 12 (SF-12) health survey [41]
Cost-analysis	● Data on health and social care service use, medication use and treatment costs, patient-bourne costs, productivity related costs, and Wysa's implementation costs

8.3 Sample and Recruitment

8.3.1 Eligibility Criteria

8.3.1.1 Inclusion Criteria

- Willing and able to provide informed consent;
- Aged 18 years or older;
- User is confident in their ability to speak and understand English at a proficient level;
- Own a mobile device capable of supporting Wysa;
- A valid email address;
- Referred or self-referred to proceed through the standard IAPT care pathway.

8.3.1.2 Exclusion Criteria

- Patients ineligible for the standard IAPT care pathway;
- Patients with previous and current known major mental illness such as Schizophrenia, severe depression, any co-morbid neurological or neuro-psychiatric condition such as epilepsy;
- Patients with current psychosis or a history of psychotic symptoms within the last 6 months
- Patients with suicidal ideation;
- Patients scoring > 15 points on PHQ- 9;
- Patients scoring > 15 points on GAD- 7;
- Patients with significant cognitive disorders;
- Patients with noted neurodevelopmental conditions such as autism or ADHD;
- Patients previously diagnosed with a personality disorder;
- Patients who been under the care of CMHT or a specialised mental health services in the last 2 years;
- Patients who failed IAPT previously;

- Patients with referrals for specialist presentations of pre-existing, diagnosed conditions requiring a specialised assessment beyond the standard clinical pathway;
- Incapable of self-consent;
- In a dependent/unequal relationship with the research or care teams or any PPI representatives.

8.3.2 Sampling

8.3.2.1 Sample Size

Approx 1100 eligible patients are seen per month at the IAPT in the CNWL NHS Foundation Trust. Preliminary work suggests that Wysa is associated with a mean clinical improvement in PHQ-9 of 5.84 (SD6.66) [28]. This study is powered to detect a clinically meaningful effect on the PHQ-9 scale [28]. Based on a SD of 6.6 and a 2:1 recruitment ratio (usual care: intervention) a sample size of 393 would allow detection of a difference in PHQ-9 of at least 2 points, with 80% power. Augmenting the sample size to 480 would allow for 20% attrition, whilst still maintaining sufficient power to detect clinically and statistically meaningful differences with a Type 1 error rate of 0.05. This inflated sample size would also allow for adjustment for stratification variables, gender, age, ethnicity, self-reported antidepressant use, and severity of depression.

8.3.2.2 Sampling Technique

Participants will be randomly allocated to intervention or control groups by a computer algorithm after they have provided informed consent and demographic information. Of this sample, a subset will be selected to participate in a semi-structured interview to collect qualitative data about patients' perceptions of Wysa.

To select this subset, a stratified random sampling technique will be used. Patients will be divided based on demographic characteristics (e.g. gender, age, socio-economic status, and ethnicity). From these subgroups, patients will be randomly selected so that the sample interviewed is representative of the UK population.

8.3.3 Recruitment

8.3.3.1 Participant Identification

Participants who are referred, or refer themselves, to IAPT for mental health support (online or by phone) will be recruited from the three provider sites of the London Community Living Well Service, run by the Central North West London NHS Foundation Trust. The service receives on average 1100 referrals a month. All referrals will be screened by the psychology assistant against exclusion criteria and those eligible for the trial will be provided with information regarding the trial via email (see 13.1 Appendix 1). The psychology assistant will then contact participants to check further exclusion criteria not clear from service referral and to take informed consent. Screening will continue through the first 6 months of the intervention period, and we expect to be able to onboard significantly more individuals than our target sample size. All participants will have access to the Wysa app (including control participants who will receive access following the control period).

8.3.3.2 Consent

Current consent for referral to service is collected through a tick box acceptance of terms during online referral. This states: 'Through completing this form you are consenting to have this information stored confidentially on a secure electronic system separate from your GP's system and for your GP to be informed of your contact with us. By providing these details you are giving consent for us to contact you regarding confidential information'

For the trial, explicit consent for participation will be collected (see 13.2 Appendix 2). When individuals self-refer or are referred to the IAPT, they will be screened against the eligibility criteria. Eligible individuals will be sent a study information sheet and then contacted by phone by a study team member to take informed consent and discuss any questions participants might have. Once the trial has started and users download the app as part of intervention they are asked during onboarding if they still consent to take part of the trial and informed of how to remove their data from the trial should they wish to do so.

8.3.4 Adherence

The study team will monitor the use of Wysa and assure the system is being used within designed parameters during the study.

8.4 Data Collection

8.4.1 Randomisation

8.4.1.1 Sequence Generation

Demographic data will be collected from all patients immediately after they complete the informed consent process, during the same phone call. Together with data from the IAPT referral, this information will be used in the randomisation algorithm to ensure that the intervention and control groups are balanced on key variables (gender, age, ethnicity, self-reported antidepressant use, and severity of depression).

8.4.1.2 Allocation Concealment Mechanism

Consenting participants will be inputted into a masked computer randomisation algorithm and the outcome will be recorded in an electronic record to conceal treatment allocation from study researchers. Participants will be sent an automatic email to inform them of their group assignment, and participants in the intervention group will receive the link to download Wysa.

8.4.1.3 Implementation

Psychology Assistant recruited specifically for the trial and covering the three London Community Living Well Service sites will enrol participants in the study. A computer will generate the random allocation sequence and assign participants to interventions.

8.4.2 Blinding

Due to the nature of the intervention, no blinding of participants will be possible in the study, as all participants will know whether or not they are using the app. Clinical treatment teams will also not be blinded as they will know through the electronic patient record if a participant has received the intervention. The evaluation team will be blinded to treatment using the randomisation algorithm.

8.4.3 Methods of Data Collection

The timeline for the data collection is detailed in Figure 5.

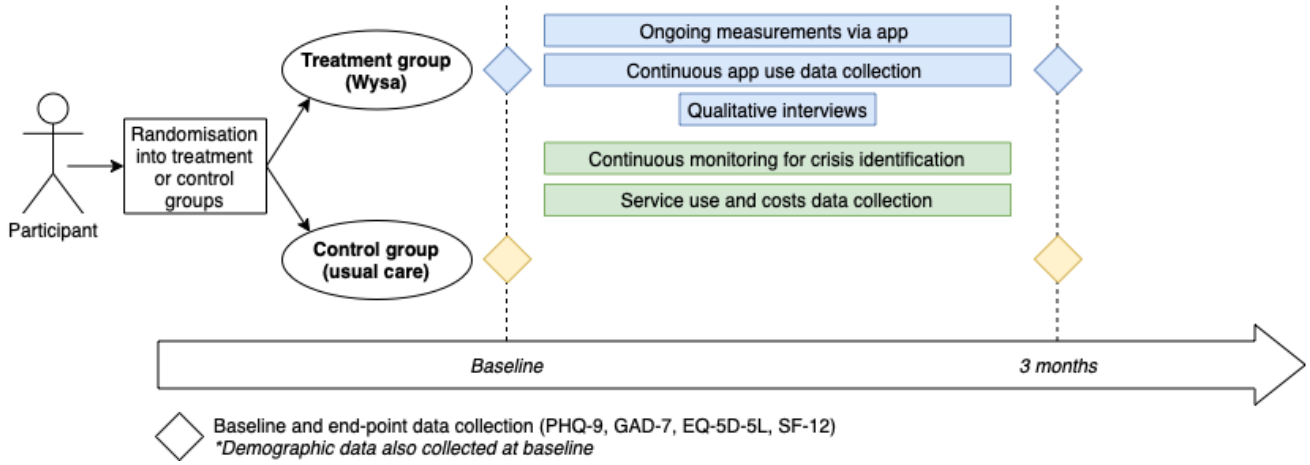

Figure 5. Data collection sequence diagram

8.4.3.1 Quantitative data collection

The quantitative outcome measures will be delivered directly to patients through the Wysa app or by Qualtrics survey (e.g. for participants in the control group). Participants in both conditions will complete four questionnaires at baseline and 3-months post-randomisation (PHQ-9, GAD-7, EQ-5D-5L, and SF-12). Outcome measures have been chosen that will not be a significant burden for participants to complete; none of the questionnaires are longer than 12 items or expected to take more than a few minutes each to complete. Together, the questionnaires should take participants from 10 to 20 minutes to complete. Patient responses will be automatically uploaded to the iaptus electronic patient records using the Mayden Prism API. App use data will be automatically stored through the app.

8.4.3.2 Qualitative data collection

A subset of study participants will also be invited to participate in a semi-structured interview, so that more in-depth, qualitative engagement and user experience feedback can be collected. A topic guide will be developed to provide a framework for the interviews. Interviews will be conducted using video or call conferencing software and recorded for later transcription (if the participants consent). If they do not want the interview recorded, notes will be taken by hand and shared with the participant following the interview for verification. See 13.3 Appendix 3 for sample interview questions.

8.5 Data Analysis

8.5.1 Statistical Methods for Primary Outcome

Descriptive statistics will be used to characterise users, assess baseline comparability, and compare side effects. Primary comparisons between intervention and control groups will be conducted for primary and secondary outcomes. Primary analyses are designed with 80% power to detect a two-sided α of 0.05. All analyses will report 95% CI around estimate of effect. Comparative analyses will be conducted on an intention to treat basis, using linear or logistic regression, with adjustment for stratification variables.

We will explore missingness in our data, be that in relation to primary outcomes, follow-up data and in WYSA analytic information. The proportion of missing data will be explored and reported on descriptively. An hypothesised scenario, where patients remove themselves from the waiting list for treatment before the duration of follow-up may lead to missing data scenario. Currently, estimates

suggest that xxx% of our cohort will 'drop-off' waiting list before our primary endpoint. We will conduct exploratory a sensitivity analyses in a complete case ('per protocol') cohort compared with the ITT analysis.

8.5.2 Other Data Analyses

Secondary analyses will include additional adjustment for factors showing possible imbalance at baseline and pre-planned exploratory analyses for differential effects of the intervention for different age groups, depression severity, and interaction (dose) of the Wysa app. Secondary analyses including adjustment for factors showing potential imbalance at baseline and pre-planned exploratory subgroup analyses for differential effects in a priori specified groups will be conducted using linear or logistic regression. For secondary analyses, where we have not specifically powered the study to detect statistical or clinical meaningful differences, we will report p-values but will focus on interpretation of 95% CI around estimates.

The qualitative semi-structured interviews will be evaluated using a thematic analysis.

8.6 Limitations

There are a couple limitations with the protocol.

Technical limitations of the system will affect the generalisability of results. At present, patients without access to any digital device would not be able to use the system and are therefore not eligible for inclusion in the study. As Wysa's algorithm is currently only compatible with the English language, non-English speaking patients will be excluded from the study, also limiting the representativeness of the sample.

Potential bias is introduced to the results by the use of qualitative interviews because of the influence of the interviewer on how participants respond (e.g. social desirability bias). This potential bias will be assessed by examining the balance of positive and negative feedback and by comparing the qualitative and quantitative data about Wysa's usability, acceptability, and impact.

8.7 Generalisability

Limitations to the generalisability of the study results were noted in the previous section. However, it is expected that the results will be generalisable to most individuals seeking general mental health support. We will also make efforts to recruit a representative sample of the UK population and include a representative subset in the semi-structured interviews.

9 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Assessment and Management of Risk and Other Ethical Issues

Standard ethical issues will be managed as follows:

- Recruitment: Participant eligibility will be determined by the screening process they undergo upon referral to IAPT. Participants who are eligible will be randomly divided by the computer into intervention and control groups with no influence from the researchers. Interview participants will also be randomly selected (from demographic groups) by a computer script of intervention users. All participants will be included in the process evaluation's quantitative analyses, thus avoiding recruitment bias.
- Power relations and other potential biases: Pre-established inclusion and exclusion criteria will be used to avoid any potential bias from the researchers as well as any coercion from participants. To prevent participation bias, only participants who would not otherwise progress down the standard care pathway will be excluded.
- Sensitivity: The outcomes measures that concern potentially sensitive topics (depression and anxiety) will be delivered to the patients' phones via the app. This allows them to avoid discussing any sensitive topics with a researcher. The semi-structured interview questions will focus only on the participants' experiences with the app (engagement and acceptability) and are intended to avoid any areas of cultural or psychological sensitivity.
- Confidentiality: To control any potential perceived issues in this area, participant confidentiality will be protected using data protection procedures that are compliant with the Data Protection Act 2018 (DPA 2018) [46] (as described in section 9.7).
- Timing: To mitigate any time concerns for participants, qualitative interviews will last for a maximum of 60 minutes.
- Study Governance: To maintain the integrity of the study and avoid any commercial influence, a research contract will be established between Wysa, the University of Plymouth (Dr Meinert's institution), and the Institute of Cancer Research (Dr Costelloe's institution) that will ensure the independence of study design and execution and the unrestricted right to publish all results.
- Acceptability of study: To ensure that there are no ethical concerns with the study that might have been overlooked by the researchers and that the design is participant-friendly, a local PPI group will be formed to collaborate with researchers throughout the study. For further details, please see the PPI section.

A comprehensive risk register and Hazard log is maintained by Wysa across its development as part of its Clinical Safety Management file. This risk register will be regularly reviewed and updated as part of the project management governance. Key risks for this project include:

- Clinical: A Structured What-IF Technique (SWIFT) analysis has been completed which highlighted that the main clinical risk of this project is unintended harm. This could be psychological or physical risk caused by unintended increase in psychological distress or the physical impact of increased reliance on screen time. We have mitigated the risk to patients by building a clinically underpinned crisis response pathway with handover capabilities to the clinical team at Central North West London NHS Foundation Trust.
- Excessive screen time: Health risks associated with excessive screen time are mitigated by ensuring that many of the strategies and skills taught by the app encourage users to complete them away from the screen. All risks and mitigations are outlined in the clinical safety management file.

- Technical: The main technical risk is that the system is not fully integrated with iaptus ready for our go live date, delaying the project. This is mitigated by completing planning works and scoping prior to the application for this award and for allowing contingency time in our project planning.
- Delays: A second risk is that information governance permissions are delayed or withheld at pilot sites - mitigated by a technical, security and privacy architecture that has already been approved by the representatives of the trust who are project partners on this award.
- Commercial: The need for good quality evidence combined with long sales cycle times in healthcare can produce a risk of limited cash flow - this is mitigated by Wysa's maturity as a company and track record of securing investment funding as needed. As a real-world use study the evidence generated by the project will help to respond to commissioners' need for a high quality evidence base, removing a core barrier to implementation.

9.2 Research Ethics Approval

The study protocol will undergo institutional and regulatory review and approval prior to commencement. To ensure that our data reporting is in line with NHS standards we will be following the Department of Health and Social Cares guidelines for good practice for digital and data driven health technologies [47]. As per the guidelines, we will be applying the Caldicott Principles for the collection and evaluation of patient data and everyone dealing with patient information will be required to complete the online training prior to starting on the project to evidence familiarity with these.

Ethical approval is being sought from the Health Research Authority and the relevant Research Ethics Committee with this submission [48]. As the IRAS system brings together these assessments, only one application is needed [48]. The protocol will therefore receive medical device review from the associated REC.

Additional independent ethical approval will be sought from the University of Plymouth. At the University of Plymouth, an application for ethical approval will be submitted through the Plymouth Ethics Online System to the Health Faculty Research Ethics and Integrity Committees (FREIC) [49].

The University of Plymouth, as the study sponsor, will ensure that the study has received ethics approval from a research ethics committee (REC) and has received Health Research Authority (HRA) approval.

9.3 Peer Review

The study will undergo peer review and ethical approval via the University of Plymouth research governance process.

9.4 Patient and Public Involvement

The CNWL NHS Foundation Trust, SW AHSN, and Institute of Cancer Research have robust PPI support infrastructures to ensure we are able to have the necessary support in place to establish our PPI framework for the research study. Partnerships with both of these institutions will ensure we align our PPI practices as we move through the research cycle. A PPI lead for the study has been recruited and is working with a number of PPI engagement groups at CNWL to support the trial.

9.4.1 Involving a lay representative on the study monitoring group

A lay representative will be appointed to the study monitoring group, additional the patient representative will be invited to key strategic and public meetings. The lay representative will be involved in all aspects of the study, specifically, these include, but are not restricted to review of

each milestone and acceptance of deliverables - seeking their views around acceptability of patient-facing materials, study procedures, and plans for translation to clinical practice.

9.4.2 Involving a dedicated PPI group

The broad aims of the PPI group are to support the governance of patient and public involvement and engagement approaches and activities within this study and ensure the public voice is present through all stages of the research cycle. Membership of the PPI group will be open to those both with a direct interest in telemedicine or mental health, but also any lay member with an interest in our broader aims. We will include patients and lay members both with and without previous experience of PPI to make sure we have a variation of skills and expertise.

We will form a bespoke PPI group for the project including existing members of the Wysa PPI community as well as members of the CNWL PPI community who are interested in progressing the use of AI in population access to mental health. We will hold a number of experience-based co-design (EBCD) workshops using storyboarding and community asset mapping to establish design and preference mapping and the group will also provide final sign off at milestone achievements in the work packages.

With input from the Imperial College PERC, we have drafted, based on NIHR Involve guidance, a term of reference, confidentiality agreement and a background assessment form to allow us to realise the broad aims of our PPI group. Membership of this Wysa PPI group is voluntary but requires members to be committed to attend meetings and to respond to emails/correspondence. The initial term of membership is for the duration of the study from early in the preparation phase (app. Dec 2021 / Jan 2022). We aim to have a minimum of four formal members at the inception of the panel and each subsequent meeting with representation from both London and the Southwest. We will seek to make participation as diverse as possible by selecting members based on 1) demographics 2) levels of PPI experience and 3) connection to telemedicine or mental health based on the results of our basic background form. We are aware that we have to ensure Wysa's product is as accessible to as wide a range of possible demographics as possible, and the first phases of setting up our PPI group will involve a wide search using networks from SW AHSN and NIHR Involve's "People in Research" platforms.

The panel will aim to convene every four months for a 90-minute formal group discussion, given the evolving Covid-19 situation, we anticipate at least some of these group discussions to be conducted via video-conferencing, with more informal discussions happening via email or phone-calls. As the study spans two sites, we envision using teleconferencing to help enable maximal participation of our participants and to lower the barriers to involvement. At both sites, a dedicated location for teleconferencing will be designated to ensure we are not excluding participants less comfortable with or less willing to use technology.

We anticipate that we will be having an ongoing dialogue with study participants both formally in the afore-described evaluation phase, and informally via ongoing feedback. As such, we anticipate that new members may be recruited to the PPI group if there are gaps in experience. The panel may choose to invite other patients/members of the public involved; other university members and/or representatives of voluntary or community organisations on a one/off or long-term basis. Observers, guests and presenters may also be invited on a one/off basis.

The meetings will be co-chaired by a lay chairperson who is nominated by all attendees of the meeting, and a professional chairperson will be a senior Wysa team member who has received formal experience in chairing PPI meetings. We have drafted a "role" specification with Imperial PERC of a chairperson which may be a different individual between meetings depending on topics of discussion.

Payments will be made in recognition of members' time based on NIHR Involve guidance on payment of fees and expenses for our members actively involved [50]. Travel expenses will be reimbursed in accordance with this policy together with other expenses and travel costs. We have budgeted based on suggested reimbursement schedules and have produced our estimates following use of the Involvement Cost Calculator.

9.4.3 Role of PPI group

We will be seeking the group's support on several key points:

1. Recruitment - PPI representatives will be included in the interview panel for any outstanding staff positions to ensure we recruit empathic and relatable staff members who will best engage the community. Due to time constraints, this may involve either the Wysa PPI team or the CNWL participation group independently.
2. Methodology - While PPI representatives have already been involved in the initial design process, we will also ask the group to review our final proposal as well as any iterations of outcome measures.
3. Tool packs - Members of the groups will be invited to brainstorm ideas for tool packs and modules to be automated into guided self-help available on the clinical version of the app.
4. Testing - Our PPI groups are an important part in our testing process prior to release of the clinical version of the app to the research cohort.
5. Dissemination - A number of our PPI groups have previously been involved in the review of academic articles, the development of public facing content, and the presentation of findings at conferences and we plan to continue this during this project.

To minimise impact on time, and in reflection of restrictions due to the Covid-19 pandemic, we run most of our engagement sessions online, making use of text- or video-based communication. We also collect feedback and input from our users through the app interface. For this award we have included a reimbursement budget to cover the time commitment of the PPI group as well as budget for The PHA Group to work with the PPI group in creating PR content.

9.5 Protocol Compliance

Bi-monthly study governance meetings will be held, alternating between monitoring and clinical reference group sessions. Monitoring meetings will include all study partners and NIHR/NHS representatives, and patient representatives. They will review progress against the study plan and budget, sign-off study deliverables and update the project's risk register. Clinical reference group meetings will include senior representatives from both clinical sites who will provide oversight of progress, approval for go-live and ongoing monitoring of delivery. A group of external academics will be appointed as a trial monitoring committee who will also perform audits to ensure compliance to procedures.

Planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and will not be used. Any accidental protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately should they happen. Immediate action will be taken towards any deviations to avoid serious breach. The Sponsor will be notified immediately should there be a serious breach of the safety or physical or mental integrity of the participants of the trial or the scientific value of the trial. The Sponsor will notify the licensing authority in writing of any serious breach.

9.6 Consent

BERA guidelines have been followed for voluntary informed consent, use of methods, and university policies in the event there are issues in delivery [51]. Prior to completing informed consent, participants will be given information that fully describes the process of the study (including the possibility of being randomly selected to be invited to participate in a semi-structured interview), including why their participation is necessary, how their data will be used, and who the results will be reported to. As many patients are understandably concerned about how their data will be used, data management will be explained in detail as part of the consent process. It will also make clear their right to withdraw from the study at any time and have their data destroyed. Patients will also be asked to separately consent for their data to be used to further studies. Declining to share this conversation data will not affect patients' participation in the study or their clinical care.

9.7 Data Protection and Patient Confidentiality

The Wysa system stores patient identifiable data directly into iaptus electronic patient records using an API built through the Mayden Prism system. This solution complies with the General Data Protection Regulation (GDPR) and was built to meet the NHS DCB0129 safety standard and the code of conduct for the use of artificial intelligence [52].

The team has specific expertise in this area as the project lead is a qualified Clinical Safety Officer and has experience of overseeing the safe integration of solutions that share patient data into the NHS. Wysa also monitors compliance with the information governance requirements set out by the Department of Health and Social Care by using the Data Security and Protection Toolkit which is also a 'live' process.

Wysa maintains a data recovery plan in case of emergency which ensures that loss of functionality does not directly impact on patient experience or safety. Wysa completes a regular internal audit of data protection and data safety as well as an annual external audit. We have clear reporting and escalation procedures in place and can provide copies of these policies as required.

A Data Protection Impact Assessment will be conducted with the organisations involved in this study, and Information Sharing Agreements will be developed in collaboration with the CNWL NHS Foundation Trust's Data Protection Officer. To mitigate patient concerns about data use, privacy, and security, these procedures will be clearly explained in the participant information sheet provided at the point of recruitment. If patients are unclear or unhappy with how their data will be protected, they will have the opportunity to refuse to consent to participate in the study without any consequences to their care. They will also be informed that they are free to withdraw their consent at any point in the study and will continue in the standard care pathway.

Interactions with the AI component will create potentially identifiable patient data which will be stored as part of the medical record in Wysa's role as data processor. Patient identifiable data will not be sold to any other party and will not be shared with any organisation unless they are a partner in the study and have an appropriate information sharing agreement in place. Strict access controls will be implemented to protect this data.

Each of the study participants will be given a unique identifier. The primary key between unique ID and participant shall be stored securely for reference purposes and provided to the participant so that they can request that their data be withdrawn from the study. This can be requested at any point prior to data aggregation and will result in all of the patient's files and data being destroyed. Data collected in the study will be analysed using the unique identifiers rather than patient names. Data subject consent forms and primary research data will be retained for 10 years following

publication of the final study results. Study participants will have the option to retain their information within the WYSA app for their onward use or to reset their data at the completion of the study.

Follow-up interview sessions shall be audio recorded by Dr Meinert and his research team. The interviews will be transcribed by a transcription service with only reference to the unique identifier provided in the audio file for transcription (the audio file will be reviewed by the CI to ensure no identifying information is in the audio recording; if any is provided it will be edited out); the risk of identification of the interview sessions shall be very low due to this measure being taken. The original audio recording will be destroyed following transcription. Only the Academic CIs and their research staff will have access to research data. The transcription service will have access only to interview audio, following the controls previously mentioned.

9.8 Stopping Guidelines

The study monitoring group will review the interim data for consideration of stopping the study early. Given that the estimated sample size is close to the minimum required for adequate power, the study will not be stopped early on the basis of efficacy or benefit. If the monitoring committee identifies any risks that have not been foreseen and mitigated against, the study will be paused while those risks are assessed.

9.9 Indemnity

The University of Plymouth holds research insurance policies which apply to this study. The Central North West London NHS Foundation Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study.

9.10 Access to code

At the time of the close of the intervention refinement period, the Wysa app version number will be recorded. Changes to the platform required to maintain safety, security or 3rd party software dependencies will be approved by the trial steering committee and ratified by an external trial monitoring committee. Changes will be validated before and after the trial by an independent software engineer on Wysa's source code change log.

9.11 Access to data

Audio recordings, transcriptions, and meta-data will be securely stored in UK data-centres with strict role-based access control. The transcription service will only have reference to the unique IDs and the audio recording will be reviewed by the CI to remove any identifying information before being shared. Patient identifiable data will not be sold to any other party and will not be shared with any organisation unless they are a partner in the study and have an appropriate information sharing agreement in place. Records of consent will be kept for ten years after the publication of final study results, but no other personally identifiable information will be stored beyond the end of the study.

10 DISSEMINATION POLICY

10.1 Dissemination Strategy

Analysis of the data will be compiled into a published peer-reviewed paper. This data will also be used to support MHRA Class IIa regulatory approval and wider adoption practices. This WP will also produce a budget impact model for each site and provide a final overall strategy for rapid adoption at other NHS sites.

The national framework for IAPT services outlines the referral and assessment pathway. WYSA has been designed to align with outcome measures stipulated in this framework whilst removing capacity restraints making it highly exploitable across the 942 IAPT service providers in England. Strong relationships across the AHSN network, central NHSX and Institute of Cancer Research will be used to disseminate the results and gain support for further deployments.

Interoperability with digital systems is an important element of this real-world evaluation study. iaptus is used across the country for data capture and patient records relating to the IAPT service. The API integration with Mayden Prism software is an important part of our current and proposed work streams, as it supports easy integration with existing systems and facilitates the incorporation of Wysa into existing care pathways. iaptus is currently the leading patient management software for psychological therapies, covering over two thirds of services, which will allow for rapid technical deployment following the results of this study.

10.2 Authorship Eligibility Guidelines and Use of Professional Writers

The International Committee of Medical Journal Editors (ICMJE) guidelines will be used to determine the study authors [53]. The ICMJE stipulates four criteria that people involved in the study must meet to be considered authors for this paper:

1. Having made a substantial contribution to the design or execution of the study;
2. Having drafted or significantly contributed to the revision of the paper;
3. Having final approval over submission for publication;
4. Agreeing to be accountable for the published work.

No professional writers will be employed.

11 DECLARATIONS

11.1 Funding

This study is supported by the NIHR AI in Health and Care Award (AI_AWARD02176).

11.2 Protocol Registration

The protocol will be registered through this IRAS submission 310377 and additionally on the database clinicaltrials.gov (NCT05533190) [54].

11.3 Competing Interests

ES is an employee of Wysa; although she was involved in the drafting and revision of the protocol, the final decision on the evaluation design lies with the academic collaboration led by the University of Plymouth.

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13 APPENDICES

13.1 Appendix 1. Participant Information Sheet

Most up to date version incorporated into IRAS documents

13.2 Appendix 2. Informed Consent Form

Most up to date version incorporated into IRAS documents

13.3 Appendix 3. Sample Question Guide for Semi-Structured Interviews

The topic guide was developed based on the Theoretical Framework of Acceptability (TFA) [34], which was created to provide a framework for assessing the multiple facets of acceptability of health interventions. The TFA has seven components: “1) affective attitude, 2) burden, 3) ethicality, 4) intervention coherence, 5) opportunity costs, 6) perceived effectiveness, and 7) self-efficacy” [34].

1. How did you feel about your experience interacting with Wysa?
2. How much effort did interacting with Wysa take?
3. What concerns, if any, did you have while interacting with Wysa?
4. How well did you understand how Wysa worked?
5. What benefits or losses did you experience while you were interacting with Wysa?
6. How much confidence did you have in Wysa’s ability to provide mental health support?
7. How comfortable and confident were you in your ability to interact with Wysa?

13.4 Appendix 4. GP Letter

[header: GP letter Participant Consented, v1.0, XX/XX/XXXX; study logo]

[GP Name]

[GP Practice]

[Address]

[Date]

[Study Address]

[Address]

[Telephone/Email/Social media]

Our ref: XXXX

Dear Dr [GP name]

Re: [participant's full name], [participant's date of birth], [participant's address]

We would like to inform you that [participant's full name] has consented to join the Wysa Study. This project is a collaboration between the University of Plymouth, the Institute for Cancer Research, Wysa Ltd, and the Central North West London NHS Foundation Trust. The project is funded by the NIHR AI in Health and Care Award (ref: AI_AWARD02176) and has full ethical approval from [Research Ethics Committee (ref: TBD)]. No action is needed on your part, but [participant's full name] has provided permission that should anything of concern arise as a result of their participation in our study, we will discuss this with you.

Our study aims to measure and characterise the impact of engaging with Wysa while waiting for their first appointment through the IAPT service on symptoms of depression and anxiety. Participants randomised into the intervention group will be invited to use the app while waiting for treatment; participants randomised into the control group will be given access to the app after 3 months.

Participation is voluntary – [participant's name] is free to withdraw from our study at any point. If you would like any further information or if there is anything you would like to discuss, then please do not hesitate to contact us.

Yours sincerely,

[CI's/PI's name] Team Member's name]

13.5 Appendix 5. SPIRIT-AI Checklist: Recommended items to address in a protocol and related documents for clinical trials evaluating AI interventions

Cruz Rivera S, Liu X, Chan A-W, Denniston AK, Calvert MJ, SPIRIT-AI and CONSORT-AI Working Group. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. Lancet Digit Health 2020 Oct;2(10):e549–e560. PMID:33328049

Section		SPIRIT 2013 Item[a]	SPIRIT-AI Item		Section No
Administrative Information					
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	SPIRIT-AI 1(i) Elaboration	Indicate that the intervention involves artificial intelligence / machine learning and specify the type of model.	1
			SPIRIT-AI 1(ii) Elaboration	Specify the intended use of the AI intervention.	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry			11.2
	2b	All items from the World Health Organization Trial Registration Data Set			Through-out protocol
Protocol version	3	Date and version identifier			1.3
Funding	4	Sources and types of financial, material, and other support			5.1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors			3, 5.4
	5b	Name and contact information for the trial sponsor			3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities			5.2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)			5.3

Introduction					
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	SPIRIT-AI 6a (i) Extension	Explain the intended use of the AI intervention in the context of the clinical pathway, including its purpose and its intended users (e.g. healthcare professionals, patients, public).	6, 7.1, 7.2, 8.2.3
			SPIRIT-AI 6a (ii) Extension	Describe any pre-existing evidence for the AI intervention.	7.2
	6b	Explanation for choice of comparators			8.2.4
Objectives	7	Specific objectives or hypotheses			7.5
Methods: Participants, Interventions and Outcomes					
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)			8.1
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	SPIRIT-AI 9 Extension	Describe the onsite and offsite requirements needed to integrate the AI intervention into the trial setting.	8.2.2
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	SPIRIT-AI 10 (i) Elaboration	State the inclusion and exclusion criteria at the level of participants.	8.3.1
			SPIRIT-AI 10 (ii) Extension	State the inclusion and exclusion criteria at the level of the input data.	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	SPIRIT-AI 11a (i) Extension	State which version of the AI algorithm will be used.	9.10
			SPIRIT-AI 11a (ii) Extension	Specify the procedure for acquiring and selecting the input data for the AI intervention.	8.2.3
			SPIRIT-AI 11a (iii) Extension	Specify the procedure for assessing and handling poor quality or unavailable input data.	8.2.3

			SPIRIT-AI 11a (iv) Extension	Specify whether there is human-AI interaction in the handling of the input data, and what level of expertise is required for users.	8.2.3
			SPIRIT-AI 11a (v) Extension	Specify the output of the AI intervention.	8.2.3
			SPIRIT-AI 11a (vi) Extension	Explain the procedure for how the AI intervention's output will contribute to decision-making or other elements of clinical practice.	8.2.3
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)			N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)			N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial			N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended			8.2.5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)			8.1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations			8.3.2.1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size			8.3.3

Methods: Assignment of Interventions (For Controlled Trials)					
Sequence generation	16A	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions			8.4.1.1
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned			8.4.1.2
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions			8.4.1.3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how			8.4.2
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial			8.4.2
Methods: Data Collection, Management, And Analysis					
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol			8.4.3
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols			8.4.3.2
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol			9.7

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol			8.5
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)			8.5
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)			8.5
Methods: Monitoring					
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed			9.4, 9.5
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial			9.8
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	SPIRIT-AI 22 Extension	Specify any plans to identify and analyse performance errors. If there are no plans for this, explain why not.	9.1
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor			9.5
Ethics and Dissemination					
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval			9.2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)			9.5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)			8.3.3.2, 9.6

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable			9.6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial			9.7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site			11
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	SPIRIT-AI 29 Extension	State whether and how the AI intervention and/or its code can be accessed, including any restrictions to access or re-use.	9.10, 9.11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation			N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions			10.1
	31b	Authorship eligibility guidelines and any intended use of professional writers			10.2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code			N/A
Appendices					
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates			13.1, 13.2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable			N/A

[a] It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.

[b] Indicates page numbers to be completed by authors during protocol development