The benefits of adopting WYSA therapeutics for patients, clinicians, services and the wider health care system

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1 STUDY INFORMATION

1.1 Full/Long Title of the Study

The benefits of adopting WYSA therapeutics for patients, clinicians, services and the wider health care system.

1.2 Short Study Title / Acronym

Evaluation of Wysa Therapeutics

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

1.0	Initial draft	5th November 2022
1.1	Revised Protocol	25th November 2023

1.4 Research Reference Numbers

IRAS Number:	320441
SPONSORS Number (if applicable):	
GRANT Number (If applicable):	N/A

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:		
Signature: 		Date: 07/12/2022
Name (please print): Dr Nicole Main.		
Position: Clinical Lead Wysa UK Europe.		
Chief Investigator:		
Signature: 		Date: 7/12/2022
Name: (please print): Dr Lila Varsani		

3 KEY STUDY CONTACTS

Table 1. Key Study Contacts

Chief Investigator	Dr Lila Varsani Wysa Limited 1 London Street, Reading, Berkshire RG1 4PN
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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
CBT	Cognitive Behavioural Therapy
cCBT	computerised Cognitive Behavioural Therapy
DPA 2018	Data Protection Act 2018
EPR	Electronic Patient Record
GAD-7	General Anxiety Disorder questionnaire
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
NHS talking therapies	Improving Access to Psychological Therapies
ICMJE	International Committee of Medical Journal Editors
IRAS	Integrated Research Application System
NHS	National Health Service
NIHR	National Institute for Health Research
PHQ-9	Patient Health Questionnaire
PPI	Patient and Public Involvement
RCT	Randomised controlled trial
REC	Research Ethics Committee
SWIFT	Structured What-IF Technique (prospective hazards analysis method)
WSAS	Work and Social Adjustment Scale

Wysa	Wysa Limited (Company Number: 11220172)

5 STUDY SUMMARY

Table 3. Study Summary

Study Title	The benefits of adopting WYSA therapeutics for patients, clinicians, services and the wider health care system.
Short title	An evaluation of Wysa therapeutics
Study Design	The study proposed is a real world quantitative evaluation to investigate the impact of Wysa therapeutics on clinical outcomes, and the experience of using the products in people with mild to moderate common mental health disorders. Outcome measures will include client satisfaction questionnaires and PHQ9 and GAD7 scores, as well as clinical and/or administrative time savings.
Study Participants	The target population of the will include individuals over the age of 16 years who are referred, or self-refer, to Improving Access to Psychological Therapies programme (NHS talking therapies) for mental health support.
Planned Size of Sample	The planned sample size is 100 individuals from 5 provider sites, two run by Dorset University Healthcare NHS Foundation Trust and three run by Lanchashire and South Cumbria NHS Foundation Trust.
Follow up duration	N/A
Planned Study Period	The study will last 18 months which includes three months of evaluation refinement, ethical approval, technical integration and testing. A further three months will be required for analysis of some secondary outcomes and preparation for dissemination.
Research Question/Aim(s)	The study aims are as follows: 1. To establish real-world evidence of the effectiveness of Wysa as a referral and triage tool. 2. To establish the impact of Wysa as a self help mental health support tool for patients waiting for treatment. 3. To establish the effectiveness of therapist enabled Wysa cCBT interventions on mental health outcomes. 4. To evaluate user experience of the range of Wysa therapeutics. 5. To establish if the adoption of Wysa therapeutics results in any service related efficiencies, for example clinical or administrative time savings.

	The main research question is: How do the range of Wysa therapeutic tools benefit patients, clinicians, services and the wider health care system?

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

A study steering board composed of the Chief Investigator, Principal Investigators, Co-Investigators, and Wysa's Adult Clinical Lead will meet every two months to review progress against the protocol to provide study governance and oversight.

5.2 Protocol Contributors

The sponsor controls the final decision regarding any aspect of the study.

Dr Nicole Main: Contributed to the study design

Dr Lila Varsani: Contributed to the study design

Dr Becky Inkster: Contributed to overseeing the study protocol.

Emma Taylor: Contributed to overseeing the study protocol.

Kelly Colbeck : Contributed to overseeing the study protocol.

Monton Jienpetivate: Contributed to overseeing the study protocol.

6 STUDY FLOW CHART

Wysa is delivered as a standalone system that patients download directly onto their personal device. Wysa will be made available to patients as a self referral and clinical triage tool, and further along the care pathway will provide a range of therapist enabled computerised CBT programmes.

This study will conduct a quantitative feasibility review of Wysa as an AI therapeutic support tool across a typical care pathway in adult NHS talking therapies services. The study will take place in a collaborating NHS service utilising Wysa as an offer for all patients who have a suitable digital device.

Wysa's suite of products can be utilised at four key points in the care pathway:

1. Referral
2. Waitlist
3. NHS talking therapies step 2 intervention
4. Post discharge

The study will compare data from patients who use Wysa throughout their NHS talking therapies journey, or for at least a part of their journey, with those who do not.

Following self-referral (either using the Wysa electronic triage tool or another method such as self referral portal or email) or professional referral, the individual is provided access to the Wysa app via a download link. The patient can then use the app for support whilst waiting for their next contact with the service. Where the clinician has identified that a Wysa cCBT programme is an appropriate treatment intervention, this will be prescribed via an additional download link.

Wysa's Triage tool collects demographic and clinical patient related information via the AI chatbot. This tool will support patients to complete a referral to NHS talking therapies services, allowing the service to collect the data (via an API to their EPR system) required for a referral to be opened and a clinician to make a decision about the patient's care. Here we will review predetermined data points to understand how patients engage with the e-triage and the types of patients who utilise the tool. We will also compare the time taken for the clinician to reach a clinical outcome decision when the Wysa e-triage is completed with the time taken when a standard assessment is undertaken.

From here the patient will be offered the opportunity to download the Wysa app as a waitlist support tool until they are offered an intervention. The Wysa app includes over 150 self care tools, conversational AI and daily check-ins and reminders via push notifications. We will analyse data collected from within the app to understand app usage and any effect use of the app may have on mental wellbeing markers during the wait period.

Patients who are then offered Wysa's cCBT by their assessing clinician will have access to diagnosis specific weekly web or app based programmes including psychoeducational videos and CBT conversational techniques, as well as periodic reviews by an NHS talking therapies clinician through a communication dashboard called the Therapist Companion, which is also fully integrated into the service EPR system. We will report on changes in clinical outcome measures and engagement metrics to understand the efficacy of these cCBT programmes.

For all patients using Wysa within the service there is a built in SOS response. Wysa has three pathways to crisis alert and response:

- Patients are able to trigger crisis help by selecting the 'SOS' button on the app.

- Crisis response will be triggered by responses to PHQ9 question 9
- Crisis response will be triggered when risk language is used (and confirmed by the chatbot) within free text.

When Wysa or the user triggers the crisis response pathway, users will be offered to complete a safety plan, engage in grounding exercises, and be provided with local or national crisis helplines. We will collect data including the number of times that the Wysa SOS response is triggered, the number of false positives identified by the AI, and SOS tool usage.

After patients have been discharged, Wysa can also be used as a support/ relapse prevention tool. All participants will have access to the AI Chatbot and self tools for 12 months from onboarding.

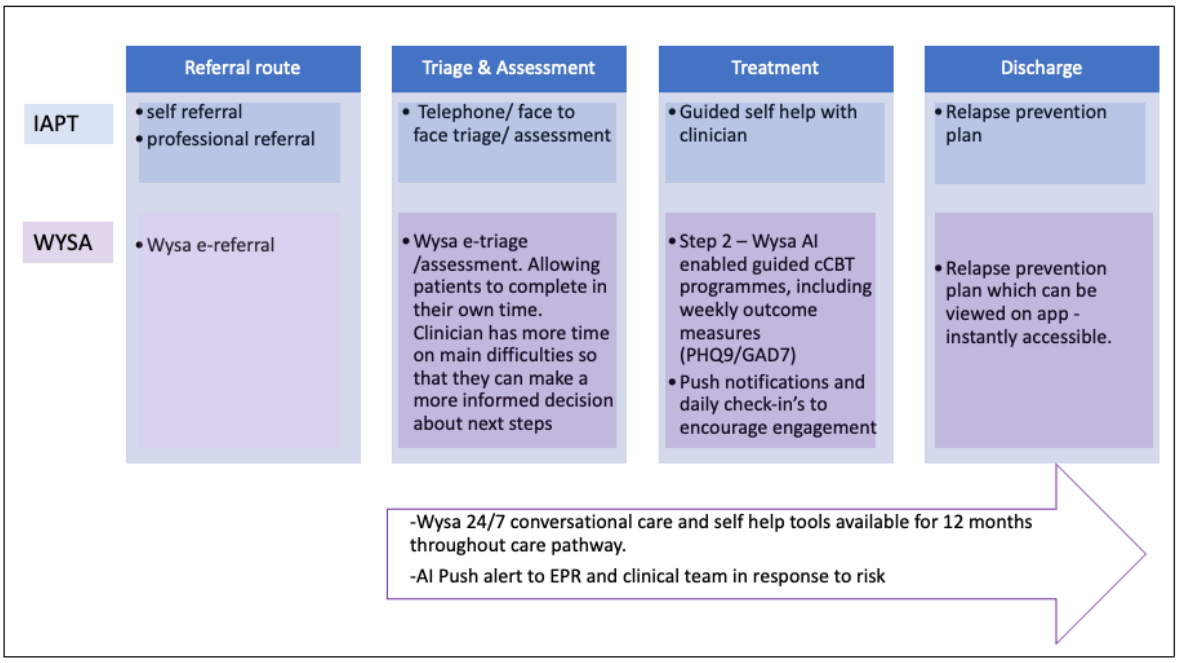

Figure 1. Current NHS talking therapies care pathway flows including Wysa therapeutics.

7 INTRODUCTION

7.1 Background

We know that 1 in 4 people will experience a diagnosable mental health problem in any given year, and also that mental health problems represent the largest single cause of disability in the UK [1]. We also know that nearly one in three people with a long-term physical health condition also has a mental health problem [2], and that poor mental health costs the UK economy at least £117.9 billion annually [3].

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 [4]. Of those people with recognised mental health conditions, negative experiences with mental health services are commonly reported [5]. Nearly half of survey respondents (44%) who had received NHS therapies in 2019 reported that they had to wait too long to access them [5]. 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 [6].

Demand for mental health services is currently outstripping capacity, and has increased significantly since the pandemic, with the Centre for Mental Health estimating that up to 10 million people, including 1.5 million children, are likely to need new or additional mental health support as a direct result of the crisis [7]

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 key performance indicators [8]. Wysa's solution is well-placed to support these goals by providing an engaging and easy to access digital intervention approach that can be implemented from the point of self-referral. This is also aligned with NHSx's mission, particularly its aim to use digital technology to improve health and care productivity and empower people to access information and services to manage their own health [9].

7.2 Rationale

A key issue with current mental health service provision is lack of timely access to therapy or professional support. NHS talking therapies services are overwhelmed with high volumes of referrals, many of which are often inappropriate due to patients living out of area, or having very complex needs which are out of the scope of NHS talking therapies interventions. We predict that automations in the referral process brought about by the use of the Wysa electronic triage will result in significant administrative and clinical time savings, by enabling a large part of these assessments to take place via the app, and may also reduce the number of inappropriate referrals, due to users with complex needs or who are ineligible or at high risk being signposted to alternative services at an earlier stage. Our solution also enables immediate, guided support at the point of referral, thus enabling patients to manage their symptoms independently whilst waiting for treatment to begin. We know from our preliminary work that using the Wysa app at the onboarding stage is likely to result in improved outcomes for those who engage highly [10]. This research will also add to the findings of an ongoing RCT looking at the effectiveness of the Wysa app as a mental health support tool for NHS talking therapies patients waiting for therapy. 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 chatbot.

Mental health services follow a stepped care model, with Step 1 being monitoring by the GP, and Steps 2-4 reflecting more intensive interventions as clinical need increases. Step 2 services typically support mild to moderate mental health conditions, while Steps 3 and 4 involve other specialised treatments for more severe or complex conditions. Whilst cCBT and guided self-help are recognised treatment options at step two, a lack of available trained therapists to assess and treat a growing demand means that there are often significant waits before these interventions are offered. Our therapist enabled cCBT solution aims to provide an alternative way of meeting some of this demand, allowing a significant proportion of the therapeutic intervention to take place via the app, at a time and a place that is convenient for the service user.

The Wysa AI and therapist assisted cCBT programmes are unique in that the programmes offer 24/7 continuous conversational care throughout the patient treatment journey, in addition to weekly psychoeducational videos, practice of specific CBT techniques through conversations with the Wysa chatbot, and daily engagement via push notifications. The programmes aim to keep the user engaged whilst learning to manage their symptoms. The treating therapist will review and guide the patient biweekly or monthly, thus allowing the patient to address any difficulties they have with any concepts/ tasks. We hope the findings from this research will add to the findings of a pilot study by Leo et al (2022), which found that users with pain related impairment who completed an 8 week Wysa digital mental health intervention as part of their orthopaedic care showed greater improvement in depression, pain interference, and physical function than patients who received usual orthopaedic care only [11].

This solution also has the potential to reduce inequalities in service provision, and is especially important for individuals from high risk groups (such as LGBTQ+ or Black and minority ethnic groups) who are least likely to seek or receive support for their symptoms [12,13]

Implementing automated support and treatment has the potential to reduce face-to-face appointments. If this is borne out, it would contribute to a reduction in the demand for travel whilst also reducing the demand of building spaces, contributing to the NHS's Net Zero Carbon goal [14]. Early interventions also have the potential to prevent further ill health, which would result in less demand, when symptoms are more chronic, often for more specialised services.

7.3 Research Question

The main research question of the study is: *What are the benefits of adopting Wysa therapeutics for patients, clinicians, services and the wider health care system?*

7.4 Aims and Objectives

The primary aim of this project is to understand the clinical benefits of Wysa AI therapeutics for patients.

The Primary objective of this study is as follows:

- Do Wysa therapeutics (e-triage, self-help tools & conversational care; guided cCBT), when deployed at referral, waitlist, and intervention, improve clinical outcomes?

The Secondary objectives of this study are to explore:

- Do Wysa therapeutics improve service referral rates and/or reduce drop outs or DNAs?

- Do Wysa therapeutics improve patients' quality of life?

- Do Wysa therapeutics have an impact on waitlist numbers or other service related resources?

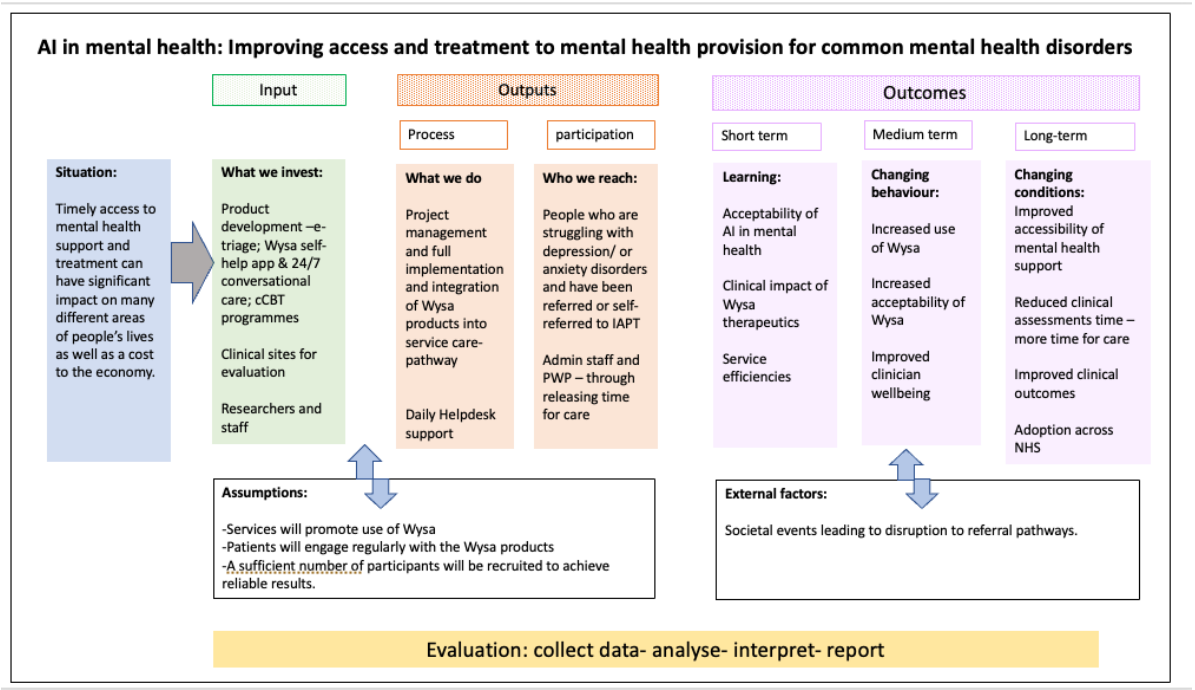

Figure 2: Wisconsin Logic Diagram

8 METHODS

8.1 Study Design

A quantitative evaluation will be used to understand the impact of Wysa's application at key points in the patients' care pathway:

- At referral
- Whilst waiting for treatment
- As an intervention

The evaluation will include an analysis of app usage data and clinical outcome data, in order to establish engagement levels with Wysa therapeutics, as well as Wysa's efficacy at improving mental health outcomes.

The study will be comprised of two parts:

Part One: Evaluation of Wysa e-triage

Part Two: Evaluation of Wysa self-help tools as waiting list support and Wysa cCBT programmes

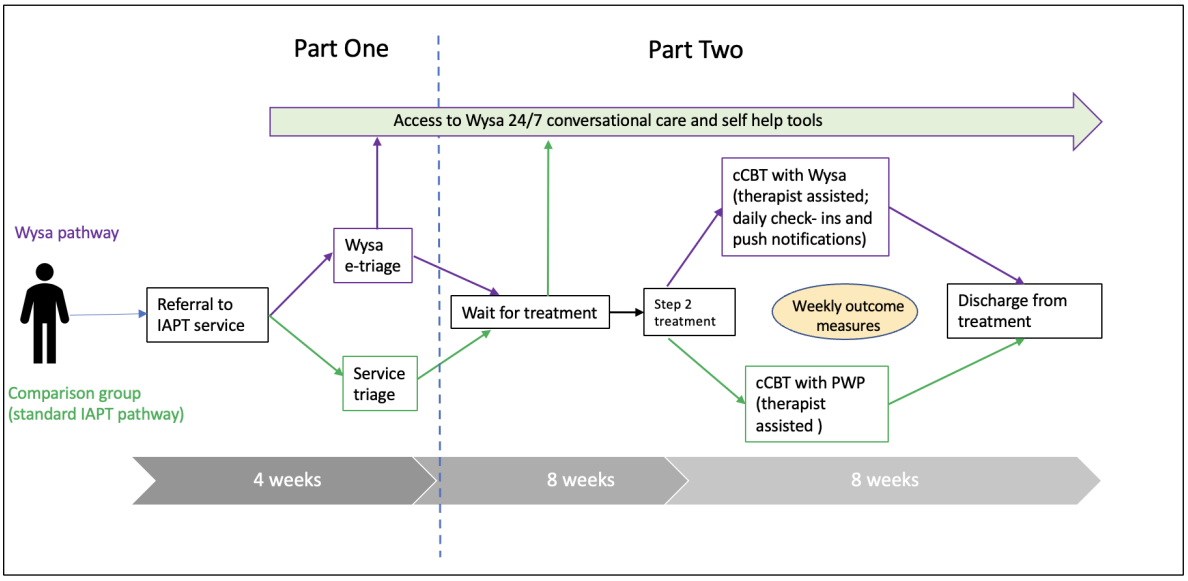

Figure 3: Participant flow Diagram

8.1.1 Timeline

The study will last for 10 months: 3 months of evaluation, refinement and technical integration, 6 months of data collection (the total time period for each participant journey will be approximately 20 weeks, thus allowing a 4 week onboarding window) , and 1 month of post-evaluation analysis and preparation for dissemination.

8.2 Study Context

8.2.1 Participants

The target population of the study will include patients who are 16+ who are referred, or self-refer to NHS talking therapies adult mental health services for support, and who at any stage of their NHS talking therapies journey, download and use any of the Wysa functionality.

The cCBT programmes will be accessed by a subset of the patients who are accepted for step 2 treatment. Step 2 treatment is usually offered to patients experiencing mild or moderate depression and/ or anxiety symptoms as recommended by NICE guidelines for stepped care in NHS talking therapies services.

8.2.2 Setting

Participants will be recruited by NHS talking therapies services where we have worked collaboratively to design and trial the use of Wysa therapeutics in the care pathway.
The Wysa interventions are accessible to users through either a web widget or a mobile phone app available on android and apple.

8.2.3 Interventions

Wysa therapeutics include;

- An electronic triage, comprising of two parts:
    - a referral triage, comprising demographic information and some limited questions around physical health and past contact with mental health services
    - a clinical assessment triage, comprising a wide range of clinical questions and standardised outcome measures.

- Waitlist support;
    - 24/7 conversational care,
    - Access to over 150 self care tools
    - Daily check-ins to increase engagement and promote behavioural change.

- A range of diagnosis specific, NICE compliant therapist enabled step 2 cCBT programmes, delivered to patients via an app or widget. Each programme consists of 6-8 weekly modules, with each module focussing on a specific CBT principle or intervention. Psychoeducation is provided through short videos, with CBT techniques introduced in each video practised through conversational AI and augmented with self care audios and editable worksheets. The programmes also include the collection of standardised NHS talking therapies clinical outcome measures.

Wysa is delivered as a standalone system which patients download directly onto their personal device. Upon e-triage self-referral or alternative route referral to NHS talking therapies services the individual is automatically sent a download link via sms, email or QR code. 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.

8.2.4 Outcomes

8.2.4.1 Primary Outcomes

In order to understand the impact of Wysa therapeutics across the care pathway we will be conducting two distinct analyses. In Part 1 we will be focusing on e-triage and in Part 2 we will be focussing on the waitlist support and cCBT programmes.

The primary analysis in Part 1 will be a comparison of the time spent by the clinician to make a decision on the treatment pathway for those who complete the Wysa e-triage, with that taken to make a decision for patients who do not. The primary outcome measure will be time taken for the clinician to make a decision, for each of these two assessment pathways.

The primary analysis in Part 2 will be a comparison of depression and anxiety scores before and after a Wysa intervention (waitlist self care or step 2 cCBT). The primary outcomes will be measured at onboarding, start of intervention and discharge from intervention. In line with the national recommendations laid out by the NHS talking therapies Manual, we will be using Wysa's AI automation to encourage users to complete the Patient Health Questionnaire (PHQ-9 [15]) and General Anxiety Disorder (GAD-7 [16]) routine outcome measures.

Table 5. Primary Outcome Measurement

	Primary Outcome	Outcome Measure
Part 1: E-triage	Clinical Time Savings	Hours/Minutes
Part 2: Waitlist and cCBT	Depression or Anxiety severity	Score on the PHQ9 and GAD7

8.2.4.2 Secondary Outcomes

There will be several secondary outcome measures (see Table 6). The secondary outcomes will also be measured at both part 1 and part 2: e-triage, whilst waiting for treatment, during treatment and at discharge from treatment.

Patient 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. Therefore, measures of app usage will also include uptake and dropout rates, and digital user feedback.

Patient experience

Wysa's acceptability will be examined through user score ratings (in app) out of a maximum of 5.

Health-related quality of life

Work and Social Adjustment Scale [17] will be used to assess quality of life. The WSAS is a reliable measure for impairment in functioning and one of the NHS talking therapies standardised questionnaires. It provides a descriptive self-assessment of the impact of mental health difficulties in 5 dimensions: work, home management, social leisure, private leisure and personal or family relationships .

Table 6. Secondary Outcome Measurements

Secondary Outcome	**Outcome Measure**
Health related Quality of life	WSAS[17]
Patient Engagement	Referral rates Dropout / discharge reason/ did not attend rates App usage data
Patient experience	Automated review questions periodically requested during general use of the tool

8.3 Sample and Recruitment

8.3.1 Eligibility Criteria

8.3.1.1 Inclusion Criteria

- Willing and able to provide informed consent;
- Aged 16 years or older;
- User is confident in their ability to speak and understand English at a proficient level;
- Own an electronic device capable of supporting Wysa;
- A valid email address, NHS number; phone number
- Referred or self-referred to proceed through the standard NHS talking therapies care pathway.

8.3.1.2 Exclusion Criteria

- Patients ineligible for the standard NHS talking therapies care pathway;
- Patients with previous and current known severe and enduring mental illnesses
- Patients with current psychosis or a history of psychotic symptoms in the last 6 months
- Patients with active suicidal ideation/ intent;
- Patients with significant cognitive disorders;
- Patients with a current diagnosis of a personality disorder;
- Patients with referrals for specialist presentations of pre-existing, diagnosed conditions requiring a specialised assessment beyond the standard clinical pathway;
- Not capable of providing self-consent;

8.3.2 Sampling

8.3.2.1 Sample Size

All patients accepted by the NHS talking therapies services and meeting the inclusion criteria will be eligible for the study. A minimum of 100 patients will be recruited in order for the study to be able to conclude statistical validity. This is primarily a quantitative feasibility review with no control arm.

8.3.2.2 Sampling Technique

Part 1: Participants will be all patients who self-refer or are referred to an NHS talking therapies service and accepted into the service.

Part 2: Participants will be patients who are accepted onto the Step 2 waiting list and consent to digital treatment.

8.3.3 Recruitment

8.3.3.1 Participant Identification

Part 1: All Participants who are referred, or refer themselves to NHS talking therapies for mental health support and are accepted for an NHS talking therapies intervention, and who meet the inclusion criteria, will be eligible to be a part of the study.

Part 2: All participants who are accepted onto the step 2 care pathway, who meet the inclusion criteria and agree to engage in a Wysa cCBT programme will be eligible to participate in the study.

8.3.3.2 Consent

To be accepted by the NHS talking therapies service participants need to consent to sharing of necessary data with their GP, as well as to data being stored safely and confidentially under GDPR regulations. Participants also need to consent to anonymised data being provided to NHSE, but can opt out of this if preferred.

Once the user downloads the app they are provided with information about how their data will be used together with an option to opt out. It will be made clear that patients have a right to withdraw from the study at any time and have their data removed. Declining consent will not affect patients' participation in the study or their clinical care.

8.3.4 Adherence

The study team will ensure that all Wysa cCBT programmes are used as intended, with the support of a qualified Psychological Wellbeing Practitioner.

8.4 Data Collection

8.4.1 Methods of Data Collection

The quantitative outcome measures will be taken during the e-triage (or for those who do not complete the Wysa electronic triage, when they onboard the App), and then every two weeks whilst engaged with the app. Participants who are in part 2 of the study will complete standard NHS

talking therapies measures on a weekly basis.

Outcome measures have been chosen that will not be a significant burden for participants to complete; none of the questionnaires are longer than 9 items or expected to take more than a few minutes each to complete. Patient responses during e-triage and cCBT treatment will be automatically transferred to the NHS talking therapiesUS electronic patient record system. App use analytics will be stored by Wysa as data controller.

8.5 Data Analysis

Descriptive and comparative statistics will be used to evaluate outcomes for those who use Wysa and those who do not, as well as clinical recovery, calculated by reduction in scores on the Standard NHS talking therapies measures as per NHS talking therapies guidelines [4]

8.6 Limitations

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 products 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.

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.

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 NHS talking therapies. Everyone who enters the NHS talking therapies pathway and meets eligibility criteria and consents will be eligible for the study.
- All participants will be included in the 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.
- 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).
- Study Governance: To maintain the integrity of the study and avoid any commercial influence, a research contract will be established between Wysa and the NHS talking therapies service that will ensure the independence of study design and execution and the unrestricted right to publish all results.
- 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. We have mitigated the risk to patients by building a clinically underpinned crisis response pathway, with handover capabilities to the clinical team for the intervention (cCBT) element of the study.
    - 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.
    - 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 [19]. As per the guidelines, we will be applying the Caldicott Principles for the collection and evaluation of patient data

Ethical approval is being sought from the Health Research Authority and the relevant Research Ethics Committee with this submission [20.

Wysa, 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 NHS Trusts involved.

9.4 Patient and Public Involvement

PPI representatives played an important part in our testing process prior to release of the electronic triage and the Wysa cCBT programmes. 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.

Payments are made in recognition of members' time based on NIHR Involve guidance on payment of fees and expenses [21]. Travel expenses are reimbursed in accordance with this policy together with other expenses and travel costs.

9.5 Protocol Compliance

Regular meetings will be held between the sponsor (Wysa) and the clinical services to ensure that the protocol is being followed. Should there be a serious breach of the safety or physical or mental integrity of the participants the Sponsor will notify the licensing authority in writing.

9.6 Consent

Service consent mechanisms will be adopted as well as consent via the Wysa App. As many patients are understandably concerned about how their data will be used, participants are able to ask Wysa for further details about their data and can speak with the Wysa team for further information. It will be made clear that patients have a right to withdraw from the study at any time and have their data destroyed. Declining consent 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 NHS talking therapiesus 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 [22].

The team has specific expertise in this area as Wysa employs a qualified Clinical Safety Officer who 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.

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 Data Protection Officers from Dorset University NHS Foundation Trust and Lancashire and South Cumbria NHS Foundation Trust. To mitigate patient concerns about data use, privacy, and security, these are clearly explained in the FAQ section on the App. 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 of the app 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. 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.

9.8 Stopping Guidelines

If the chief investigator identifies any risks that have not been foreseen and mitigated against, the study will be paused while those risks are assessed. There is no maximum recruitment threshold.

9.9 Indemnity

The NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study.

9.11 Access to data

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.

The national framework for NHS talking therapies services outlines the referral and assessment pathway. WYSA has been designed to align with NHS talking therapies guidelines including minimum dataset requirements. Strong relationships across the AHSN network and central NHSX 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. 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. NHS talking therapiesus is currently one of two leading patient management systems for UK NHS talking therapies 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 [23]. 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 Protocol Registration

The protocol will be registered through this IRAS submission 320441

11.2 Competing Interests

NM/LV/ET is an employee of Wysa; although they were involved in the drafting and revision of the protocol, the final decision on the evaluation design lies with the NHS talking therapies service/ NHS trust.

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