Southern Health NHS
NHS Foundation Trust

See Yourself Differently (SYD) for NHS

Pilot evaluation of a personalised, prevention mHealth partner, SYD, and its impact on Quality of Life of NHS staff

PROTOCOL Version 2.0, 13/04/2022

Chief Investigator:	Prof Shanaya Rathod: Southern Health NHS Foundation Trust
Co-Investigators:	Dr Ameet Bakhai: Amore Health Ltd; Royal Free London NHS Foundation Trust Dr Pedro M. D. Henriques: iamYiam Dr Peter Phiri: Southern Health NHS Foundation Trust Liba Stones: iamYiam
Sponsor:	Southern Health NHS Foundation Trust

Chief Investigator	
Prof Shanaya Rathod Consultant Psychiatrist & Director of Research Southern Health NHS Foundation Trust Research and Development Clinical Trials Facility Tom Rudd Unit Moorgreen Hospital Southampton SO30 3JB shanayarathod@nhs.net	
Co-Investigators	
Dr Pedro M. D. Henriques Head of Bioinformatics iamYiam Floor 3 207 Regent Street London W1B 3HH pedro.henriques@iamyiam.com	Liba Stones Research Consultant IamYiam Floor 3 207 Regent Street London W1B 3HH
Dr Ameet Bakhai Amore Health Ltd, Pinewood Avenue, London HA5 4BN Royal Free London NHS Foundation Trust Pond Street, London NW3 2QG. abakhai@googlemail.com	Dr Peter Phiri Southern Health NHS Foundation Trust Research and Development Clinical Trials Facility Tom Rudd Unit Moorgreen Hospital Southampton, SO30 3JB peter.phiri@southernhealth.nhs.uk
Data Protection Officer for iamYiam	
Constantin-Lucian Galea Head of Tech and Infrastructure iamYiam Floor 3 207 Regent Street London W1B 3HH lucian.galea@iamyiam.com	

Table of Contents

1 Summary of Trial Design

Title	Pilot evaluation of a personalised, prevention mHealth partner, SYD, and its impact on Quality of Life of NHS staff
Short Title/acronym	SYD (See Yourself Differently) for NHS
IRAS number	294071
Sponsor name & reference	Southern Health NHS Foundation Trust
Funder name & reference	iamYiam
Design	Randomised Controlled Trial and Controlled Before and After Study
Overall aim	To quantify the change in Quality of Life (QOL) following an intervention with SYD, a personalised preventive mHealth partner. Measures of mental health (stress, anxiety and depression) will also be tracked as a way to assess the wellbeing potential of this non-clinical intervention.
Primary endpoint	Determine the impact of SYD on Quality of Life of NHS Staff over 3 months, as measured through Generic and Anxiety Specific Quality of Life instruments: 1. EuroQoL EQ-5D-5L (Health-related QOL) 2. WHO Quality of Life-BREF (WHOQOL-BREF) survey (Global QOL)
Secondary endpoints	1. Determine the efficacy of SYD in reducing levels of stress, anxiety and depression, as measured through the Perceived Stress Scale (PSS-4) and Hospital Anxiety and Depression Scale (HADS). 2. Determine user satisfaction and engagement with SYD 3. Determine the persistence of primary endpoint changes over 6-month time frame
Target accrual	500 participants randomised 1:1 to Control Group (=250) and Intervention Group (=250).
Inclusion criteria	1. Active NHS staff with an NHS email address which can be used for this study 2. Age ≥ 18 years 3. Own a personal smartphone device (iOS or Android-based) which can be used for this study 4. Sufficient English language ability to familiarise themselves with and engage with SYD and study assessments 5. Hospital Anxiety and Depression Scale (HADS) test score between 8 and 14 inclusive, indicating mild to moderate anxiety or depressive symptoms 6. Provision of informed consent
Exclusion criteria	1. Unwilling or unable to participate 2. Any other concurrent psychological interventions 3. Concurrent participation in an interventional clinical trial 4. Considered clinically extremely vulnerable from COVID-19 https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19)

Anticipated duration of recruitment	Approximately 12 months
Duration of trial	Approximately 22 months. The start of the trial is expected to be 1st June 2021 and the end of trial by 31st March 2022.
Definition of end of trial	The study end date is deemed to be the date which Health Research Authority is notified of the end of study.

2 Background

2.1 The global burden of preventable diseases

Preventable diseases are a leading cause of ill health, contributing to a decrease in quality of life for individuals suffering from these conditions. Cardiovascular disease, type 2 diabetes and musculoskeletal disorders alone contribute to an estimated 5.5 Million years lost to these conditions (Disability Adjusted Life Years, DALYs) in the UK alone (James et al., 2008), and mental health conditions such as stress, anxiety and depression are estimated to affect 1 in 4 people at some point in their lives. The chronic disease burden affects individuals from all ages, socio-economic conditions and professions.

In addition to these chronic diseases, the COVID-19 pandemic has had a significant impact in the wellbeing and mental health of Britons (Fancourt et al., 2020, Office for National Statistics, 2020). A recent survey shows that 79% of responders report lower levels of quality of life and increased levels of anxiety and psychological distress compared to a similar period in 2019 (Fujiwara et al., 2020).

It is widely acknowledged that health and wellbeing of NHS staff is adversely affected by the high-risk workplace environment, with high prevalence of mental health (anxiety and depression) conditions (NHS staff survey, 2019). 58% of frontline and social care workers meet the criteria for having significant anxiety, depression and PTSD. NHS staff have reported SAD to be the primary reason for absenteeism (~21%), totalling 472,426 days lost in that month alone.

Levels of psychological distress have further increased during COVID-19 with the added pressure on the healthcare system in dealing with increased hospitalization rates, increased hospital mortality rates and fears of infection from working in locations with high risk of exposure to the virus and concerns regarding the provision of personalised protective equipment (Kisely et al., 2020; Holmes et al., 2020).

2.2 Lifestyle changes and their impact on Quality of Life

The observed continuous increase of the burden of preventable chronic diseases across the globe indicates that current strategies, which have mainly focused on treatment after the fact, have not been effective in tackling the prevention component of this issue adequately. Healthcare treatment is estimated to contribute to only 10% of premature deaths in the United States, while behavioural patterns such as tobacco smoking and dietary habits contributing to around 40% (Schroeder, 2007). Thus, while improving health care systems is important, switching the paradigm with a focus on prevention by improving behavioural choices, rather than treatments, is of crucial importance.

The burden of preventable chronic diseases can be reduced, by adherence to lifestyles that reduce the known risk factors. To the individual, lifestyle changes have the potential to increase their quality of life with the downstream potential of delaying or averting preventable diseases (Eriksson et al., 2006, 2010, Toobert et al., 2003).

Likewise, a focus on health as multidimensional construct that joins objective measures of health such as causes of death and life expectancy with more subjective measures of wellbeing (emotional, social, environmental, etc.), commonly referred to as Quality of Life (QOL), is essential to tackle the health burden across the world (Audureau et al., 2013, Kyu et al., 2018).

Quality of life (QoL) is a measure of perceived quality of an individual's daily life, incorporating their perspective of physical, mental, and social well-being in the context of the culture and value systems in which the individual lives and in relation to their goals, expectations, standards and concerns (World Health Organization, 1995).

QoL is closely related to physical and mental health, as individuals living with conditions such as obesity (Sach et al., 2007), diabetes, cardiovascular risk factors (Sullivan et al., 2007), anxiety (Olatunji et al., 2007), stress (de Frias et al., 2015) and depression (Ruo et al., 2003), consistently report lower levels of QOL. Lifestyle interventions such as supervised exercise training (Eriksson et al., 2010) or personalised counselling (Lindström et al., 2006), have shown success in increasing and sustaining individual's QOL in the long run, however, these interventions frequently report reduced effectiveness due to poor attendance and adherence rates.

Several factors have been identified to predict lower adherence to lifestyle interventions, including unrealistic expectations, lower baseline mood or gaps in knowledge (Burgess et al., 2017). Indeed, behavioural treatment strategies such as self-monitoring (Mahoney et al., 1973), self-reinforcement and goal-setting with specific, measurable, attainable, realistic and time-framed goals (Bovend'Eerdt et al., 2009), have been shown to be some of the most important drivers in improving adherence to lifestyle modifications with behavioural change most likely to be achieved when it is self-motivated, personalised to each individual and rooted in positive thinking (World Health Organization, 2003).

To tackle these issues, mobile health (mHealth) interventions can provide a solution to increase individual's adherence to health and wellbeing recommendations (Vlahu-Gjorgievska et al., 2018). The widespread use of smartphones, as well as integration with other health-oriented devices, such as fitness trackers, allows for recommendations to be personalised based on each individual's lifestyle patterns, personality, environment, personal choices and goals. In turn, individuals are more likely to be engaged with their own progression towards significant behavioural changes, with the ultimate goal to increase their quality of life over the long term.

2.3 SYD – a personalised preventative mHealth partner for everyone

iamYiam has developed a platform and a mobile app named SYD, that use an AI-powered predictive engine to give recommendations for personalised preventative actions to users, with the goal to improve the quality of life. Its main focus is to support the prevention of lifestyle-related conditions in a non-invasive and non-clinical intervention that empowers individuals to take control of their own wellbeing through small meaningful and personalised steps.

SYD tracks each individual's health and wellbeing through 300+ variables mapped to 9 high-order dimensions (hereby referred to as Life Quality Indices, LQIs) based on Stanford's Well for Life dimensions of well-being (Heaney et al., 2017): physical health, emotional health, financial health, purpose, social life, brain power, self-esteem, environment, and career.

SYD incorporates published models and validated scales to quantify each individual's risk of cardiovascular disease (CVD), risk of developing type 2 diabetes, level of musculoskeletal disorders (MSK) such as back and neck pain, as well as levels of stress, anxiety and depression, providing each individual with a detailed assessment of their physical and mental health risks.

An internal (unpublished) assessment of iamYiam's active users of SYD over a period of 19 months amongst 350 users, has shown an increase on all LQIs, averaging at 30% across all dimensions and reaching as high as +61% (self-esteem).

These 300+ variables are generally presented to the individual in the form of questions, many of which are extracted from validated questionnaires/surveys or indices, such as the National Health Interview Survey (NHIS), the Pittsburgh Sleep Quality Index (PSQI), the Patient Health Questionnaire (PHQ-9) or the UK Biobank.

The user can answer these questions throughout their journey and interaction with SYD, which is mediated through a conversational agent that creates a bridge between the user and the content on the iamYiam platform, while keeping the interaction fun and engaging. SYD uses natural language understanding and generation to predict the context of

the conversation and user intents, providing relevant and useful information in an intuitive way. It also appreciates context – as an example, vegetarians are not presented options for supplements derived from fish or meat.

2.4 SYD's evidence-based personalised lifestyle recommendation model

Our research evidence framework employs a strict assessment of the scientific evidence for each actionable recommendation within SYD, accounting to an evidence base of >2,500 meta-analyses and systematic reviews evaluating results of >10,000 research papers. Peer-reviewed articles are automatically fetched, scored and prioritised based on article-level metrics (normalised citation-based and altmetrics). These are analysed and curated by a team of expert scientists to validate and extract relevant features such as effect and population sizes, inclusion/exclusion criteria and demographics of the groups. Evidence for effect of lifestyle interventions on a given health dimension are then aggregated and normalised effect sizes are used to estimate the change attributed to an individual performing a recommended action. These are normalised to account for the frequency and amount that individuals perform the recommended action, which is estimated by feedback and scheduling through the SYD app. To estimate the current health states of the individual, SYD uses AI state estimation models (multidimensional Kalman filters) accounting previous state estimations, covariance between states and uncertainty through time.

By analysing each individual's past behaviour and preferences, and using aggregated data from similar users, SYD's recommender system predicts and presents lifestyle recommendations for which the individual is more likely to be interested and act on, and which are expected to have the most significant impact on their wellbeing. Each recommendation is presented in a succinct manner while providing information of the scientific evidence (references and abstract links and a simplified summary of that evidence), driving those recommendations. Information on which LQIs are expected to be affected and the estimated mean effect and timeframe of those changes are also shown. By interacting with SYD and performing recommendations, the user can track their progress through each LQI in an intuitive way (with training to enable this), allowing them to observe the effect of behavioural changes through time.

To ensure that SYD adapts to each individual as they journey life, it provides the user with the ability to give feedback on any aspects of the platform including recommendations, goals, and conversations with SYD and on the app design itself. This allows SYD to evolve locally in line with user feedback, as well as more widely by prompting iamYiam to adapt to insights on what needs to change for its users to increase and/or maintain their engagement to enabling healthier lifestyle choices in the long run.

With this study, we aim to provide NHS healthcare staff with SYD, a research based, conversational wellbeing companion, to see if this will positively impact their quality of life, given that they are amongst those most likely to require support, particularly during COVID-19 pandemic and aftermath.

3 Aim and Objectives

3.1 Aim

This study aims to measure the change in Quality of Life (QOL) following an interaction with SYD, a personalised preventative mHealth partner. Measures of mental health (stress, anxiety and depression) will also be tracked as a way to assess the wellbeing potential of this non-clinical intervention. At this point, physical parameters are not formally the focus of any change such as blood pressure or weight, but these data points are already on the platform to receive data in the future.

3.2 Primary objectives

Determine the impact of SYD on Quality of Life of NHS Staff over 3 months, as measured through:

1. WHO Quality of Life-BREF (WHOQOL-BREF) survey (Global QOL)
2. EuroQoL EQ-5D-5L (Health-related QOL)

3.3 Secondary objectives

1. Determine the efficacy of SYD in reducing levels of stress, anxiety and depression, as measured through the Perceived Stress Scale (PSS-4) and Hospital Anxiety and Depression Scale (HADS).
2. Determine user satisfaction and engagement with SYD
3. Determine the persistence of primary endpoint changes over 6-month time frame

3.4 Compliance with regulations and Guidance

As defined in the European Commission Green Paper (EC, 2014), as an app providing lifestyle guidance and prevention information only, SYD is considered a mobile Health (mHealth) product. SYD is compliant with the legislative requirements applicable to all mHealth products outlined in the Green Paper framework, including relevant data protection and data security regulations.

As a software intended for lifestyle and wellbeing purposes SYD is not classed as a medical device under EU Medical Device Regulation 2017/45 and as defined by the Medicines and Healthcare Products Regulatory Agency (MHRA) guidance on the classification of stand-alone software including apps (MHRA, 2018); therefore it does not require CE marking.

The design of this trial follows the principles of best practice standards for evaluating effectiveness of Digital Health Technologies (DHTs) as outlined in National Institute of Health and Clinical Excellence (NICE)'s Evidence Standards Framework for Digital Health Technologies (2019) developed in collaboration with NHS England, NHS Digital and other stakeholders. The framework provides a functional categorisation of DHTs based on their clinical impact and potential risk. Using this framework, SYD is classified as 'Tier 3a: DHTs for preventing and managing diseases' for which interventional trial designs incorporating a comparison group are recommended as best practice method of evaluating effectiveness.

This protocol was developed with a multidisciplinary team (MDT) approach of consultants, nurses, physician associates and researchers in order to ensure the best possible outcome for the study participants.

3.5 Trial Design

Design considerations:

The trial is designed carefully and deliberately to fully and prospectively elucidate all elements of comparison of the impact of SYD. Participants would be randomly assigned to one of the two trials cohorts (PHE, 2020).

For cohort one, the study allows data collection as part of a 'Before and After Study', with SYD as the intervention provided to participants, to engage with, for 3 months as a minimum.

Additionally, by having a further cohort (cohort two) without SYD being engaged for the first 3 months, the study allows 'Case Controlled' cross comparisons between the two cohorts.

Additionally, by collecting data on the first cohort further to 6 months, we can review persistence of effects from 3 to 6 months of SYD and whether participants voluntarily continue using SYD or not beyond the primary endpoint.

Bringing on board the second cohort to have SYD switched on after 3 months, allows a comparison within this cohort 'Before and After' at a different time-point to the switch on for cohort one. This allows for any effects of SYD to be evaluated as COVID-19 levels themselves change over time.

Meanwhile comparing the two cohorts after the second cohort is exposed to SYD will allow comparisons of an early (in second cohort) versus a more experienced group (first cohort) using SYD contemporaneously.

We feel these design elements have not been considered for previous mHealth interventions and given the non-blinded nature of this trial design, it is imperative to establish the exact value of SYD itself to remove temporal, experiential or environmental comparisons.

Participants:

NHS staff, 18 years and over, who took part in the 'Psychological impact of the Coronavirus (COVID-19) pandemic and experience: An international survey' study (PIoC19 study; IRAS Project ID 282858; REC reference 20/HRA/1934), and provided informed consent to be contacted for future versions of the study ($n \approx 3500$), will be invited to participate in the 'SYD for NHS' trial via email. Once this pool of potential participants is given the opportunity to participate, then the study will be offered to all NHS organisations who may wish to participate in the trial as Participant Identification Centres (PIC). PIC sites will be provided with an open link of the study website to share with their current staff.

Any interested potential participants will be directed to the study website and asked to familiarise themselves with the information provided in the Patient Information Sheet. Those participants who are interested to take part in the study will be asked to complete questions to confirm eligibility, following which they will be asked to consent to undertake a Hospital Anxiety and Depression Scale (HADS) test. Optional consent to be contacted for future ethically approved research in the field of mental health and digital health technologies will be sought. Potential participants who score between 8-14 inclusive will be eligible, as these scores indicate individuals most likely to benefit from interventions of wellbeing like SYD and to be considered safe as higher scores may indicate depression/anxiety levels needing formal psychological evaluation. Participants with HADS scores 15 and over will be advised that they might need to contact their GP for further support. Individuals with low levels of anxiety often do not engage well with wellbeing measures (Singer et al. 2009).

Following confirmation of informed consent, and confirmed eligibility from the screening questionnaire, participants will be randomised 1:1 to one of two groups: Control Group and Intervention Group. People considered clinically extremely vulnerable for COVID-19, are excluded to avoid conflict with government advice. (https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19)

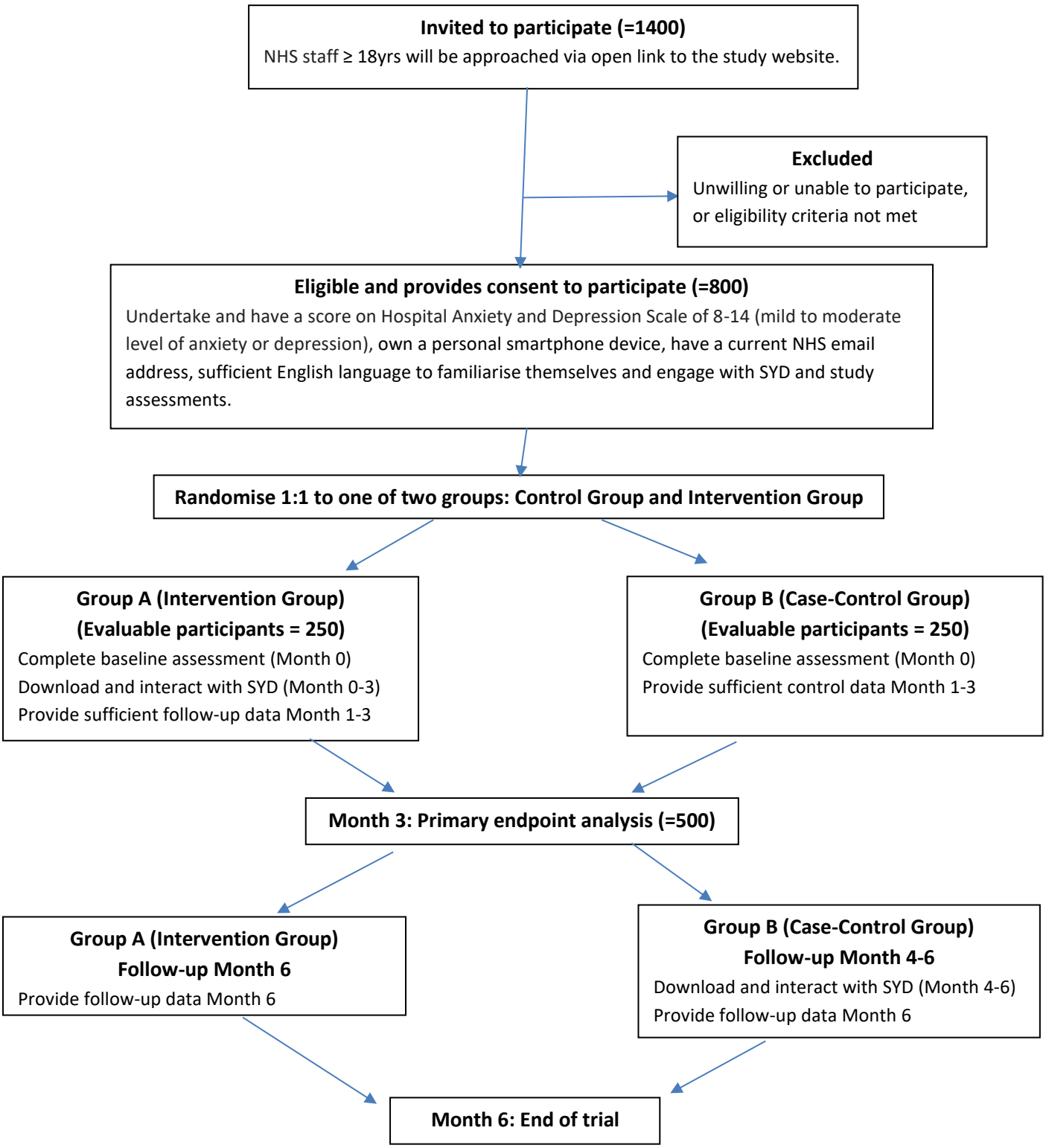
Intervention Group: Participants in the Intervention Group will be asked to complete baseline assessments (Month 0) and download / interact with the SYD app (Months 0-3). Participants will complete monthly assessments for a period of 3 months (Months 1-3) to analyse the primary endpoint. A final assessment will be performed at Month 6, to monitor longer term effects of the intervention.

Control Group: Participants in the Control Group will be asked to complete baseline assessments (Month 0) and monthly assessments (Months 1-3) to provide control data in a comparable population. Participants will be advised that they will be invited to download / interact with the SYD app at Month 4 and that study data collection will continue for further 3 months thereafter (Months 4-6).

SYD (See Yourself Differently) for NHS
Use beyond the Trial:

Participants in both groups will continue to have access to SYD after the end of the trial for their personal use. The last data capture point will be 6 months after the last participant has entered the trial and completed data entry. Data for the purpose of the study will not be collected beyond the 6-month time point unless otherwise mandated by the data and safety monitoring committee for valid reasons.

3.6 Trial Schema



3.7 Primary Endpoints

Determine the impact of SYD on Quality of Life of NHS Staff over 3 months, as measured through:

1. WHO Quality of Life-BREF (WHOQOL-BREF) survey (Global QOL)
2. EuroQoL EQ-5D-5L (Health-related QOL)

3.8 Secondary endpoints

1. Determine the efficacy of SYD in reducing levels of stress, anxiety and depression, as measured through the Perceived Stress Scale (PSS-4) and Hospital Anxiety and Depression Scale (HADS).
2. Determine user satisfaction and engagement with SYD
3. Persistence of Primary endpoint changes over 6-month time frame

3.9 Statistical analysis and sample size calculation

Approximately 3,500 NHS staff, 18 years and over, who took part in the PIoC19 study, and provided consent to be contacted will be invited to join the SYD for NHS trial.

We estimate that ~800 NHS staff will be interested and eligible to participate. As it is currently not known how many participants are likely to interact sufficiently with SYD and provide sufficient trial data, we have assumed that up to 800 participants will have to be randomised to achieve a target of 500 evaluable participants, 250 in each group. Data on all randomised participants will be evaluated and the drop-out rate in the intervention group will be determined.

As this is a pilot study to evaluate the impact of SYD, and not a superiority trial, we have estimated 500 patients being available to have reasonable confidence intervals of any changes in quality of life scales, if available. A previous study of the eBalance app showed significant lifestyle changes within 14 weeks in 85 participants with only 56 participants using the app (Safran Naimark, 2015).

4 Study group

The study participation will be offered initially to healthcare professionals who participated in PIoC19 study. NHS staff, 18 years and over, who took part in the PIoC19 study and provided informed consent to be contacted for future versions of the study will be invited to participate in the SYD for NHS trial. Participants will be asked to undertake the Hospital Anxiety and Depression Scale test and score between 8-14 inclusive to confirm that they remain eligible. It is not expected that sites will be required to confirm ongoing capacity and capability.

Once this pool of potential participant is given the opportunity to participate, the study will then be offered to all NHS organisations who may wish to participate as PIC and offer to their staff aged 18 years and above. Participants will be approached via social media and local Trusts' staff communication which will include an open link to the study website.

4.1 Inclusion criteria

1. NHS staff with an NHS email address which can be used for this study
2. Age ≥ 18 years

SYD (See Yourself Differently) for NHS

3. Own a personal smartphone device (iOS or Android-based) which can be used for this study
4. Sufficient English language ability to familiarise themselves with and engage with SYD and study assessments
5. Hospital Anxiety and Depression Scale (HADS) test score between 8 and 14 inclusive, indicating mild to moderate anxiety or depressive symptoms
6. Provision of informed consent

4.2 Exclusion criteria

1. Unwilling or unable to participate
2. Any other concurrent psychological interventions
3. Concurrent participation in an interventional clinical trial
4. People considered clinically extremely vulnerable from COVID-19: https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19)

5 Approaching participants to join the study

The study group will be invited to take part in the SYD for NHS study via email sent by the research team at Southern Health NHS Foundation Trust. Where the prior collected data allows, we will invite staff with NHS email addresses. The invitation will include an outline of the proposed trial and the SYD intervention. Potential participants will be directed to a dedicated study website developed on the Qualtrics online website survey platform. The study website will contain a Participant Information Sheet providing a detailed description of the study, including the SYD intervention, study assessments and risks/benefits of taking part. Potential participants will be encouraged to read the Patient Information Sheet carefully before providing informed consent to undertake the screening assessment and joining the study. Contact for the study team will be provided to answer any questions regarding participation. A SYD familiarisation session may also be provided. Any individual who is currently an NHS staff and aged 18 years, whose organisation has agreed to participate will be approached via social media and local Trusts' staff communication which will include an open link to the study website.

5.1 Screening and Eligibility Assessment

Participants who decide to take part in the study will be asked to provide informed consent to complete a brief screening and eligibility assessment on the study website to indicate if they meet the eligibility criteria. This will include completion of a Hospital Anxiety and Depression Scale and a score between 8 and 14. This group is deemed to be a group which will most likely engage with and has a potential to benefit from the SYD intervention.

5.2 Informed Consent

Eligible participants will be invited to complete the main study informed consent prior to joining the study. The informed consent procedure will take place online in the form of ticking a tick box. Online versions of the Participant Information Sheet and Informed Consent will be presented to the participants detailing the exact nature of the study, what it will involve for the participant, the implications, benefits and or risks associated with participation in this study. It will be clearly stated that participation is voluntary; participants will be free to withdraw from the study at any time for any reason without prejudice to future care and with no obligation to give the reason for withdrawal.

6 Study interventions

Baseline and follow-up assessments

Participants who have provided informed consent will be asked to complete the following baseline self-assessments on the study website at the time of joining the study, monthly for the period of 3 months (month 1 – 3) and at month 6 after joining the study:

1. WHO Quality of Life-BREF (WHOQOL-BREF) survey, which consists of 26 items related to the individual's quality of life, mostly referring to the preceding 2 weeks (World Health Organization, 1996).
2. EQ-5D-5L survey, which consists of 5 items related to the individual's health-related quality of life and VAS scale (Herdman et al., 2011)
3. Perceived Stress Scale (PSS-4) questionnaire, which consists 4 items related to the individual's perceived stress in the preceding month (Cohen, 1988).
4. Hospital Anxiety and Depression Scale (HADS) questionnaire, which consists of 14 items related to the individual's perception of anxiety and depression in the preceding week (Zigmond et al., 1983).

Interaction with the SYD application

Participants in the Control Group (Group B) will be invited to install and interact with the SYD smartphone mHealth app at Month 4. Participants in the Intervention Group (Group A) will be invited to install and interact with the SYD smartphone mHealth app at Baseline.

The following information will be collected from within the SYD app:

1. Participant characteristics including age, sex, demographics, self-assigned ethnicity and relevant medical conditions (e.g. Cardiovascular disease, Type 2 Diabetes, hypertension, etc.): will be collected when the participant first interacts with the SYD app
2. Self-rated measures related to 9 key dimensions of wellbeing (physical health, emotional health, financial health, purpose, social life, brain power, self-esteem, environment, and career)

7 Study schedule of assessments

Study Intervention	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Informed consent	X						
SYD intervention – Control Group					X	X	X
SYD intervention – Intervention Group		X	X	X	X	X	X
WHOQOL-BREF - Control Group	X	X	X	X			X
WHOQOL-BREF - Intervention Group	X	X	X	X			X
EQ-5D-5L - Control Group	X	X	X	X			X
EQ-5D-5L - Intervention Group	X	X	X	X			X
HADS - Control Group	X	X	X	X			X
HADS - Intervention Group	X	X	X	X			X
PSS-4 - Control Group	X	X	X	X			X
PSS-4 - Intervention Group	X	X	X	X			X

8 Study duration

The recruitment phase of the study is expected to last for up to 12 months.

The total duration of the trial data collection will be from the date of randomisation of the 1st participant to the date on which the last randomised participant reaches 6 months follow-up time point (including two weeks grace to allow timely response).

Therefore, the key dates of the study are:

- Recruitment start date: 1st June 2021
- Recruitment end date: 15th April 2022
- Study data collection end date: 29th October 2022

Participants in the Control Group (Group B) will complete baseline assessments (Month 0), monthly assessments - control data (Months 1-3) and receive intervention (Months 4-6) / complete follow up assessment (Month 6).

Participants in the Intervention Group (Group A) will complete baseline assessments (Month 0), receive intervention / complete monthly assessments in (Months 1-3). A final assessment will be performed after 3 months (Month 6) to assess longer term effects of the intervention.

We aim to undertake the primary analysis after the last participant in the Intervention Group has reached Month 3 data capture point and completed final data entry. Further analysis to assess longer term effects of the intervention will be undertaken after the final study completion.

9 Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early at any time and without giving a reason. Participants can withdraw from the study but data obtained up until the point of withdrawal will be retained for use in the study analysis. No further data would be collected after withdrawal.

10 Statistics and data analysis

10.1 Data handling and analysis

Study data will be collected via the Qualtrics online website built for this study. The Qualtrics survey software has advanced analytics tools built online and analyses will only be descriptive. Data will be analysed by Investigators at the Sponsor organisation (Southern Health NHS Foundation Trust). No data queries will be raised for participants.

Primary endpoint analysis will be undertaken using data collected throughout a period of 3 months of SYD application usage by the study participants. Further analysis of longer-term effects will be undertaken at 6 months after the participant first interacted with the SYD application.

WHOQOL-BREF surveys will be scored according to the general guidelines (World Health Organization, 1996), deriving scores for the 4 main domains (Physical health, Psychological, Social relationships and Environment).

EQ-5D-5L surveys will be scored according to the general guidelines (Herdman et al., 2011), deriving scores for the 5 main domains of the instrument (Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression), and

the 1-dimensional EQ VAS. An EQ-5D index value will be derived from EQ-5D-5L scores using the latest value set for England (Devlin et al., 2018).

PSS-4 scores will be derived according to the general guidelines (Cohen, 1988).

HADS scores will be subdivided into anxiety (HADS-A) and depression (HADS-D) subdomains and scored according to general guidelines (Zigmond et al., 1983).

WHOQOL-BREF, 5Q-5D-5L, EQ-5D index, HADS-A, HADS-D and PSS-4 scores will be modelled using linear mixed effects models. These models will be used to test the effect of group, time of measure and app-related metrics such as type of recommendations done by participants and level of interaction with the SYD app. Baseline characteristics of participants will be used to adjust the models. Imputation procedures will be used to impute missing values where deemed plausible. Effect size measures and p-values will be reported for all group comparisons. The Null hypothesis is of no significant change in Quality of Life.

11 Ethical and regulatory compliance

The study will only commence once evidence of Health Research Authority (HRA) approval is in place. This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate. In conducting the trial, the Sponsor, Southern Health NHS Foundation Trust, shall comply with all laws and statutes as amended from time to time, applicable to the performance of clinical trial.

12 Data Management

12.1 Data security

Data submitted via the study website

Data submitted as part of the study will be held on a secure online cloud-based survey platform called Qualtrics Core XM. Qualtrics Core XM has an array of features dedicated to and confirming its cyber security, GDPR compliance and online analytics tools that allows researchers to retain data within the site. A unique study identifier for each new participant visit to the site will be created.

Data exported from the survey platform will be stored and managed in password protected files in a password protected computer at the sponsor organisation. Only members of the sponsor research team will know the passwords and will therefore be able to access the electronic data.

Study documentation will be archived in accordance with guidelines for Good Clinical Practice and in an NHS approved, secure and adequate archiving facility. The results of this study will be presented in aggregate form with no individuals being identified.

Data submitted via the SYD application

iamYiam will act as the Data Controller for data submitted via the SYD platform. Personal identifiable data related to gender, year of birth, email address, first and last name, personal IP address and personal health information will be gathered through the SYD application. This data will be held in secured and encrypted servers from Amazon's AWS

SYD (See Yourself Differently) for NHS
Cloud Computing Service located in the UK. User authentication is achieved through AWS's Cognito service so that each app session uses a security token to validate and retrieve only the individual's data. The data held in the data repositories is encrypted so that operational staff cannot use operational tools to read the data. Any changes to data are audited and logged so that any anomalies can be detected. Data sent to the AWS server is encrypted using the TLS 1.2 protocol.

iamYiam is compliant with the General Data Protection Regulation (GDPR) and ISO 27001. As part of the sign-on process all users are provided with and encouraged to carefully read User Terms (https://syd.iamyiam.com/en/terms/) and Privacy Notice (https://syd.iamyiam.com/en/user-privacy/). The Privacy Notice sets out how IamYiam Limited collects and processes personal data through use of the SYD application and the user registration process. Users are encouraged to read these terms carefully as part of the registration process. We have worked with the Oxford University Data Ethics Team to produce easy to read information to improve engagement with users and ensure that users are fully aware of how and why we are using their data.

12.2 Confidentiality

Data submitted via the study website

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018. Participants will be asked to confirm their email address and name for the purpose of recording informed consent. Name and email addresses will be collected and stored separately on the online Qualtrics survey platform. The processing of the personal data of participants will be minimised by making use of a unique participant study number (RCTxxxx). No other identifiable data will be collected.

The study staff will ensure that the participants' anonymity is maintained at all times. Access to data collected via the Qualtrics platform will be restricted to study investigators at the Sponsor organisation (Southern Health NHS Foundation Trust). All identifiable and non-identifiable data downloaded from Qualtrics will be stored on computers and encrypted devices in accordance with the Sponsor Data Protection policies. The participants will be identified only by their study number during data analysis. All documents will be stored securely and only accessible by study staff and authorised personnel.

Data submitted via the SYD application

Personal identifiable data related to gender, year of birth, email address, first and last name, marital status, personal IP address and personal health information will be gathered through the SYD application and stored in a secured and encrypted AWS cloud server. These data are relevant to the advice being recommended. The study staff will ensure that the participants' anonymity is maintained at all times.

Individual data cannot be fully anonymised due to the need to associate it with the user such that recommendations and LQI can be tailored to each individual. However, if anyone were to intercept the communication and manage to also decrypt the data, because of the way iamYiam distributes the user data, user information can only be appreciated with having access to both the database and AWS Cognito user pool, which is even more unlikely.

AWS user data can only be accessed by iamYiam's two system admin level users with credentials and the appropriate permissions and through encrypted Apple laptops, which includes one of the co-investigators of this study. No individual information will be stored outside the secure AWS environment.

12.3 Data sharing

The study is a research collaboration between Southern Health NHS Foundation Trust (Sponsor) and iamYiam, a company developing and testing the SYD application. Southern Health NHS Foundation Trust and iamYiam have entered into a collaboration agreement stating their responsibilities in connection with this study. Both parties have Data Controller responsibilities in relation to their respective datasets generated by this study. Data will not be shared with anyone outside of the Sponsor and iamYiam research project teams, unless needed to independently verify results at the request of regulators.

All study participants will be allocated a randomised study number at the time of joining the study. A record of participant study numbers linked to participants names and email addresses will be kept in a password protected document on the Sponsor's drive, with access strictly restricted to identified members of the research team. The primary endpoint analysis will be carried out by the Sponsor using data collected on the study website.

The Sponsor shall transfer pseudonymised study data via a secure transfer method to iamYiam for analysis and for the purpose of further research related to the SYD application use. The research study data sharing plan will be detailed on the Participant Information Sheet (PIS) and specific consent sought as part of the informed consent process.

13 Quality Assurance Procedures

Southern Health NHS Foundation Trust Quality Assurance Manager (AT) will provide the study monitoring plan. Access will also be granted to the authorised representatives of the inspecting regulatory bodies, the Sponsor organisations and the funding body to ensure the study maintains protocol and regulatory compliance and adherence to Standard operational procedures and local policies.

14 Study Monitoring

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Lead researchers involved in the study will have up to date GCP training.

15 Protocol Deviations

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

Of note, SYD might have routine research updates for the duration of the trial, namely to the recommendations it provides to its users. This material is continually reviewed by a clinical advisory group and updated if evidence is considered sufficiently strong to indicate benefit to its users or employers.

SYD (See Yourself Differently) for NHS
The reporting procedure for any potential protocol breaches will be for the study team to report to Professor Shanaya Rathod at Southern Health NHS Foundation Trust. Any potential breach will be assessed by Professor Shanaya Rathod and at least 2 of the following from Dr Ameet Bakhai, Dr Pedro Henriques, Dr Peter Phiri and Mr Andrew Trousdale to assess whether a non-compliance / deviation may be a potential serious breach. If Professor Rathod is unavailable, Dr Peter Phiri or Dr Ameet Bakhai will deputise as lead for timely evaluation of protocol breaches.

16 Funding

iamYiam is providing funding to undertake this study.

17 Indemnity

The Sponsor (Southern Health NHS Foundation Trust) is providing indemnity to meet the potential legal liability for harm to participants arising from the design, management and conduct of the research arising from the Sponsor's negligent performance. iamYiam has indemnity to meet the potential legal liability for a data breach in relation to the use of the SYD application.

18 Intellectual Property

The study is being conducted via a research collaboration between the Sponsor (Southern Health NHS Foundation Trust) and iamYiam, a company developing and testing the SYD application. Both partners retain the ownership of any background intellectual property which they contribute to this research collaboration. Both partners grant the other a royalty-free, non-exclusive licence to use its background intellectual property for the purpose of carrying out this clinical research collaboration. iamYiam will own the results of the study and intellectual property rights subsisting in the results.

19 Presentation and publication plan

Research outputs and outcomes will be submitted for publication in healthcare journals and may be presented at relevant conferences or used for any subsequent guidance discussions with NHS executive bodies. Participants will not be identifiable from any summary of findings or papers written for publication. A Steering Committee chaired by the Chief Investigator, formed to supervise the conduct of this research study, will authorize publications and presentations relating to the study. Named authors on the main study publication will include the Chief Investigator and other investigators who have contributions to the design, delivery, and analysis of the study.

20 End of Trial

The end trial will be the date on which Health Research Authority is notified of the end of study. This is expected to be submitted by 31st March 2022.

At the end of trial, the Sponsor will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made, after discussing with any regulators any new claims to be allowed for SYD. Ideally patient identifiable data would be removed or archived after 12 months, unless the steering committee have sufficient rationale to defer this.

21 References

1. Audureau, E., Rican, S. and Coste, J., 2013. Worsening trends and increasing disparities in health-related quality of life: evidence from two French population-based cross-sectional surveys, 1995–2003. Quality of life research, 22(1), pp.13-26.

2. Bovend'Eerdt, T.J., Botell, R.E. and Wade, D.T., 2009. Writing SMART rehabilitation goals and achieving goal attainment scaling: a practical guide. Clinical rehabilitation, 23(4), pp.352-361.

3. Burgess, E., Hassmén, P., Welvaert, M., & Pumpa, K. L. (2017). Behavioural treatment strategies improve adherence to lifestyle intervention programmes in adults with obesity: a systematic review and meta-analysis. Clinical obesity, 7(2), 105-114.

4. Department of Health & Social Care, Public Health England (2020) Guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19, https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19

5. Devlin, N.J., Shah, K.K., Feng, Y., Mulhern, B. and van Hout, B., 2018. Valuing health-related quality of life: An EQ-5 D-5 L value set for England. Health economics, 27(1), pp.7-22.

6. Cohen, S., 1988. Perceived stress in a probability sample of the United States. (survey questions and scoring retrieved from: https://ohnurses.org/wp-content/uploads/2015/05/Perceived-Stress-Scale-4.pdf)

7. de Frias, C.M. and Whyne, E., 2015. Stress on health-related quality of life in older adults: The protective nature of mindfulness. Aging & mental health, 19(3), pp.201-206.

8. Dunn, K.M., Croft, P.R., Main, C.J. and Von Korff, M., 2008. A prognostic approach to defining chronic pain: replication in a UK primary care low back pain population. PAIN®, 135(1-2), pp.48-54.

9. European Commission (2014) Shaping Europe's Digital Future, Green Paper on mobile health ('mHealth'), https://ec.europa.eu/digital-single-market/en/news/green-paper-mobile-health-mhealth

10. European Commission (2014) Shaping Europe's Digital Future, Commission Staff Working Document on the existing EU legal framework applicable to lifestyle and wellbeing apps, https://ec.europa.eu/digital-single-market/news/commission-staff-working-document-existing-eu-legal-framework-applicable-lifestyle-and

11. Eriksson, K.M., Westborg, C.J. and Eliasson, M.C., 2006. A randomized trial of lifestyle intervention in primary healthcare for the modification of cardiovascular risk factors The Björknäs study. Scandinavian journal of public health, 34(5), pp.453-461.

12. Eriksson, M.K., Hagberg, L., Lindholm, L., Malmgren-Olsson, E.B., Österlind, J. and Eliasson, M., 2010. Quality of life and cost-effectiveness of a 3-year trial of lifestyle intervention in primary health care. Archives of internal medicine, 170(16), pp.1470-1479.

13. Fancourt, D. Bu, F. Mak, K. and Steptoe, A., 2020. COVID-19 Social Study. Results Release 5. London, UK: University College London.

14. Frendl, D.M. and Ware Jr, J.E., 2014. Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. Medical care, pp.439-445.

15. Fujiwara, D., Dolan, P., Lawton, R., Behzadnejad, F., Lagarde, A., Maxwell, C., Peytrignet, S., 2020. The Wellbeing Costs of COVID-19 in the UK. An Independent Research Report by Simetrica-Jacobs and the London School of Economics and Political Science. https://www.jacobs.com/sites/default/files/2020-05/jacobs-wellbeing-costs-of-covid-19-uk.pdf

16. Herdman, M., Gudex, C., Lloyd, A., Janssen, M.F., Kind, P., Parkin, D., Bonsel, G. and Badia, X., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research, 20(10), pp.1727-1736. (https://euroqol.org/wp-content/uploads/2019/10/Sample_UK__English__EQ-5D-5L_Paper_Self_complete.pdf)

17. Holmes, E.A., O'Connor, R.C., Perry, V.H., Tracey, I., Wessely, S., Arseneault, L., Ballard, C., Christensen, H., Silver, R.C., Everall, I. and Ford, T., 2020. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. The Lancet Psychiatry.

18. James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A. and Abdollahpour, I., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet, 392(10159), pp.1789-1858.

19. Kisely, S., Warren, N., McMahon, L., Dalais, C., Henry, I., & Siskind, D. (2020). Occurrence, prevention, and management of the psychological effects of emerging virus outbreaks on healthcare workers: rapid review and meta-analysis. BMJ, 369

20. Kyu, H.H., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A. and Abdollahpour, I., 2018. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet, 392(10159), pp.1859-1922.

21. Lindström, J., Ilanne-Parikka, P., Peltonen, M., Aunola, S., Eriksson, J.G., Hemiö, K., Hämäläinen, H., Härkönen, P., Keinänen-Kiukaanniemi, S., Laakso, M. and Louheranta, A., 2006. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. The Lancet, 368(9548), pp.1673-1679.

22. Mahoney, M.J., Moura, N.G. and Wade, T.C., 1973. Relative efficacy of self-reward, self-punishment, and self-monitoring techniques for weight loss. Journal of Consulting and Clinical Psychology, 40(3), p.404.

23. Maruish, M.E., Maruish, M., Kosinski, M., Bjorner, J.B., Gandek, B., Turner-Bowker, D.M. and Ware, J.E., 2011. User's manual for the SF36v2 Health Survey.

24. Medicines & Healthcare products Regulatory Agency (2020), Guidance: Medical device stand-alone software including apps (including IVDMDs); https://www.gov.uk/government/publications/medical-devices-software-applications-apps

25. National Institute for Health and Care Excellence, 2019. NICE Evidence Standards Framework for Digital Health Technologies. March 2019

26. NHS England. NHS staff survey 2019. May 2020. http://www.nhsstaffsurveys.com/

27. Office for National Statistics, 2020. Coronavirus and the Social Impacts on Great Britain: 23 April 2020. London, UK: Office for National Statistics.

28. Olatunji, B.O., Cisler, J.M. and Tolin, D.F., 2007. Quality of life in the anxiety disorders: a meta-analytic review. Clinical psychology review, 27(5), pp.572-581.

29. Public Health England (2020) Guide to Evaluating Digital Health Products: 30 January 2020 https://www.gov.uk/guidance/before-and-after-study-comparative-studies

30. Ruo, B., Rumsfeld, J.S., Hlatky, M.A., Liu, H., Browner, W.S. and Whooley, M.A., 2003. Depressive symptoms and health-related quality of life: the Heart and Soul Study. Jama, 290(2), pp.215-221.

31. Sach, T.H., Barton, G.R., Doherty, M., Muir, K.R., Jenkinson, C. and Avery, A.J., 2007. The relationship between body mass index and health-related quality of life: comparing the EQ-5D, EuroQol VAS and SF-6D. International journal of obesity, 31(1), pp.189-196.

32. Safran Naimark J, Madar Z, Shahar D.R., 2015. . The impact of a Web-based app (eBalance) in promoting healthy lifestyles: randomized controlled trial. J Med Internet Res. 2015 Mar 2;17(3):e56. doi: 10.2196/jmir.3682. https://pubmed.ncbi.nlm.nih.gov/25732936/

33. Schroeder, S.A., 2007. We can do better — improving the health of the American people. New England Journal of Medicine, 357(12), pp.1221-1228.

34. S Singer 1, S Kuhnt, H Götze, J Hauss, A Hinz, A Liebmann, O Krauss, A Lehmann, R Schwarz. Hospital anxiety and depression scale cutoff scores for cancer patients in acute care. Br J Cancer. 2009 Mar 24;100(6):908-12. doi: 10.1038/sj.bjc.6604952. Epub 2009 Feb 24.

35. Sullivan, P.W., Ghushchyan, V., Wyatt, H.R., Wu, E.Q. and Hill, J.O., 2007. Impact of cardiometabolic risk factor clusters on health-related quality of life in the US. Obesity, 15(2), pp.511-511.

36. Toobert, D.J., Glasgow, R.E., Strycker, L.A., Barrera, M., Radcliffe, J.L., Wander, R.C. and Bagdade, J.D., 2003. Biologic and quality-of-life outcomes from the Mediterranean Lifestyle Program: a randomized clinical trial. Diabetes care, 26(8), pp.2288-2293.

37. Vlahu-Gjorgievska, E., Mulakaparambil Unnikrishnan, S. and Win, K.T., 2018. mHealth applications: a tool for behaviour change in weight management. Stud Health Technol Inform, 252, pp.158-163.

38. World Health Organization, 1995. Constitution of the world health organization.

39. World Health Organization, 1996. WHOQOL-BREF: introduction, administration, scoring and generic version of the assessment: field trial version, December 1996 (No. WHOQOL-BREF). World Health Organization.

40. World Health Organization, 2003. Adherence to long-term therapies: evidence for action. World Health Organization.

41. Zigmond, A.S. and Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta psychiatrica scandinavica, 67(6), pp.361-370.