Non-CTIMP Study Protocol

Treating Anxiety after StroKe (TASK)—feasibility randomized controlled trial

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NA	NA

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
CBT	Cognitive behavioural therapy
CI	Chief Investigator
CRF	Case Report Form
EQ5D5L-VAS	EuroQol 5D 5L Visual Analogue Scale
FQ	Fear Questionnaire
GAD	Generalized Anxiety Disorder
GAD-7	7-item Generalized Anxiety Disorder Questionnaire
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
mRS	Modified Rankin Scale
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
RCT	Randomized Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient Ischaemic attack

1 INTRODUCTION

1.1 BACKGROUND

Anxiety affects around a quarter of stroke patients and can be disabling. A Cochrane review in 2017 concluded that the three randomized controlled trials (RCT) of anxiety intervention in stroke carried high risk of bias and were of small sample size, thus provided insufficient evidence to guide treatment.

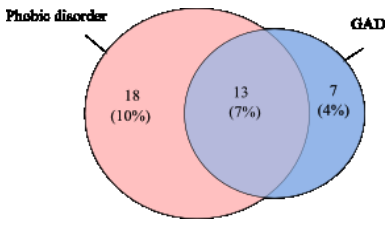
We carried out an observational study using psychiatric interviews to determine the commonest anxiety subtypes and anxiety-provoking situations to inform the targets of a psychological intervention. Based on these findings we developed a complex intervention consisting of cognitive behavioural therapy (CBT) techniques specifically adapted to the anxiety issues reported by patients following a stroke or transient ischaemic attack: the TASK-CBT intervention.

Scientific basis for TASK-CBT

Phobic disorder was the predominant anxiety subtype after stroke (Figure 1) in our prospective cohort (n=175), consistent with three earlier studies that conducted psychiatric diagnostic interviews (1). Phobic anxiety is characterized by fear disproportionate to defined situation(s) and marked avoidance. Generalized anxiety disorder (GAD) is persistent & unremitting anxiety about multiple daily events. In non-stroke populations, exposure therapy is effective at treating phobic disorders in RCTs(2), while GAD responds to selective serotonin reuptake inhibitors, short-term benzodiazepines, and/or other cognitive behavioural techniques e.g. cognitive restructuring, problem solving(3, 4). Anxiety disorder at 3 months post-stroke was associated with poorer functional independence and quality of life even in a mild stroke & TIA sample(5).

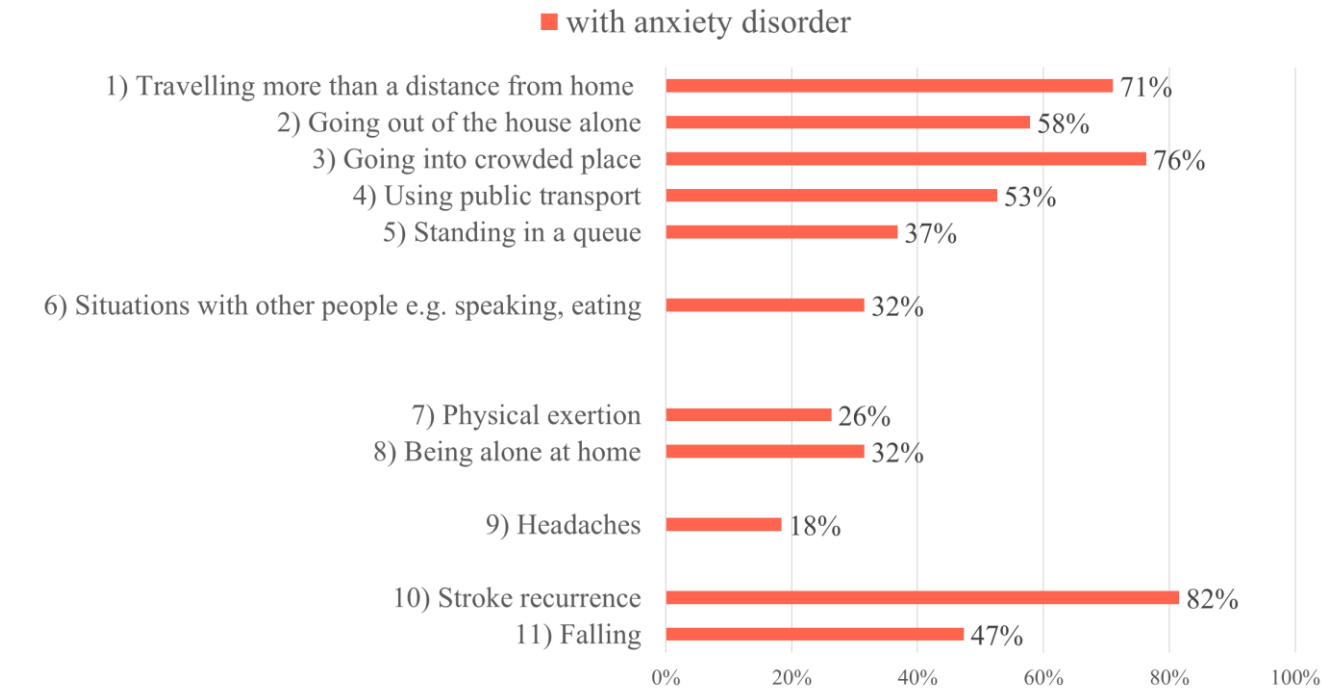
We hypothesize that an intervention that does not target phobic anxiety after stroke is not effective at alleviating anxiety symptoms and will not improve functional independence and quality of life after stroke.

Figure 1. Frequency of phobic disorder and GAD at 3 months after stroke (n=175) (5)



To include exposure therapy in CBT there must be defined feared situation(s)/ stimuli. We quantified in our observational study, for the first time, the common anxiety-provoking situations/stimuli and maladaptive cognitive patterns affecting stroke survivors (Figure 2), and their associated avoidant behaviour. These findings informed targets for cognitive restructuring and exposure techniques used in the TASK-CBT intervention.

Figure 2. Common anxiety-provoking situations/stimuli in 38/175 with anxiety disorder)(5)



The TASK-CBT intervention and TASK-Relax (active comparator)

TASK-CBT intervention: Telephone-guided web-based CBT

There are two key modes of delivery within the TASK-CBT intervention:

1) **A course of 6 weekly telephone-guided sessions** (30-40minutes each) delivered over 6-12 weeks using the 'TASK therapist's manual & record'. Therapist (any stroke health professional—stroke nurse, rehab therapist, stroke doctor) receives training by Dr Alan Carson. Therapist meets with Dr Carson and reviews record. All telephone-guided sessions are audio-recorded and transcribed to aid validation of the therapist's record.
2) **TASK-CBT treatment website** displays information, graphics, treatment videos, and online tasks covering all components of TASK-CBT

For participant's experience, please visit xxxxxxxxxxxxx.
Temporary login: xxxxxxxxxxxxx password: xxxxxxxxxxxxx

The active comparator intervention: TASK-Relax website

- TASK-Relax is an online self-guided course of relaxation techniques.
- One telephone session (20 minute) at the start to guide participant how to use the TASK-Relax website
- The course is structured with 5 online tasks. An introductory video (with subtitles) provides simple instructions on how to use the TASK-Relax website throughout the trial period.
- The tasks contain videos of breathing exercise, muscle relaxation, relaxing imagery and sound clips to teach participants various relaxation techniques
- Participants are encouraged to take at least 5 minutes to practice a relaxation task daily in the long-term

For participant's experience, please visit xxxxxxxxxxxxxxxx
Temporary login: xxxxxxxxxxxxx password: xxxxxxxxxxxxx

Additional features common to both TASK-CBT and TASK-Relax intervention

- **Ongoing 'anytime' access** to the allocated website up to the end of the TASK trial period
- **Useful links** to external stroke resources—Chest Heart Stroke Scotland and Stroke Association websites
- **Regular text reminders** to improve intervention adherence & completion of data collection in the TASK trial. The text reminders continue throughout the trial period until data completion at primary endpoint
- Every participant is informed they will receive access to the website given to the other group
- Every participant receives a **TASK participant card as follow**:


Task

NHS Lothian

CHIEF SCIENTIST OFFICE

A clinical trial of web-based treatments for anxiety after stroke
Participant card

Your first allocated treatment website: www.tasktreatment2.org

Your login:
Your password:
Please do not pass on your login details to other people

Contact us if you require assistance

TASK mobile: 0745 320 7061
Email: task.trial@ed.ac.uk

TASK CBT participant card front

Date Day Time
Sessions

1 ____ ____ ____ TASK 1 ☐
2 ____ ____ ____ TASK 2 ☐
3 ____ ____ ____ TASK 3 ☐
4 ____ ____ ____ TASK 4 ☐
5 ____ ____ ____ TASK 5 ☐
6 ____ ____ ____ TASK 6 ☐

Study Survey 1 ____ ☐

Study Survey 2 ____ ☐

Feedback Survey ____ ☐

Continue to use the website to help you manage your anxiety

Handy tips

- Monitor your anxious feelings, thoughts and
- Challenge unhelpful thoughts
  - Have a conversation with yourself
  - Be kind to yourself
- Frightened of a specific situation?
  - Face your fear in small gradual steps
  - Stay until the anxiety level starts to decrease

You will receive a link to the treatment given to the other group on completion of Study Survey 2

TASK CBT participant card back

Task

A clinical trial of web-based treatments for anxiety after stroke
Participant card

Your first allocated treatment website: www.tasktreatment3.org

Your login:
Your password:

Please do not pass on your login details to other people

Do not hesitate to contact us if you require assistance

TASK mobile: 0745 320 7061
Email: task.trial@ed.ac.uk

TASK-Relax
participant card front

Date	Day	Time	Sessions
1			TASK 1 ☐
2			TASK 2 ☐
3			TASK 3 ☐
4			TASK 4 ☐
5			TASK 5 ☐
6			TASK 6 ☐

Study Survey 1 _____ ☐

Study Survey 2 _____ ☐

Feedback Survey _____ ☐

Continue to use the website to help you manage your anxiety

Handy tips

- Monitor your anxious feelings, thoughts and
- Challenge unhelpful thoughts
  - Have a conversation with yourself
  - Be kind to yourself
- Frightened of a specific situation?
  - Face your fear in small gradual steps
  - Stay until the anxiety level starts to decrease

You will receive a link to the treatment given to the other group on completion of Study Survey 2

TASK-Relax
participant card back

1.2 RATIONALE FOR STUDY

Research question

Is it feasible to compare the effectiveness of the telephone-guided web-based TASK-CBT with web-based self-guided TASK-Relax in a web-enabled randomized controlled trial?

Why is this study important to patients, health service and current policies?

Anxiety problems afters stroke are common and disabling. There is little research evidence to guide how to treat anxiety after stroke. Access to psychological care after stroke is difficult. We need to deliver an anxiety intervention to large number of stroke and TIA patients, efficiently and economically to ensure its long-term sustainability in the NHS. Our intervention is developed in line with the Scottish Mental Health Strategy for 2017-2027.

Treatment to be tested

We know that cognitive behavioural therapy (CBT) works for anxiety in people who have not had a stroke. Many anxiety issues reported by stroke patients can potentially be targeted by CBT. We developed CBT treatment that are specifically tailored to stroke survivors. Before we can provide TASK-CBT to a large population of stroke survivors, we need to test whether these treatments have any real benefits to patients in a clinical trial setting.

Feasibility of our method to minimize bias in a RCT of psychological intervention

The type of comparator group in an RCT of psychological intervention can influence effect size(6). Rather than using a 'treatment as usual' (TAU) or waitlist control as comparator, we are comparing group receiving TASK-CBT & group receiving TASK-Relax (active comparator).

Establishing any harms of our intervention

It is not clear, but important to establish whether there is any potential harm of a telephone-guided web-based CBT intervention for stroke and TIA patients. We will do that by asking participants to complete a feedback survey at the end of the study period.

Feasibility in conducting a nationwide web-enabled RCT conducted by a single centre

We designed the trial procedures with the view of conducting a large-scale clinical trial that will recruit nationwide from a single centre in the future. We will use the feasibility data from this present study to refine our trial design.

Feasibility of measuring objective outcomes using a wrist-worn wearable device (a substudy)

Wearable device can collect objective physiological and behavioural measures, complementing and potentially replacing self-reported outcomes used in clinical trials of a wide range of interventions in

stroke and TIA patients. In a substudy we will assess the feasibility and acceptability of the GENEActive Original device in a clinical trial setting of stroke and TIA patients with anxiety.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objectives

Objective 1: Feasibility of web-enabled RCT procedures

Objective 2: Feasibility of TASK-CBT & TASK-Relax interventions

Objective 3: To establish any harm arising from TASK-CBT or TASK-Relax interventions

2.1.2 Secondary/ substudy objectives

Objective 4: Feasibility of wearing wrist-worn device (GENEActiv) for up to 210 days

2.2 ENDPOINTS

2.2.1 Feasibility outcomes

For objective 1: Feasibility of trial procedures

a) *Feasibility of online 'Sign up' process & electronic informed consent form (ICF)*
   i. Number of participants recruited per month
   ii. How were participants recruited?
      - Self-recruited via website (%)
      - Via website with TASK team's assistance (%)
      - In person, not via website (%)
   iii. How did participants complete ICF?
      - Electronic ICF(%)
        - actually eligible (%)
      - Paper ICF (%)

b) *Feasibility of remotely confirming eligibility of potential participants with 3 different method*

   Time (in days): date of randomization – date of data request made
   - via TRAK
   - via general practice request for summary sheet to be faxed/ emailed (via nhs email) to TASK researchers
   - via Scottish Stroke Care audit

c) Feasibility of online self-completed surveys at data collection time points (% completion)
   - Pre-randomization (T0)
   - At end of intervention—between 6-12 weeks (T1)
   - At primary endpoint between 20-30 weeks (T2)

For objective 2: Feasibility of assessing intervention fidelity (delivering intended content)

a) Data recorded by therapist on the *'TASK-CBT Therapist's manual & record'* (TASK-CBT only)
    - which content(s) has been delivered, and in which session

b) A third person from outside the TASK research team validates the therapist's record with anonymised transcript of audio-recording for each telephone session (TASK-CBT only) (% agreement)

c) Website analytics to analyse usage of website content and videos (TASK-CBT & TASK-Relax)
    - Duration spent on each page of TASK-CBT website (minutes) vs TASK-Relax

d) Completion of online tasks (TASK 1 - 6): data automatically captured on RedCap (TASK-CBT only) (%)

For objective 3: To establish any unwanted effects arising from TASK-CBT or TASK-Relax interventions

a) Online participant feedback survey at the end of data collection at T2
    - % participants found the allocated intervention helpful for their anxiety
    - % participants reported unwanted effects from allocated intervention
    - Free-text feedback

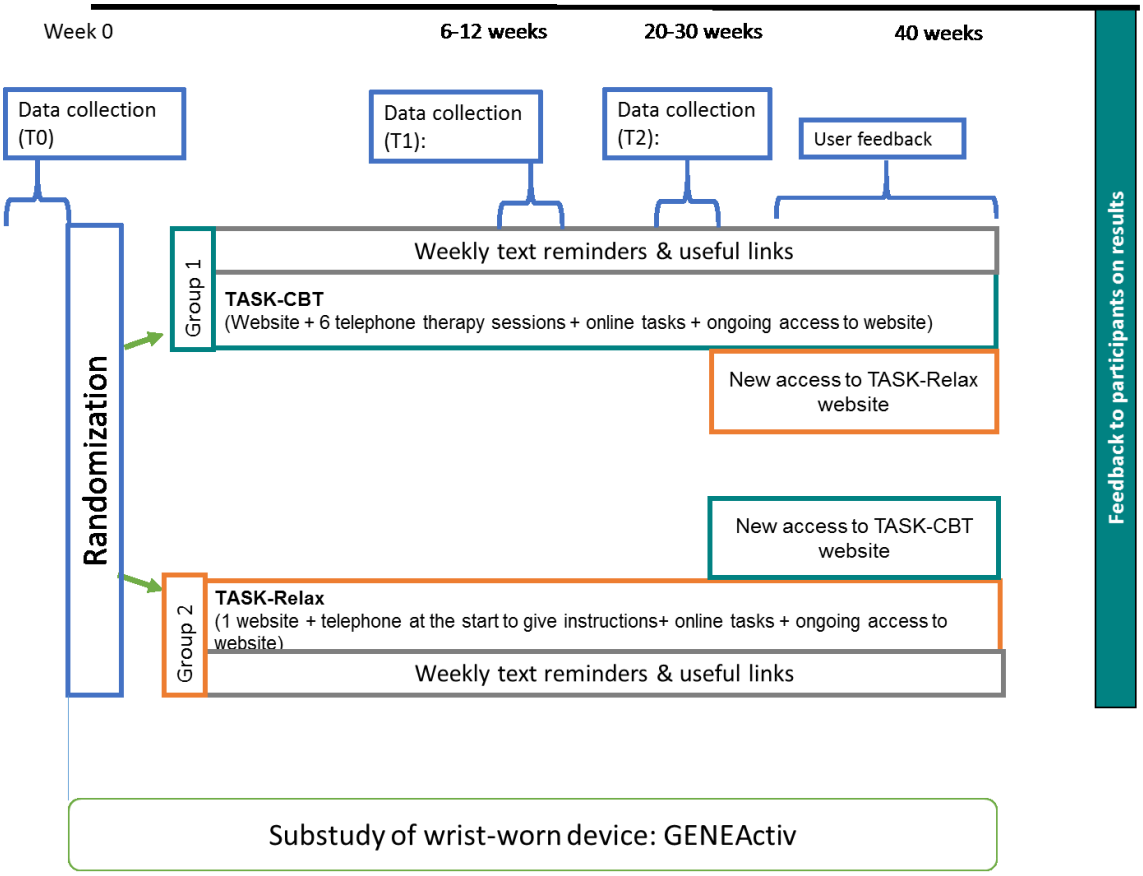
For Objective 4 (Substudy): Feasibility of wrist-worn device for measuring objective outcomes

a) Duration of useable data from device in total (days)
b) Practical issues on delivering and collecting the device by courier service/ recorded delivery at the start, and at 60 day intervals throughout the trial period (free-text)

3 STUDY DESIGN

- A parallel randomized controlled trial comparing TASK-CBT and TASK-Relax

Study schematic



- Method of masking/ blinding of participants to intervention allocation:
  - Participants are informed they will receive all TASK treatments designed for this trial by the end of the study period
  - Both interventions are referred to as TASK treatments in Participant Information Sheet (PIS)
  - The PIS electronic and paper versions) simply states that we are testing different treatments: ways to overcome anxiety, relaxation techniques, useful videos, weekly tasks, regular text reminders
  - Participants are not aware of what type of treatment is given to the other group until they get access to it after the primary endpoint

- The purpose of this design is to reassure participants that they are getting an active intervention

- ***Substudy of the wrist-worn device GENEActiv Original***

  - The GENEActive Original device is a CE-marked wrist worn device used for in may research studies. https://www.activinsights.com/actigraphy/geneactiv-original/
  - The device measures light, temperature and acceleration data
  - Participants in this substudy are asked to try to wear this watch as continuously as possible for up to 60 days

- Simple instructions will be given to wear it on the non-paretic hand; avoid covering the light sensor; remove for shower/ bath and put it back on afterwards; remove if any skin irritation occurs and inform the TASK research team

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

- We aim to recruit 40 participants into this feasibility RCT from NHS Lothian, 20 of whom for the substudy of the wrist-worn device

4.2 INCLUSION CRITERIA

1. Diagnosis of stroke (ischaemic, haemorrhagic), probable or definite transient ischaemic attack (TIA) & ocular TIA
    - For clinic patients diagnosis has to be at least one month ago
    - For ward patients, at least one month after discharge to community
2. Age 18 or over
3. Has access to internet and telephone
4. Has anxiety symptoms (at least one positive response to the 6 anxiety questions on the 'Sign up form') and would like to receive treatment
5. Has capacity to give informed consent
6. Able to talk on the telephone (assessed by research team + verbal fluency test on telephone)
7. Living within Lothian (all EH postcodes and FK1)

4.3 EXCLUSION CRITERIA

- Non-English speaking
- Already taking part in a clinical trial of treatment (drug or non-drug) intended to improve psychosocial outcomes e.g. stress, anxiety, depression, emotionalism, fatigue, social functioning, quality of life (as taking part in our study would affect the results in another trial)

*Being on a mood altering medication is not an exclusion criterion in TASK. We record whether participant is on a mood-altering medication during our data collection.

4.4 CO-ENROLMENT

- Participants cannot be co-enrolled to other clinical trials of treatment (drug or non-drug) intended to improve psychosocial outcomes e.g. stress, anxiety, depression, emotionalism, fatigue, social functioning, quality of life as co-enrolment is likely to influence outcomes in these trials
    - Our study sign-up form includes a routine question on whether the potential participant has already enrolled onto another research study. This is verified by the TASK research team
- Co-enrolment in an observational study, including one measuring psychosocial outcomes is permitted, but we will ask participant to first consider the potential burden of taking part in more than one research study.
    - Burden of co-enrolment in another observational study on psychosocial outcomes
        - Similar questionnaires
        - Follow ups may coincide with telephone sessions within TASK-CBT intervention

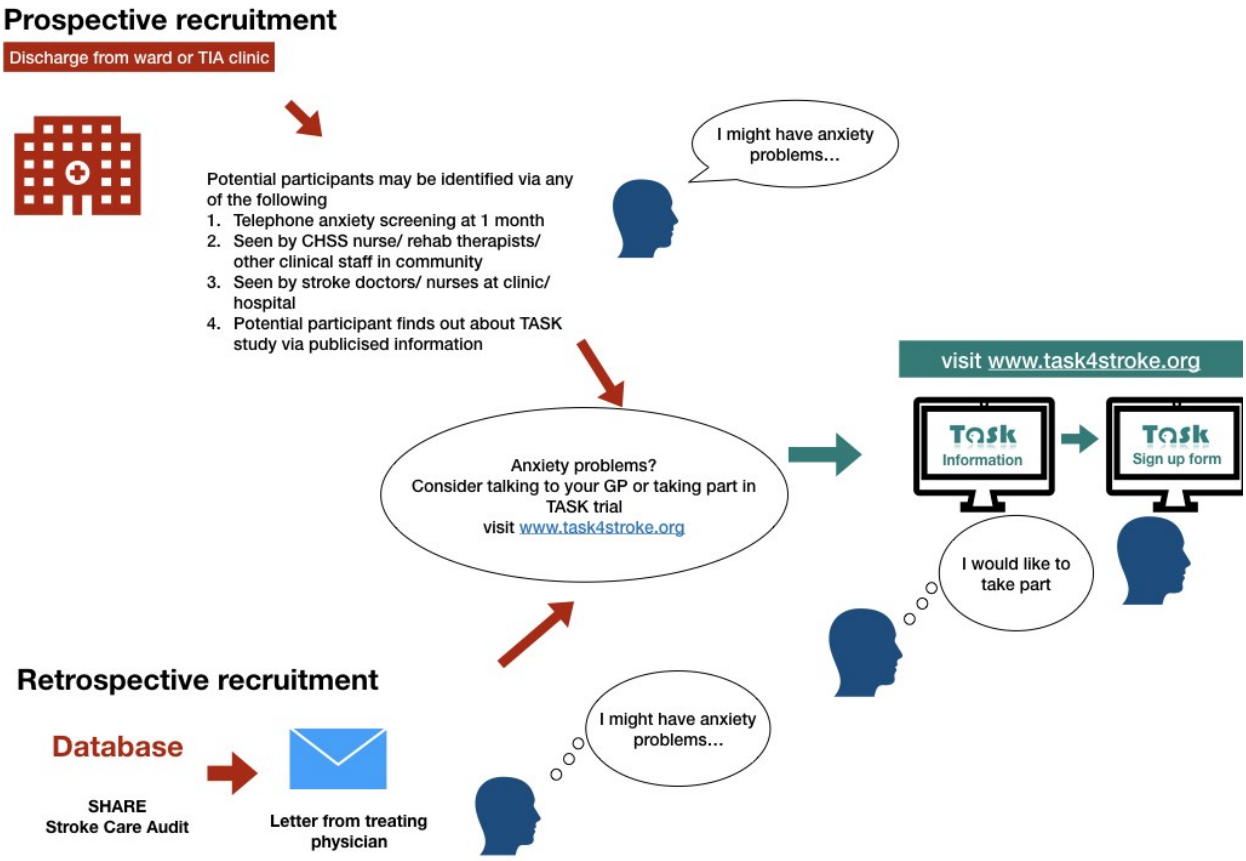
- Once enrolled onto the TASK trial we will make an entry onto TRAK record

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

There are two methods of identifying potential participants. All methods encourage potential participants to visit the TASK recruitment website www.task4stroke.org where potential participants can begin the online sign up process themselves.

Recruitment method



For participant's experience, please visit www.task4stroke.org

i) *Prospective recruitment:*

Participants who are identified as having anxiety symptoms by clinical staff or at 1-month telephone screening* are encouraged to visit www.task4stroke.org

*part of clinical care, as recommended by the latest Royal College of Physician's Guideline Fifth Edition 2016 (2.12.1).

ii) *Retrospectively:*

TASK researchers Dr Yvonne Chun, Prof Martin Dennis, Prof Gillian Mead, and Dr Will Whiteley are also part of the direct care team for stroke and TIA patients at the Royal Infirmary of Edinburgh. They will identify potentially eligible participants from the Scottish Stroke Care Audit

database and SHARE (www.registerforshare.org) and check eligibility on hospital electronic health system (TRAK).

Letters of invitation and a 'TASK business card' will be sent to the potential participants on behalf of their treating physician. The letter advises patients to either seek GP advice or consider taking part in a clinical trial by visiting www.task4stroke.org if they are experiencing anxiety issues

We will publicise the TASK recruitment website www.task4stroke.org by disseminating TASK 'business card', PIS widely across the stroke services as above, on social media and via stroke charities.

TASK study recruitment website 'business' card

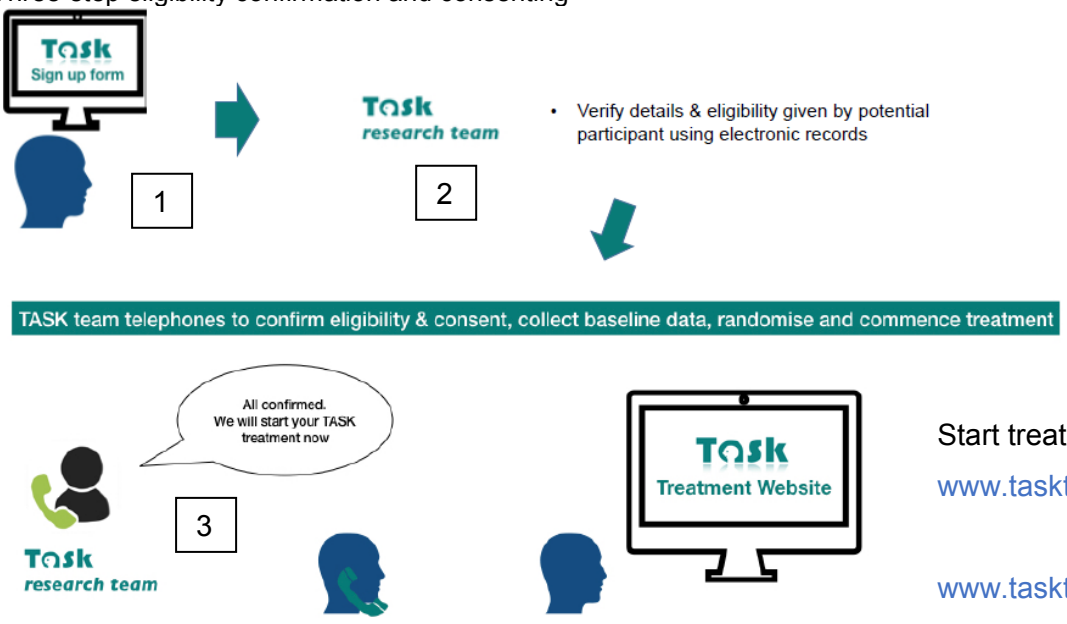
Any interested potential participant can either

i. sign up themselves using the *'Sign up form' on* www.task4stroke.org
ii. contact the TASK research team by phone/ email for assistance in completing the online *'Sign up form'* or request its paper version

5.2 CONSENTING PARTICIPANTS

There is a three-step 'eligibility confirmation and consenting process'

Three-step eligibility confirmation and consenting



- TASK researcher phones potential participant, confirms eligibility and consent., countersigns electronic consent form and emails a copy to participant

1) Potential participant completes online *'Sign up form'* which comprises of A) Eligibility checklist, B) Informed Consent Form (ICF), and C) Personal details

2) TASK research team verifies participant's details and eligibility on the *'Sign up form'* by checking TRAK/Scottish Stroke audit/GP summary sheet

3) TASK research team phones potential participant for final verification of identity, eligibility, and confirmed the potential participant has personally provided the electronic signature on the ICF. TASk researcher countersigns the electronic consent form, emails copy to participant

Once 3) is completed, while still on the telephone with the participant the TASK researcher

- completes baseline data collection (including participant's baseline [T0] survey)
- randomizes participant and provides login and password for the allocated treatment website
- schedule the first telephone session for TASK-CBT participants
- provides simple instructions for TASK-CBT and TAS- relax participants to log on to their treatment website

The TASK researcher also

- sends participant an electronic copy of the fully signed informed consent form by email
- sends participant a TASK participant card for the allocated treatment by post

Other considerations

- Interested potential participants are encouraged to read all the information on the PIS (website or paper), and take as much time as they need before completing the *'Sign up form'*
- Paper version of the TASK study ICF is available on request
- Easy-access version of the '*Sign up form'* is available online with text-to-speech function
    - Potential participants with sight impairment should complete this version with assistance from family member/ friend

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by one of the TASK trial investigators. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from

(i)all aspects of the trial but continued use of data collected up to that point
(ii) all aspects of the trial with removal of all previously collected data.
(iii) all aspects of the trial with removal of previously collected

"Stopping rules" and "discontinuation criteria"

- Participant loses capacity during the study period

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

Who completes the assessment(s)	**T0:** baseline (before randomization)	**T1:** at end of intervention (6-10 weeks post randomization)	**T2** primary endpoint: (20-30wks post-randomization)	
Participant	Generalized Anxiety Disorder-7 (GAD-7) Fear Questionnaire (FQ) Patient Health Questionnaire-2 (PHQ-2) Modified Rankin Scale (mRS) EuroQol5D5L-Visual Analog Scale (EQ5D5L-VAS)	GAD-7 FQ PHQ-2 mRS EQ5D5L-VAS On medication for mood or anxiety Y/N	GAD-7 FQ PHQ-2 mRS EQ5D5L-VAS On medication for mood or anxiety Y/N	Participant feedback on first intervention
TASK-CBT participant only		Throughout the first intervention (TASK-CBT only): 5 online TASKs--self-completed questions		
TASK researcher	Demographics Date of index event Diagnosis Current psychiatric treatment Past medical history Past psychiatric history			
TASK Therapist	Audio-recording of all 6 telephone-guided sessions Therapist's manual & record'			
Wearable device (GENEActiv)	Wearable for the entire study period (20-30 weeks)			

7 DATA COLLECTION

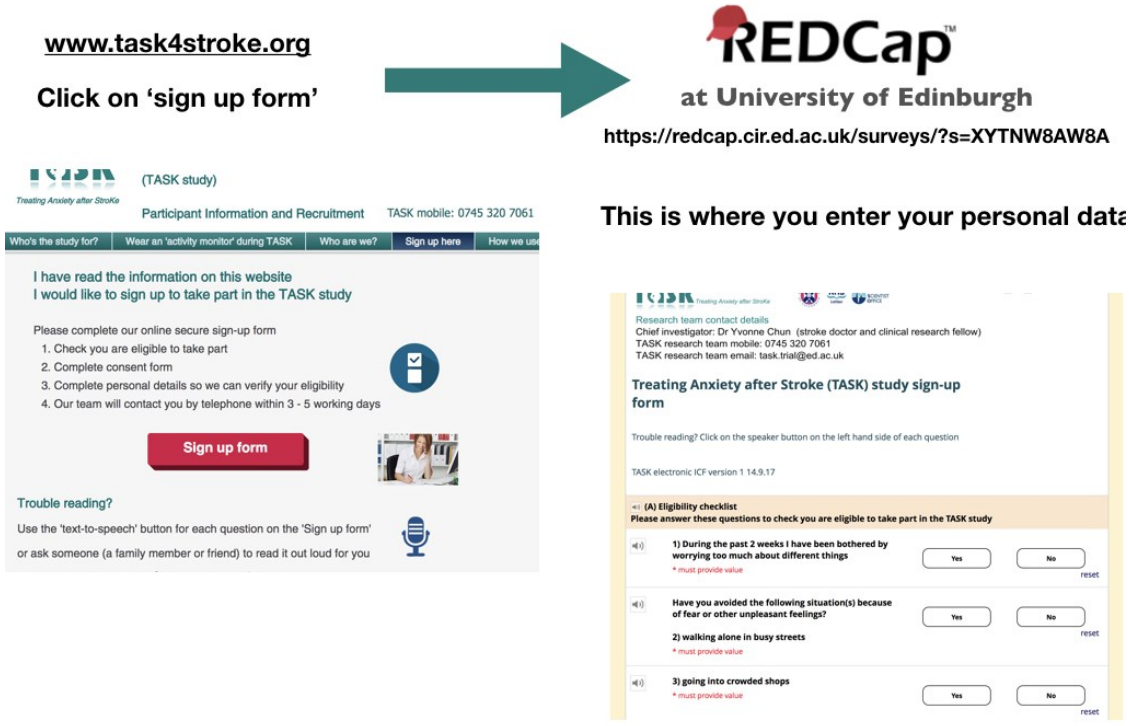
- All data collection, including the consent form is carried out online via electronic data collection instruments created in REDCap (Research electronic data capture, hosted by the University https://redcap.cir.ed.ac.uk/)
- The detailed security arrangements of REDCap are found in 11.2.7
- Our websites provide web links for participants to click on. Once clicked participants are taken to the relevant redcap web address to complete the questionnaire (see diagrams below).
- All personal data are stored on the REDCap database, hosted by the University of Edinburgh's server (see 11.2.7)
- Other than the participant's email address, no personal data are entered on the websites

The following diagrams demonstrate how all of TASK trial's data are collected from the initial 'sign up':

1) The REDCap 'Sign up form'

Potential participants are interested in taking part in the TASK trial and visits our website www.task4stroke.org

- By clicking on 'Sign up form' button participant is taken to a REDCap's web address hosted by the University of Edinburgh, where participant can enter their details on the 'sign up form'
- All data entered are stored in the REDCap database at University of Edinburgh



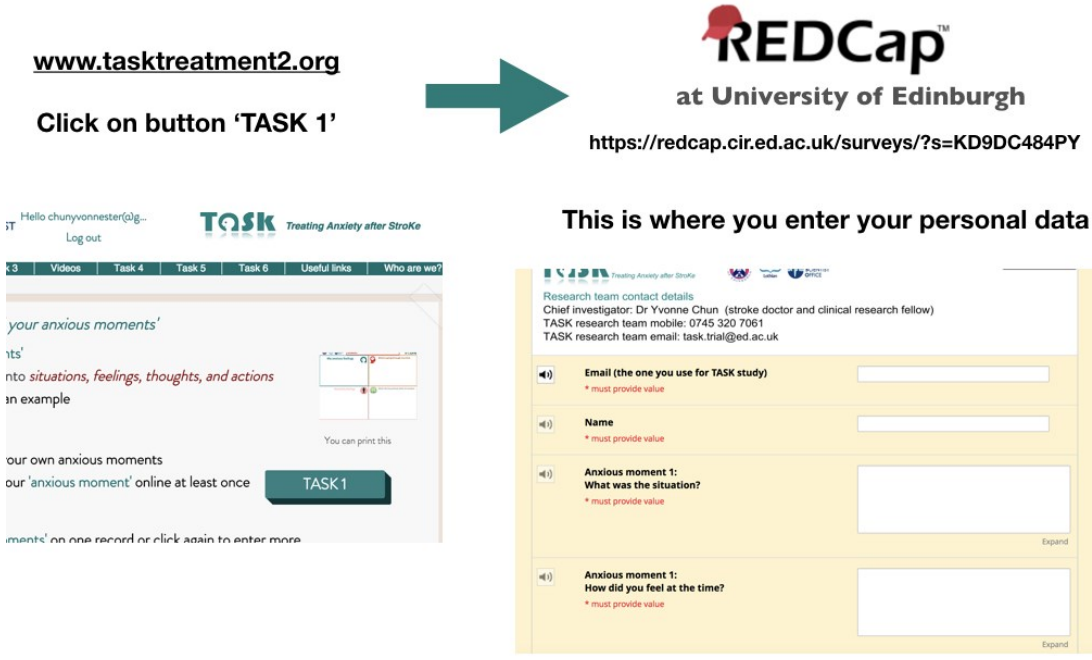
Visit www.task4stroke.org to see example of the 'Sign up form'

This form also comes in paper version as the TASK ICF

On this REDCap 'sign up form' potential participants provide consent for us to contact them using their personal data which they provide on this form--surname, last name, date of birth, postal address, telephone number.

2) **TASK researcher confirms consent and collect baseline (T0) data over the phone.**
   - TASK researcher
     - phones the potential participant who has completed the 'Sign up form'
     - confirms eligibility and consent over the phone
     - countersigns the electronic consent with an electronic signature
     - emails participant a copy of the countersigned consent form
     - collects baseline data from participant over the phone
     - randomizes the participant into one of two treatments
     - provides login instruction and email address to the treatment website
     - makes a telephone appointment (if allocated to the TASK-CBT group)

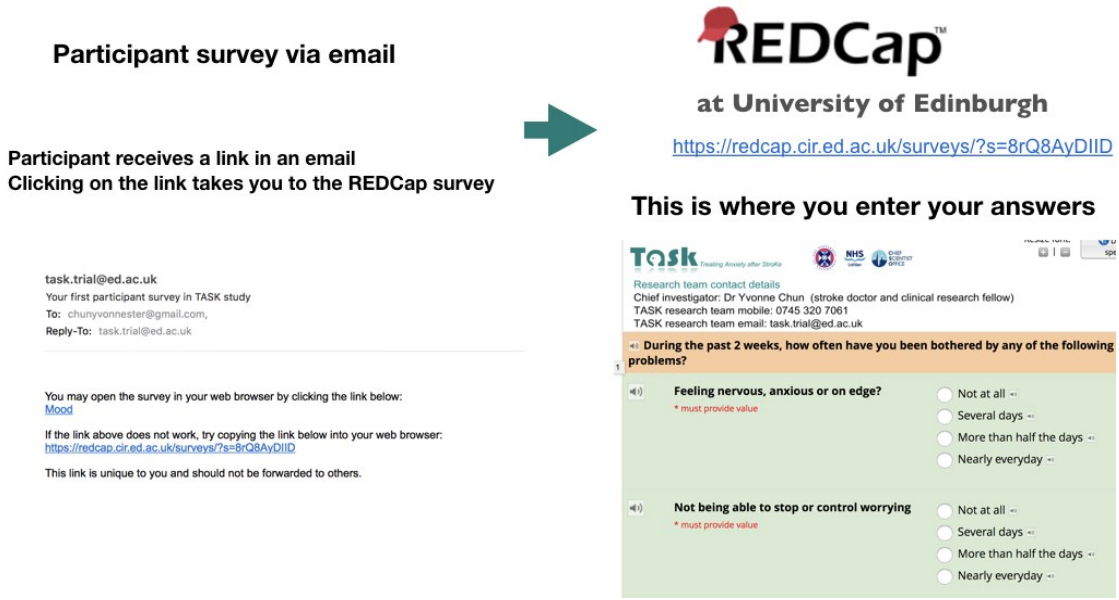
3) **The 5 online tasks** on the TASK-CBT website (www.tasktreatment2.org)
   By clicking on each 'TASK' button participant is taken to the relevant REDCap web address hosted by the University of Edinburgh, where participant can complete a simple questionnaire. Diagram below shows what happens when participant clicks on 'TASK 1'.



It works the same way when you click buttons 'TASK 2', 'TASK 3', 'TASK 4', 'TASK 6' on www.tasktreatment2.org

Visit www.tasktreatment2.org (Temporary login: tasktrialteam@gmail.com password: talt7061) to see these online tasks.

4) **Follow up surveys at T1 and T2**
   We use the REDCap database management system to send participant an email (see example below) containing a link (url) to the follow up survey. Clicking on the link takes the participant to the REDCap survey at University of Edinburgh



- To maximise completeness of data collection
  - we send a text reminder to each participant to complete each survey
  - each participant is posted a TASK participant card so they can record whether they have completed all three surveys and any online tasks
  - If surveys remain incomplete despite the above measures, TASK research team contact the participant to complete the survey over the telephone

- Wearable substudy participants are offered a brief report on the activity and sleep at the end of their participation

7.1 Source Data Documentation

- All study data are first captured electronically on REDCap and then printed as a pdf file to be filed as paper Case Report Form (CRF) to be stored in the Investigator Site File (ISF)
- Any additional paper record of participant's data e.g. GP's summary sheet of past medical and drug history is stored with the paper CRF in the ISF

7.2 Case Report Forms

- Electronic CRFs are stored on REDCap database and printed as PDF files to be kept in physical storage in the ISF

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

- As this is a feasibility RCT designed for process evaluation, we did not calculate sample size
- We aim to recruit around 40 participants in this feasibility trial

8.2 PROPOSED ANALYSES

- Feasibility endpoints as listed in 2.2.1 –these are summarized as proportions (%) and free text
- Descriptive data (mean, standard deviation) from clinical outcomes at T0, T1, T2
  - mRS, EQ5D5L-VAS, GAD-7, PHQ-2, FQ
- Between group differences in clinical outcomes
- Missing answers within each clinical outcome measure is unlikely as values must be provided to complete the electronic survey
- Non-completion—missing answers/ surveys despite all attempts to contact participant for completion is a feasibility outcome in this trial
- Anonymised raw data obtained from the GENEActiv device in the sub-study are sent to data scientist (Dr Thanasis Tsanas) at the Usher Institute at University of Edinburgh for analysis

9 ADVERSE EVENTS

- It is possible that participants experience emotional distress, or worsening of their anxiety or mood during the TASK trial
- The TASK therapist is also a stroke physician and geriatrician with experience at delivering CBT in neurology patients. Stroke physicians are experienced in handling emotional sensitive topics and anxiety and will act in accordance with clinical needs of situation this may include postponing call for another day or on other occasions it may be appropriate to slightly prolong call in order to provide the required reassurance

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 RISK ASSESSMENT

The Research Governance and QA office (University of Edinburgh) will review the study and determine if an independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to decide (a) if monitoring is required and (b) if so, at what level. An independent risk assessment may also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before, during and.or after the study and if so, at what locations and at what frequency

10.3 STUDY MONITORING AND AUDIT

As 10.2.

There is no data monitoring committee planned for this study

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate PIS (online or paper version) and Informed Consent Form (ICF) (online or paper version) will be provided.

The oral explanation to the participant will be carried out either via video of Chief Investigator on www.task4stroke.org, or in person by the Chief Investigator or qualified delegated person, and covers all the elements specified in the PIS and ICF.

All interested potential participants are encouraged to take time to read through the TASK recruitment website including the electronic PIS before completing the 'Sign up form'. They are encouraged to contact the TASK research team via telephone or email to clarify understanding.

All interested potential participants can take as much time as they need before completing the 'Sign up form'

The online recruitment video, our PIS (electronic and paper) and the ICF emphasize that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The TASK investigator countersigns the electronic ICF or paper ICF. The participant will receive a copy of this document electronically to their email and a paper copy is filed in the Investigator Site File (ISF).

11.2.2 Data Recording

The Chief Investigator is responsible for the quality of the data recorded in the CRF.

11.2.3 Investigator Documentation

- This study is single-site only where all ISFs are stored

11.2.4 GCP Training

All researchers have undertaken GCP training

11.2.5 Confidentiality

All Investigators and the database manager involved with this study comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to

individuals from the research team, system administrators of the REDCap database, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

11.2.6 Data Management & Data Protection

Personal data are only stored in REDCap (Research Electronic Data Capture) hosted by the University of Edinburgh **https://redcap.cir.ed.ac.uk/ .**

Our participants provide us with their personal details, and give us informed consent to use these details to contact them in order to carry out the TASK trial. They provide us these personal details by completing the 'Sign up form' (see Section 7), hosted by the University of Edinburgh.

Web links (URLs) to these REDCap surveys are embedded in our websites and emails we send to participants. By clicking on these web links participants are taken to the secure REDCap surveys hosted by the University of Edinburgh

The websites are hosted by wix.com and there are no databases built within our websites. The only piece of information required by wix to use the treatment websites is the participant's email address and a password we create for the participant. If the participant would prefer not to use their personal email address, the TASK team is happy to recreate a new one to be used just for the TASK trial. No personal data (except email address) are stored on our websites/ wix.com.

We hold all personal data in the REDCap database at the University of Edinburgh; As this is a clinical trial, data cannot be destroyed without sponsor approval. When the system has completed its purpose, and with sponsor's approval all confidential personal information will be permanently destroyed/erased together with all hard or soft copies of the same, only the anonymised dataset will be archived and stored indefinitely due to its of long-term research value.

REDCap
All data collection instruments (including the 'Sign up form', online tasks, and participant surveys) of the TASK trial are created using REDCap (Research Electronic Data Capture). REDCap is run by the Surgical and Perioperative Health Research (SPHeRe), University of Edinburgh under licence from Vanderbilt University. REDCap was developed specifically around HIPAA-Security guidelines. It is hosted within the University of Edinburgh Virtual Machine architecture which is physically secured (for technical information see (http://www.ed.ac.uk/information-services/computing/computing-infrastructure/virtual-hosting/technical) . Linux web servers running apache2/php5 host the application. Web browser communication to the server is SSL-encrypted by default. All other ports are firewall protected. Data is stored in MySQL databases on a separate server. This server is behind a firewall and can only be accessed from the IP address of the web server. An SSL tunnel encrypts communication between the web and databases servers. File upload is secured between servers using the WebDAV protocol with SSL. "At rest" encryption is in place on the database server. Daily back-ups are made of both servers and stored for two weeks prior to being deleted. Operating security updates are installed automatically. Antivirus software runs to a scheduled protocol on the web server. User passwords are managed directly. Accounts are disabled after 5 failed login attempts. Users are auto logged out after 30 mins of no activity. Users are forced to change password after 42 days. Password strength: AT LEAST 9 CHARACTERS IN LENGTH and must consist of AT LEAST one lower-case letter, one upper-case letter, and one number. Daily audit tracking of users is in place with removal of unused user accounts.

Audit trails are kept automatically to monitor any activity or alterations made to the data and any of the data collection instruments.

Physical records of participant data
All physical records are kept in a locked cabinet in a 'keypad'-locked office within the Centre for Clinical Brain Sciences (CCBS) which itself has restricted access to pass holders only. The CCBS is a secure and alarmed building. Paper files are stored for 12 months after the end of the study and will then be destroyed confidentially.

Office best practice: Local policies are operated i.e. nightly clear desk, clear screen, locking of computer, password protection on screen savers, locking of file cabinets.

Audio-recorded data and transcripts

Audio-recording of telephone session using a digital recorder takes place within the CCBS. The digital recorder is stored in a locked cabinet in a 'keypad' locked office within the CCBS.
Audio-recording is sent electronically to an external transcription service without any personal identifiable information. Transcription data will be held no longer than necessary; when the system has completed its purpose all confidential personal information will be permanently destroyed/erased together with all hard or soft copies of the same. Any storage media will be destroyed using contracted University of Edinburgh service. Only anonymised datasets will be archived indefinitely due to their long-term research value.

Anonymised dataset will be retained/stored in perpetuity in the University of Edinburgh by the research team.

Text messages via TASK team mobile phone

Only Record ID is stored with the participant's telephone number in the 'Contacts' of the TASK team mobile phone. When communicating via text messages no additional personal details other than the participant's name are used. All text messages are erased weekly. At the end of the trial the TASK team mobile will be wiped using factory reset and sim card will be physically destroyed

Wearable device-GENEActiv Original

GENEActiv Original device does not carry any personal identifiable information. We record the serial number of each device given to participant to wear during the study. Any data recorded on the device will be lost in the event of the device being lost or stolen. The serial number can only be linked to the participant's identity in our RedCap database.

Data recorded on the device is downloaded and analysed at the Usher Institute at University of Edinburgh

Website analytics (Wix & Googleanalytics) collect aggregate anonymised data

Our TASK websites (www.task4stroke.org; www.tasktreatment2.org; www.tasktreatment3.org) are hosted by wix.com—a commercial cloud-based web development platform for website building. Like most website operators, Wix websites collect non-personally-identifying information of the sort that web browsers and servers typically make available, such as the browser type, language preference, referring site, and the date and time of each visitor's request. These anonymised web usage data are collected by wix.com, and Googleanalytics.

Participant's email as login to our treatment websites

We ask participants to provide only their email address in order to be used as a login for our treatment websites. Our research team can provide an alternative email login if participants do not wish to use their own. No personal data are entered onto the TASK websites. Both treatment websites www.tasktreatment2.org & www.tasktreatment3.org require this email login.

We developed all of our TASK websites using Wix.com, industry's leading cloud-based development platform. All three domains of our websites are purchased from Wix.com and connected to the Wix servers. All three domains have private registration in the WHOIS database.

SSL Certificate

All of the TASK websites (www.task4stroke.org; www.tasktreatment2.org; www.tasktreatment3.org) have a Secure Sockets Layer or SSL certificate. This allows our site visitors to view our sites over an HTTPS connection. It secures the connection between site visitor's browser and the sites.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

12.3 SERIOUS BREACH REQUIREMENTS

If a potential serious breach is identified by the Chief investigator, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.4 STUDY RECORD RETENTION

All paper study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.5 END OF STUDY

The end of study is defined as the last participant's completion of access to the second treatment website. Access to the second treatment website ceases about 10 weeks following primary endpoint.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Access to all TASK treatment websites ceases about 10 weeks following participant's completion of data collection at primary endpoint

12.7 INSURANCE AND INDEMNITY

The Chief investigator and all co-investigators are either employed by the University of Edinburgh and NHS Lothian (honorary contracts). The NHS indemnity scheme will apply where an NHS contract (including honorary contracts) is in place.

The protocol has been designed by the Chief Investigator and co-investigators employed by the University of Edinburgh. The University has insurance in place (which includes no fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

We intend to publish the research findings in peer-review scientific journals within 1 year of the end of the study. A public summary will be available and emailed to our participants.

Ownership of the data arising from this study resides with the study team.

14 REFERENCES

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