Medicines & Healthcare products Regulatory Agency

MHRA

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19/07/2022

Our ref: CI/2022/0033/GB

Dear Dr Kalnad

CLINICAL INVESTIGATION: NO OBJECTION

Manufacturer	: Avegen Ltd
Model Name	: STOP app
Model Number	: Version 1.x (V1.x), where x refers to any possible future updates to the STOP app
Description	: STOP is a mobile app for either android or iOS platforms that delivers standalone Cognitive Bias Modification for Interpretation therapy (CBM-I), using content specifically relevant to paranoia. The app is a 12-week prescription digital therapeutic for individuals with clinically mild to moderate symptoms of paranoia. The app delivers one therapeutic session per week, each session comprising 40 training items and taking approximately 40 minutes to complete. Training items are short written scenarios, illustrated with sound and graphics, that participants read.
Your notification dated	: 25/05/2022
Protocol version number	: v3.1_290622

I hereby notify you that MHRA has no grounds for objection to the making available of the above medical device for the purposes of a clinical investigation as declared in the above notification.

MHRA Comments

Please ensure that you note and understand the requirements set out below for reporting adverse events to MHRA. In addition, please submit summary SAE reports **quarterly.**

- Please provide a short safety and performance report after 20 patients have been treated. MHRA will review the report and respond but no further patients should be treated until a positive response from the MHRA has been received. However, please note that recruitment can continue throughout this period.

- Any favourable opinion given by a research ethics committee (REC) is subject to the condition that the clinical investigation is registered on a publicly accessible database no later than six weeks after recruitment of the first participant.

- Please provide MHRA with your registry reference number for this clinical investigation. If you have not already done so please notify the REC of the registration details as soon as possible. If a deferral of registration has been granted by HRA, please provide details of this.

  Further information on conditions of REC opinion and registries can be found here: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/#clinical

- The device(s) must be labelled "*exclusively for clinical investigations*".

- You are encouraged to consider adding a section in your CIP on how the study will be conducted during a global pandemic/regional epidemic or natural disaster.

Please read carefully and ensure that all requirements listed in the appendix to this letter are understood and adhered to.

Yours sincerely,



Daniel Hill
Regulatory Affairs Advisor (Clinical Investigations)
MHRA Scientific Research and Innovation Division

(on behalf of MHRA)

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Appendix

Before commencing the clinical investigation

You should ensure that you have the following in place before commencing the study in the UK:

- Favourable REC opinion letter (required for all studies)
- Signed contract/agreement with participating NHS organisation(s)
- NHS Permission Letter (for studies conducted at NHS/HSC organisations in Northern Ireland and Scotland)
- HRA and HCRW Approval letter (for studies conducted at NHS organisations in England and Wales)

	Studies conducted in England	Studies conducted in Northern Ireland, Scotland and Wales	Provide to MHRA when available	Keep available for MHRA
Favourable REC opinion letter	x	x	x	
Signed contract/ agreement with participating NHS organisation(s)	x	x		x
NHS Permission Letter		x		x
HRA approval letter	x			x

If not already provided as part of the notification to MHRA, please provide us with a copy of the ethics committee favourable opinion letter as soon as it becomes available. The clinical investigation must not commence at any UK centre until the relevant ethics committee favourable opinion is obtained.

Each individual site in this clinical investigation must have confirmed management permission. NHS organisations in England provide this by confirming that they have the capacity and capability to take part in the study. In Northern Ireland, Scotland and Wales NHS organisations provide a letter of NHS Permission. Non-NHS organisations should confirm their management permission and receive a favourable Site-Specific Assessment from the Research Ethics Committee. Please note that this clinical investigation must not commence in any UK site until you have received the relevant confirmation for that individual site.

In addition, this clinical investigation must not commence in any NHS site in England until it has received HRA Approval.

Full details can be obtained from the Health Research Authority website (http://www.hra.nhs.uk/) or by emailing hra.queries@nhs.net. When seeking advice from the Health Research Authority you should make it clear that the investigation involves a non-UKCA / CE / CE UK NI marked medical device.

Following commencement of this clinical investigation:

Adverse Event Reporting

You are reminded that Regulation 16(10)(a) of the UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended)(UK MDR 2002)and Part II of the UK Medical Devices Regulations 2002, Annex X [as modified by Schedule 2A to the UK Medical Devices Regulations 2002] require you to record fully all adverse events and report all serious adverse events occurring in all participating centres to MHRA.

Such reports should be made to the MHRA (devices) Adverse Incident Centre and should include all serious adverse events, whether initially considered to be device related or not, that have occurred in all participating centres, regardless of global location.

A “serious adverse event” is an adverse event that:

a) led to a death, injury or permanent impairment to a body structure or a body function.
b) led to a serious deterioration in health of the subject, that either resulted in:
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness
c) led to foetal distress, foetal death or a congenital abnormality or birth defect.
NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

NOTE Device deficiencies that might have led to a serious adverse event where a suitable action had not been taken or an intervention had not been made or if circumstances had been less fortunate are handled under the serious adverse event reporting system.

Such adverse events should be reported as soon as possible. When reporting these events please include the total number of patients treated in the UK at the time of reporting.

MEDDEV 2.7/3 provides guidance on the requirements for reporting serious adverse events with timelines and provides a template form to use for this purpose. This document can be downloaded from: http://ec.europa.eu/growth/sectors/medical-devices/guidance/

In the case of a blinded control clinical investigation using a UKCA / CE /CE UK NI marked device as control, all adverse events should be reported to MHRA in line with the requirements above.

Where an un-blinded controlled clinical investigation is being carried out using a UKCA / CE /CE UK NI marked device as the control, adverse events involving the UKCA / CE /CE UK NI marked devices should be reported to MHRA in line with vigilance guidelines.

Please use the MEDDEV 2.7/3 reporting Excel spreadsheet to report serious adverse events. Please email the complete spreadsheet to **aic@mhra.gov.uk** quoting MHRA’s CI reference number or upload through MORE https://aic.mhra.gov.uk/ including the MHRA’s CI reference number in the ‘incident description’ field. **Please ensure that sufficient information is included in the table to allow MHRA to understand what happened in each incident and that all fields are complete.** Failure to do so will result in further requests for additional information on each individual case, therefore please ensure the following:

a. ALL sections are completed in FULL, especially sections where a decision is required as to whether or not the event is device / procedure related.

b. Any deaths reported should have the cause of death recorded.
c. Reports should be made in a timely manner as per regulatory requirements.

Please note that adverse events involving a medicinal product should also be reported to MHRA Medicines by the manufacturer of the medicine or sponsor of the study. Information on the requirements for reporting of such events can be found here https://yellowcard.mhra.gov.uk/

Summary reports

In addition to the reporting of individual serious adverse events as detailed above, please provide summary reports of all serious adverse events. Please refer to the MHRA Comments section at the top of this letter for details of the frequency required.

When providing these summaries please include in tabular format the following information broken down by event type:

- number of serious adverse events
- number of participants affected by those events
- percentage of the total number of enrolled participants affected by those events

Event type	Number of events	Number of participants affected	% of participants affected
e.g. Stroke			
e.g. Heart Failure			

Please also include a summary analysis of the serious events together with the manufacturer's conclusions. Please also ensure the following when submitting a table of adverse events:

- ALL sections are completed in FULL, especially sections where a decision is required as to whether or not the event is device / procedure related.
- Any deaths reported should have the cause of death recorded.
- Reports should be made in a timely manner as per regulatory requirements.
- Incomplete tables will not be assessed and will be returned to you.

Amendments

You must notify MHRA of all proposed changes to this investigation and await our letter of no objection before you implement them. This includes changes relating to the device, study documentation including the clinical investigation plan, investigators or investigating institutions, and changes made upon the request of an ethics committee. Failure to notify us of proposed changes could result in the manufacturer being liable to prosecution.

When notifying changes, please provide the following information:
- the reference number shown at the top of this letter.
- In tabular format - a summary of each proposed change with the rationale and justification for each change.
- red lined and clean copies of all amended study documentation.

- a signed statement by or on behalf of the manufacturer that the proposed change(s) do not predictably increase the risk to the patient, user or third party.

The MHRA retains the right to request a new clinical investigation notification if the amendments are thought to increase the risk to either the patient or the user, or if the MHRA considers that the amendments constitute a new investigation in accordance with Regulation 56(3) (UK MDR 2002).

Where being undertaken, feasibility / pilot studies should be complete before conducting a pivotal study. Increases to the sample size and/or number of centres participating in the study will only be considered with appropriate justification.

If there is a delay in starting the clinical investigation in the UK, before proceeding you should consider whether there have been any technological or clinical advances in the area under investigation which may invalidate the original basis for conducting the investigation.
Where such advances have occurred please provide MHRA with relevant details and either:

- Notice that the clinical investigation will not proceed
- A notification to amend the clinical investigation
- Justification for continuing with the clinical investigation as originally notified

Study deviations

You must notify MHRA of all deviations to the study as soon as you have been made aware of them. Please provide details about the nature of the deviation, when it occurred, where it occurred, and any proposed corrective actions.

Final Report

Under Regulation 16(11) and 29(10) of the UK MDR 2002, you are required to notify MHRA of the end of this clinical investigation. In the case of premature termination, a justification for the premature termination is also required. A letter informing MHRA of when the trial has been completed would be appreciated.

Under Regulation 16(10) and 29(9) of the UK MDR 2002the written report of a completed clinical investigation must be kept available for the Secretary of State if required. MHRA request that a copy of the written report is provided when available.

Note to Sponsor

This letter should be shared with your chosen Notified Body / UK approved body and should be included in the Clinical Evaluation Report submitted as part of your conformity assessment. The Notified Body / UK approved body should be aware of any conditions or comments contained in this letter.

We ask that you notify us when you begin your conformity assessment or when you self-certify (class I) for this device. If there is involvement of a Notified Body / UK approved body, we ask that you inform us which Notified Body / UK approved body has been applied to. On occasion we may need to communicate directly with the Notified Body / UK approved body.

UKCA / CE /CE UK NI Marking

MHRA would be interested to know when the device under investigation is UKCA / CE /CE UK NI marked and would be most grateful for notification of this once completed.

We request that at the same time MHRA are also provided with a summary report of the clinical data from this clinical investigation that was used to support the UKCA / CE /CE UK NI mark.

MHRA actions

The assessors who assisted with the evaluation of your notification will be sent a copy of this decision, for information only and strictly "in confidence". Our decision will also be notified to the relevant ethics committee(s) and HRA if you have confirmed that you are happy for us to do this. If you have not, then you may wish to advise them of this decision yourself.

We will retain all the documentation provided by you for one month from the date of this letter. After this time the documentation (except for one copy, retained for record purposes only) will be destroyed, unless you request its return.