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MANCHESTER 1824

Rapid Evidence Synthesis: Longitudinal Multi-Modal Cognitive Remote Tracking for Neurodegeneration

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Cite as:

Norman, G. (2021). Rapid evidence synthesis: Longitudinal Multi-Modal Cognitive Remote Tracking for Neurodegeneration. NIHR ARC Greater Manchester: University of Manchester

Rapid Evidence Synthesis:

Rapid Evidence Syntheses (RES) are produced by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration Greater Manchester (ARC-GM). The methods used are based on a framework set out in Norman et al. 2022 and previously registered on the Open Science Framework (OSF).[1,2]

RES use evidence synthesis approaches and draw on the GRADE Evidence to Decision framework[3] to provide rapid assessments of the existing evidence and its relevance to specific decision problems. In the first instance they focus on evidence from guidance and existing evidence syntheses. They are undertaken in a real-time context of decision-making around adoption of innovative health technologies and are designed to provide a "good-enough" answer to inform decision problems in a short timescale. RES methods are flexible and adaptive. They have evolved in response to user feedback and differ depending on the nature of the assessment undertaken.

RES are not intended to serve as a substitute for a systematic review or rapid review of evidence.

This RES used some unpublished information supplied in confidence which we do not have permission to publish. Removal of this information did not alter the text; places where this information would have been redacted if necessary are marked in the text.

We welcome feedback and are particularly interested to hear how you have used this Rapid Evidence Synthesis.

Please send any queries or comments to:

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Additional information:

This work was undertaken by the National Institute for Health Research (NIHR) Applied Research Collaboration Greater Manchester (ARC-GM). The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

[1] Norman, G. Rapid evidence synthesis to support health system decision making. *OSF registration.* 2020 [cited 2023]; Available from: osf.io/hsxk5

[2] Norman, G., et al., Rapid Evidence Synthesis To Enable Innovation And Adoption in Health and Social Care. *Systematic Reviews,* 2022. 11: p. 250. https://doi.org/10.1186/s13643-022-02106-z

[3] Alonso-Coello, P., et al., GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ,* 2016. 353: p. i2016.

1. Summary

We did not find any evidence for the impact on health outcomes of being screened, perhaps repeatedly, using this platform. There is some randomised evidence that screening may not change medium-term health outcomes and may have acceptability issues. Neither the UK National Screening Committee nor the United States Preventative Services Taskforce currently recommend screening the general population for dementia or cognitive impairment; the UK recommendation is against such screening. NICE recommendations for interventions to reduce risk of, or delay the onset of, dementia relate to population-level interventions promoting healthy lifestyle.

1.1 Screening using multi-modal cognitive remote tracking platform (effect on health outcomes)

We did not find any evidence for the impact on health outcomes of being screened, perhaps repeatedly, using this platform.

1.2 Screening for cognitive impairment (effect on health outcomes)

There is some randomised evidence from a large US trial that being screened for cognitive impairment using other methods may make no difference to health outcomes at 12 months and may have acceptability concerns. This is likely to be relevant to a UK older age population.

1.3 Screening using multi-modal cognitive remote tracking platform (identification of cognitive impairment)

There is some limited evidence that the methods (tests) supported by the platform may be useful for distinguishing older people with cognitive impairment from older people without impairment. It is not clear that this is directly relevant to repeated use or to people who do not yet have a diagnosis of mild cognitive impairment or early dementia. There is more evidence for the use of non-digital single-use versions of these tests.

1.4 Screening for cognitive impairment (identification of cognitive impairment)

There is more, but limited, evidence that mobile or home-based screening methods may be useful for distinguishing older people with cognitive impairment from older people without impairment. It is not clear that this is directly relevant to people who do not yet have a diagnosis of mild cognitive impairment or early dementia.

The UK National Screening Committee recommends against screening the general population for dementia. This recommendation is made on the basis that there are:

- no screening tests which could find people with dementia before they show symptoms,
- no evidence that current treatments for dementia are effective and
- concern about how people diagnosed by screening may be affected by dementia related screening.

The US Preventative Services Taskforce also states that there is insufficient evidence and that the benefits and harms of screening for mild cognitive impairment cannot be determined.

1.5 Interventions for reducing risk of or delaying cognitive impairment

NICE has issued guidance on mid-life approaches to reduce risk of or delay the onset of disability, dementia and frailty, but these relate to population-level interventions promoting healthy lifestyle.

2. Methods

2.1 Description of the innovation

The innovation is described as a rapid, point-of-care mobile-based health screening and monitoring platform for "brain health" which is intended to be deployed both in clinics and remotely. The intention is stated to be to obtain repeated measures of variables over time. This is designed as a platform to incorporate a suite of measures which are described as neurocognitive, neuromotor and neuropsychological. Supporting documentation indicates that these comprise metrics derived from an immediate and delayed recall test, analogous to those employed as part of the Mini Mental State 2 Examination (MMSE)[1] and a digital clock drawing task which is a digital version of an assessment tool paper-based test [2] which is an FDA Class-II medical device used as a screening test and outcome measure for possible cognitive impairment. Metrics derived from performance on these tasks are used to produce an overall assessment of cognition. It appears to be aimed at older people (unclear but appears to be 65+ years) who do not have a clinical diagnosis related to cognitive impairment (i.e. minor cognitive impairment or dementia). Because the intervention is a screening test it generates multiple key questions related to the impact of implementation as well as test performance

2.2 Key questions

Question 1. What is the effect on clinical outcomes* for older people without diagnosed cognitive impairment of being (repeatedly) assessed using the proposed platform and test battery?

Question 2. What is the predictive value of screening older people without diagnosed cognitive impairment, using the proposed platform and test battery?

Question 3. What is the effect on clinical outcomes* for older people without diagnosed cognitive impairment, of being screened for signs of cognitive impairment?

Question 4. What is the predictive value of screening older people without diagnosed cognitive impairment?

Question 5. What is the evidence for the effectiveness of interventions to support or treat older people identified as having or being at risk of cognitive impairment by a screening tool, or otherwise.

* Cognitive impairment-related measures including diagnosis of dementia, health-related quality of life and outcomes related to mental health such as depression and anxiety.

2.3 Search

We searched the following sources: the websites of the sponsor (Linus Health), the UK National Screening Committee, and NICE; the databases PubMed and the Cochrane Library, which includes the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials. We also searched the website of the Cochrane Dementia and Cognitive Improvement Group.

Searches were conducted between 4th and 10th May 2021. Search terms included: screening OR detection; dementia OR minor cognitive impairment/MCI; terms for specific relevant screening tools (Mini mental state examination (MMSE); clock drawing task (CDT)) and terms for mobile technology.

3. Results

3.1 Impact on clinical outcomes of repeated assessment using the proposed platform/test battery (question 1)

The sponsor (Linus Health) submitted research papers, both published and unpublished – and lists further conference abstracts and published papers on its website – which relate to the digital clockdrawing task (DCTclock). [3-6] This task is a digital version of a paper-based test [2] which is an FDA Class-II medical device used as a screening test and outcome measure for possible cognitive impairment. It has been widely used in this form. Another paper assesses use of mobile technology for the repeated assessment of cognitive decline.[7] None of the studies appeared to assess the impact on clinical outcomes of the testing process. We did not identify further studies assessing this. ***One of these studies [5] is represented in an unpublished abstract which we do not have permission to publish. However the text is not redacted because the summary given here accurately reflects the information in the public domain.*** We consider the impact of screening for dementia or cognitive impairment more generally in (3) below.

3.2 Predictive value of screening using the proposed platform/test battery (question 2)

As noted for (1) above the submission referenced studies of a digital clock-drawing task (DCTclock).[3-6] The studies reported look at the relationship between Alzheimer's disease-related biomarkers (beta-amyloid, tau protein) on brain imaging, and cortical thinning, where evidence for an association with disease process is more established in Alzheimer's disease than in other forms of dementia. They also consider the ability of the test to differentiate between people with and without a diagnosis of either mild cognitive impairment or early Alzheimer's disease (considered as a group).[6] The relationship between test results and biomarkers is indirectly relevant to the relationship between test results and meeting diagnostic criteria for a disease. Similarly the ability of a test to discriminate between people with and without a clinical diagnosis is also indirectly relevant to the ability to identify people who do not yet have a diagnosis but who may meet diagnostic criteria in the future.

Alzheimer's disease is the most common form of dementia, but there are many other causes. Dementias with different aetiologies may show different clinical progression; subclinical early signs may also differ. Any evidence for an association between a particular screening test and markers for Alzheimer's disease may therefore be only indirectly relevant to any non-Alzheimer's cognitive impairment, while studies undertaken using participants with Alzheimer's disease may not be directly relevant to the general population where participants with undiagnosed impairment may have a variety of aetiologies. The relationship between mild cognitive impairment and dementia is also unclear and detection of mild cognitive impairment with a diagnostic test at one timepoint may have limited prognostic value for subsequent dementia diagnosis.[8, 9]

The company submission also referred to a number of other studies which looked at the properties of mobile psychometric/neuropsychological assessment tools in younger populations, including military personnel, and also studies which looked at the relationship of spoken language characteristics (and assessment of these) to markers of dementia such as amyloid concentrations or status of having or not having a diagnosis of dementia or impairment. Other studies looked at

exposure to risk factors for a future diagnosis of dementia or the presence of an active episode of migraine. The findings of these studies generally showed that there were correlations between the variables assessed and the reference marker. The relevance of many of these studies to screening the population of older adults is very unclear and there are methodological issues with these studies. There are known issues with publication bias in this field; small studies with positive results are published more often than those without and significant associations may be prioritised.[10]

The company submission included a study of 60 elderly people in France assessed five times daily for a week using monitoring of multiple facets of behaviours and compared the results to those of traditional neuropsychological tests and imaging.[7] We identified several relevant systematic reviews for these approaches to cognitive impairment.[11-14]

One of these was a scoping review.[11] One included a literature search and some systematic methods.[12] This identified only four studies in older adults, one of which is that submitted here.[7] The others were small cohort studies which reported that computer-based methods could discriminate between healthy older people and those with either diagnosed MCI or early dementia. No formal quality assessment was undertaken but the review noted the heterogeneity and small 4 sample sizes of the included studies. These studies do not assess the identification of people who do not yet have a diagnosis.

A 2017 systematic review of mobile cognitive assessment found 12 small to medium-size studies, mostly in healthy adults with a wide range in age.[13] It also included the study submitted by the sponsors.[7] The studies were short duration and most had a focus on assessing the psychometric validity of the process and tools. This review had some reporting limitations, but the main issue is that the evidence presented is non-clinical and indirectly relevant to the validity of use of these technologies in older adults to screen for a major health condition.

A final review looked at electronic devices for assessing cognitive impairment in older people. [14] This included many more studies, the great majority of which were computer (desktop or laptop) based and were not designed to be administered at home. This makes the findings of this generally reliable review only indirectly relevant to the question addressed here.

3.3 Impact on clinical outcomes of screening using tools designed to assess cognitive impairment (question 3)

We identified guideline recommendations from the UK and also the United States. Although there are multiple extant reviews, including a suite of Cochrane reviews, (e.g. Creavin et al)[15] we have cited only reviews used to inform the guidelines. Because we identified current guidelines we have not provided an assessment of the certainty of the evidence, but have briefly summarised the recommendations and, where appropriate, evidence which contributed to these.

The UK National Screening Committee (NSC) continues to recommend against screening of the general population for dementia.[16,17) Its last update was completed in April 2019, based on the original evidence report from 2014.[17] This evidence report is informed by the US Preventative Services Task Force from 2013 which reviewed the evidence for screening for cognitive impairment.[18] This review has subsequently been updated (2020) but the conclusions remain unchanged.[19] The UK evidence review is an expanded review of an evaluation of screening for Alzheimer's (2010) to encompass all classes of dementia. Although this evidence review was

undertaken in 2014 the NSC did not find evidence to cause it to change its recommendations in 2019; this recommendation is not due to be updated until 2022/3. They state that their recommendation is made for the following reasons:

- There are no screening tests which could find people with dementia before they show symptoms.
- There is no evidence that current treatments for dementia are effective.
- There is concern about how people diagnosed by screening may be affected by dementia related screening.

The recommendations are based on the following evidence:

- Systematic review of test accuracy of available instruments against gold standard of clinical diagnosis of either dementia or mild cognitive impairment.[18]
- Systematic review of attitudes and preferences towards screening for dementia.[20]
- Multiple systematic reviews of both pharmacological and non-pharmacological treatments designed to prevent or slow (either permanently or temporarily) cognitive decline; systematic reviews of non-pharmacological interventions for carers or families (multiple references; see the evidence report).[17]

The updated US Preventative Services Task Force report considered the evidence base insufficient to assess benefits and harms of screening for Cognitive impairment. This was based on an updated evidence report and systematic review in 2019.[21,22]

This review identified a trial of 4000 older participants (mean age 74 years) that assessed the effect of primary care screening for cognitive impairment on health-related quality of life (HRQoL), health care utilisation, and measures of advance care planning. [23] The well-designed trial found no differences in these outcomes at 12 months. 38% of eligible participants refused to participate and 66% of those who did participate and screened positive refused diagnostic assessment and followup. Both these refusal rates are limits on the certainty of the evidence from the trial; they also may be indicators of the acceptability of screening and potential impacts of a positive screen for the people identified. The authors identify the need for longer term follow-up and economic evaluation. Although the trial was conducted in the US, the older age of the population means that concerns about access to healthcare may not reduce its relevance to the UK, due to the impact of Medicare coverage.

3.4 Predictive value of screening using tools designed to assess cognitive impairment (question 4)

Current UK and US guidelines found that their evidence reviews did not evidence that screening would enable the identification of people with dementia before they show symptoms.[16,19] The reviews conducted included studies of the MMSE for screening (this was the most commonly assessed tool) and also the clock drawing test.

3.5 Effectiveness of interventions to support people identified as having cognitive impairment (question 5)

The company submission refers to appropriate early behavioural interventions. Current UK and US guidelines found that their evidence reviews did not identify evidence that screening would enable effective treatment of people identified by the process as having dementia or mild cognitive impairment.[16,19] The reviews conducted identified very large numbers of studies of different types of treatments for dementia, including both pharmaceutical (e.g. cholinesterase inhibitors or memantine) and non-pharmaceutical interventions.

NICE has issued a guideline which makes recommendations for promoting a healthy lifestyle in order to delay the onset of disability, dementia and frailty.[24] This recommends the development and support of population-level initiatives to make it easier for people to stop smoking, be more physically active, reduce alcohol consumption, adopt a healthy diet and achieve or maintain a healthy weight. It further recommends the use of local regulatory and legal powers to encourage these. This is supported by three evidence reviews.

Importantly, these are population level recommendations; the guideline does not address the targeting of interventions for healthy behaviour at individual people identified as at risk. The guideline also looks at behaviours in people in midlife rather than at those who are older.[24]

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Produced by the NIHR Applied Research Collaboration Greater Manchester
May 2021.

The information in this report is correct at the time of printing.