Correspondence

Feedback - November 30 2020

To the attention of
Prof. Karla Soares-Weiser (ksoares-weiser@cochrane.org)
Editor-in-chief of the Cochrane Library

Dear Professor Soares-Weiser,

We are writing to you out of the great respect that we hold for the Cochrane. We refer with concern to the recent publication of numerous reviews by the Cochrane Dementia and Cognitive Improvement Group (often authored by its editors), which we believe are misleading. Several of these reviews promote the idea that the use of generic scales/questionnaires can lead to the differential diagnosis of dementia, and allow a precise etiological diagnosis, for instance of Alzheimer's Disease (see examples in the attached list). We are convinced that this is wrong and not evidence-based, as these short severity scales cannot distinguish among different causes of dementia (see e.g. an editorial highlighting this issue). These scales measure severity across a wide range of different diseases. There is a huge difference between 'dementia', which is a syndrome encompassing a great number of diseases, and a specific condition, such as Alzheimer's disease, which expresses itself with a specific phenotype that has been precisely defined in recent years. The diagnosis of neurodegenerative disorders is now clinical-biological, relying on the evidence of specific clinical phenotypes (which differ from one disease to another, because they reflect different underlying pathologies).

The Cochrane reviews therefore, attributing (sometimes mainly in their titles), specific diagnostic effectiveness to severity scales, are theoretically specious and may have a negative clinical impact. As a general point, even if the methods are sound, we fail to appreciate the need to review the validity of single cognitive tests that would validate the existence or not of phenotypes for which the community no longer has any interest.

Given the eminence of the Cochrane, this long series of reviews is moving the field backwards. We feel that this potentially harmful message cannot go unchallenged but before taking any action, we would like to hear your views on the matter.

We are grateful for your attention. Kind regards.
Yours truly,

(in alphabetical order)

- Hélène Amieva, Professor, Director "Psychoépidémiologie du vieillissement et des maladies chroniques", Bordeaux, France
- Paulo HF Bertolucci, Behavioral Neurologist, Sao Paulo, Brazil
- Andrea Brioschi Guevara, Psychologist, Centre Leenaards de la mémoire, Lausanne, Swtzerland
- Sonia M. Dozzi Brucki, Neurologist, Coordinator of Cognitive and Behavioral Unit, Sao Paulo, Brazil
- Stefano Cappa, Professor of Neurology, Head of Dementia Clinical Research, Pavia, Italy
- Mathieu Ceccaldi, Professor of Neurology, Marseille, France
- Jeffrey Cummings, Professor of Brain Science, Director of Chambers-Grundy Center for Transformative Neuroscience, Las Vegas, USA
- Nilton Custodio, Neurologist, Instituto Peruano de Neurociencias, Lima, Peru
- Myriam De la Cruz Puebla, Neurologist, Global Brain Health Institute, San Francisco, USA
- Sergio Della Sala, Professor of Human Cognitive Neuroscience, Edinburgh, UK

- Jean-Francois Démonet, Professor, Head of Department of Clinical Neurosciences, Lausanne, Switzerland
- Bruno Dubois, Professor, Director of the Behavioural Neurology Department and of the Dementia Research Center at Salpétrière, Paris, France
- Lissette Duque Peñailillo, Neurologist, Cognitive Disorders Unit, Quito – Ecuador
- Giovanni B. Frisoni, Professor, Hôpitaux Universitaires de Genève, Geneva, Switzerland.
- Christian González-Billault, Professor, Director Geroscience Center for Brain Health and Metabolism, Santiago, Chile
- Agustin Ibanez, Director Cognitive Neuroscience Center, Buenos Aires, Argentina
- Daniel Jiménez F., Assistant Professor, Departamento de Ciencias Neurológicas Oriente, Santiago, Chile
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- Pierre Krolak-Salmon, Professor, Fédération des Centres Mémoire, Lyon, France
- Robin Morris, Emeritus Professor of Neuropsychology, King's College Institute of Psychiatry, Psychology and Neuroscience, London, UK
- Olivier Piguet, Professor of Clinical Neuropsychology, Director, FRONTIER Frontotemporal Dementia Research Group, The University of Sydney, Australia
- Maritza Pintado Caipa, Neurologist, Global Brain Health Institute, San Francisco, USA
- Tomás León Rodríguez, Psychiatrist, Atlantic Fellow for Equity in Brain Health, Institute of Neuroscience, Dublin, Ireland
- Olivier Rouaud, Neurologist, Centre Leenaards de la mémoire, Lausanne, Switzerland
- Philip Scheltens, Professor, CEO Alzheimer Center Amsterdam, The Netherlands
- Andrea Slachevsky, Memory and Neuropsychiatric Clinic, Santiago, Chile.
- Antonio L. Yaakov Stern, Professor, Chief Cognitive Neuroscience Division, New York, USA
- Antonio L. Teixeira, Professor of Psychiatry and Neurology, Houston, USA
- Nicolas Villain, Neurologist, Cognitive and Behavioural Neurology, Paris, France

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CDCIG Response - 25 January 2021

We thank the authors for their detailed feedback on our portfolio of test accuracy systematic reviews. In the Cochrane Dementia group, our core values are transparency and encouraging critical debate. So, we welcome the helpful comments received and the opportunity to respond. Some of the authors' comments are valid and result from issues with terminology within the evidence synthesis field. Others reflect a difference of opinion in a field where there are no absolutes. The issues raised are not new, from inception our test accuracy reviews have attracted criticism from some dementia research groups while other research groups have strongly supported our work. Our Cochrane group, like all Cochrane groups, are guided by the available data and we strive to produce evidence synthesis that is free from bias, conflict of interest or personal opinion.

Our starting point is that our test accuracy reviews, like Cochrane reviews in general, are intended to inform clinical practice. The authors state in their letter and editorial that there is no need for reviews of cognitive tests. However, short cognitive tests or informant questionnaires are used at multiple points in the clinical pathways that lead to a diagnosis of dementia. The authors state that '*These scales measure severity*'. While the assessments are used to quantify progression of cognitive decline in research, in clinical practice the use of these tools is more varied. Some are used almost exclusively for opportunistic screening or to inform referral decisions from primary care. Others have wider use in multiple settings, including primary and general secondary care, or as part of a specialist secondary care diagnostic work-up. The motivation for many of our test accuracy reviews comes from requests from the clinical community and our DTA reviews have informed clinical guidelines and policy. For example, we worked in partnership with the UK guideline body NICE in their recent dementia assessment guidelines as they recognised the importance of screening

tools in clinical practice. Our test accuracy reviews consistently rank amongst our most cited and most accessed content. While we accept that the screening tools are blunt instruments and are unlikely to be used in highly specialist research centres, it would be wrong to claim that these reviews have no value in practice.

The authors state that *'..the diagnosis of neurodegenerative disorders is now clinical-biological, relying on the evidence of specific clinical phenotypes*..'. We are aware of the changing landscape in the dementia research field and the move towards pathological diagnoses based on imaging and tissue biomarkers. These are exciting developments and will improve diagnostics, but even specialist societies like the National Institute on Aging agree these technologies are still primarily a research tool and not yet ready for application at scale in clinical practice. In Cochrane we take a global view of healthcare and must be cognisant of the fact that precision dementia phenotyping is simply not an option for most international healthcare systems. Thus, we challenge the authors' claim that the clinical phenotype of dementia is no longer of any interest to "*the community*". On the contrary, we know from prioritisation work with multiple stakeholders, that the clinical dementia diagnosis is exactly what interests people living with dementia, their families and the many healthcare workers at the coalface of older adult care. People facing cognitive problems are interested above all in function - their ability to maintain daily activities and retain independence. This crucial factor is captured in the dementia label. More detailed dementia subtyping, or identification of the clinical-biological phenotype, is of secondary importance in clinical practice, having only a relatively minor effect on management and outcomes in current practice.

The authors correctly state that short screening tests should not be used to make a dementia subtype formulation. We agree with the authors that short cognitive tests are not diagnostic of dementia. The gold standard diagnosis of dementia remains multidisciplinary clinical assessment, informed by history, examination, neuroimaging, laboratory tests and neuropsychological assessment as needed. Our group have authored editorials, educational materials and commentaries all emphasising the distinction between screening and diagnosis. It is our editorial policy that test accuracy reviews include a detailed description of the use of a test in the clinical diagnostic pathway. We have reviewed the fourteen Cochrane Dementia titles that the authors suggest are problematic. Some of these were methods papers or prognosis reviews and not relevant to diagnosis. Of the test accuracy reviews, no review suggests that any of the short tests included may be used alone to make a diagnosis of dementia. In our test accuracy reviews we mandate that authors include explanatory text on this important point, so that readers of the review are clear that these tests are not diagnostic.

It is possible that the authors' view was shaped by the wording of the titles of our reviews, and we agree that there is some potential for misunderstanding the scope of the reviews when looking at the titles alone. In evidence synthesis reviews, the terminology preferred and recommended by the Cochrane Diagnostic Test Accuracy Methods Group is 'diagnostic test accuracy'. In keeping with Cochrane policy, and for consistency with other reviews, when we began formulating a suite of reviews, we were advised to use the term 'diagnostic' in our titles. For some of our older titles we used the title format 'test xx for diagnosis of Alzheimer's disease and other dementias'. The paradigm that underlies the studies included in these reviews is the comparison of an index test (in this case, the cognitive test) with a reference standard (in this case clinical diagnosis of dementia). This does not imply that the tests are used for diagnosis, rather comparison with clinical diagnosis allows an anchoring point for quantification of test properties. We hoped that our author teams had made the clinical purpose of the tests clear throughout the reviews, but we accept that when viewed in isolation, the titles could suggest a different scope. This applies just as much to our test accuracy reviews of tissue biomarkers and neuroimaging as it does to our reviews of brief cognitive tests. We acknowledge that the title of a review may be the only part of a review that a busy clinician may read.

We also acknowledge that some of the review titles may be misconstrued as suggesting that a short cognitive test can be used to make a dementia subtype diagnosis. Again, this misunderstanding may stem from the standard descriptive text that our author teams were advised to use in the relevant review titles.

No review in the Cochrane portfolio claims that any of these short tests can be used to determine dementia aetiology, but we agree that the titles may not make this sufficiently clear. In particular, our earlier test accuracy review titles refer to detection of *Alzheimer's disease and other dementias*. The reason for this formulation is that many research studies have used Alzheimer's disease dementia (diagnosed using contemporaneous clinical criteria) as their target condition. In formulating our titles, we wanted to demonstrate that we were including all dementia subtypes, of which Alzheimer's disease is the most commonly included in the primary research. We were concerned that if the review title referred to detection of dementia only, this may be interpreted as only including studies where the reference standard was undifferentiated dementia. We regret if this gives the impression that the index tests in question could be used to distinguish between dementia subtypes and indeed in many of our later reviews we have chosen to refer only to dementia in the review titles and then elaborate on the eligible reference standards within the review text.

We are mindful that the field of dementia, perhaps more than other fields, is characterised by strongly held and sometimes conflicting opinions. We believe that debate and critique is healthy and would encourage and support people who are passionate about dementia to voice their opinions, even if they differ from our own clinical and person-centred approach. However, we were disappointed with the negative language used in the authors' letter and editorial, describing Cochrane Dementia with terms such as 'spurious', 'misleading' and 'moving the field backward'. We were surprised that the authors describe our output as 'not evidence based'. We would pride ourselves on being completely evidence based in all our activity. We had not been aware that some of the authors on the letter had published editorial content directly criticising Cochrane Dementia and our reviews. It is regrettable that materials have been published with no correspondence with our group and no opportunity for right to reply. It does not seem fair to the authors of our reviews that their efforts have been openly criticised in the public domain without their knowledge.

We are grateful to the group for bringing these issues to our attention. We have taken the comments seriously and discussed within our core editorial group, broader international editorial board and with the senior management team at Cochrane. In view of the feedback received our discussions with all the relevant stakeholders and in keeping with our complaints policy, we have agreed to make the following changes in order to clarify the scope of the reviews:

- We will update the titles of our reviews of screening tests that use the descriptor "diagnosis", changing to the descriptor "detection". (Full list of original titles and modifications as appendix)

- We will update the titles of our reviews of screening tests that use the descriptor "Alzheimer's disease and other dementias", changing to the descriptor "dementia". (Full list of original titles and modifications as appendix)

- In the spirit of transparency and encouraging reflection we suggest that the authors' letter and our response are published and signposted on the Cochrane website and would be grateful if you could let us know whether you would be comfortable for the letter of complaint including all the signatories and this response letter to be published.

- We will contact all authors of our cognitive test accuracy reviews and share the contents of the editorial, letter of complaint and this response. (Details of the distribution included as appendix to the letter)

- In Cochrane Dementia we are always keen to represent the entirety of the dementia community, in this regard, if any of the letter authors would be interested in joining our editorial board we would be happy to hear from them.

Sincerely

Terry Quinn
Joint Co-ordinating Editor
Cochrane Dementia and Cognitive Improvement Group

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Further feedback - 13 February 2021

To the attention of
Dr Terry Quinn - Joint Co-ordinating Editor, Cochrane Dementia and Cognitive Improvement Group
Dr Jenny McCleery - Joint Coordinating Editor, Cochrane Dementia and Cognitive Improvement Group
Cc. Dr Robert Boyle Senior Editor Mental Health and Neuroscience Network, Cochrane

Dear Dr Quinn, Dear Dr McCleery,
Thank you for considering our concerns. We are satisfied that you acknowledge that some of the titles of the reviews in your portfolio were misconstrued and that you will change them. We also appreciate the proposed transparency and agree that our letter and your response be published on the Cochrane website. Indeed, we will like to circulate the documents more widely, sending them to national and international dementia and Alzheimer's disease associations as well as relevant learned societies. We believe, however, that your response is misrepresenting some of our points, and we agree to publish the documents only if accompanied by this joiner, which rectifies the misstatements. We trust that you will consider this acceptable.

You write: "The authors state in their letter and editorial that there is no need for reviews of cognitive tests." Instead, we objected to reviewing the validity of single screening tests aimed at diagnosing specific phenotypes, such as Alzheimer's disease, as this implies that a single test could detect clinical phenotypes. Similarly, we never claimed that the clinical phenotypes of dementia are of no interest per se. We maintain that the use of single screening tests attempting to detect specific phenotypes has no validity, is of no interest and should not be proposed (or reviewed) to such end.
You state that "… it would be wrong to claim that these reviews have no value in practice." Nowhere had we denied the clinical value of reviewing the literature on screening instruments or severity scales. We object to the implicit support of these reviews to the use of these tests as diagnostic tools for specific dementias. In other words, we argue against the use of tests like the MMSE, Mini-Cog or the MoCA for the detection of Alzheimer's disease or any other specific dementia.

You agree that short screening tests are not diagnostic of dementia, but maintain that the misunderstanding comes from the titles only, as no review implies that any of the short tests included may be used alone to make a diagnosis of dementia. However, this contrasts with the aims of several of these reviews and several statements therein. For example, in one review, the objective was "to determine the diagnostic accuracy of the Mini-Cog for diagnosing Alzheimer's disease dementia"; in another the primary objective was "to determine the diagnostic accuracy of the Mini-Cog for detecting Alzheimer's disease"; or again, in another the aim was "to evaluate the strength of evidence for the accuracy of the MMSE for diagnosing Alzheimer's disease". Indeed, the implications for future research in one review invites to find "the optimum threshold of the MoCA for the diagnosis of dementia and its sub-types". Perhaps, you would like to rectify these statements, as well as the titles.

Thanks again for your detailed response, which progresses in acknowledging that severity scales and screening tests should not be considered diagnostic tools for dementia phenotypes.

Sincerely,

(in alphabetical order)

- Hélène Amieva, Professor, Director "Psychoépidémiologie du vieillissement et des maladies chroniques", Bordeaux, France
- Paulo HF Bertolucci, Behavioral Neurologist, Sao Paulo, Brazil
- Andrea Brioschi Guevara, Psychologist, Centre Leenaards de la mémoire, Lausanne, Swtzerland
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- Agustin Ibanez, Director Cognitive Neuroscience Center, Buenos Aires, Argentina
- Daniel Jiménez F., Assistant Professor, Departamento de Ciencias Neurológicas Oriente, Santiago, Chile
- Silvia Kochen, Director Neurosciences and Complex Systems Unit, Buenos Aires, Argentina
- Pierre Krolak-Salmon, Professor, Fédération des Centres Mémoire, Lyon, France
- Robin Morris, Emeritus Professor of Neuropsychology, King's College Institute of Psychiatry, Psychology and Neuroscience, London, UK
- Olivier Piguet, Professor of Clinical Neuropsychology, Director FRONTIER Frontotemporal Dementia Research Group, Sydney, Australia
- Maritza Pintado Caipa, Neurologist, Global Brain Health Institute, San Francisco, USA
- Tomás León Rodríguez, Psychiatrist, Atlantic Fellow for Equity in Brain Health, Institute of Neuroscience, Dublin, Ireland
- Olivier Rouaud, Neurologist, Centre Leenaards de la mémoire, Lausanne, Switzerland
- Philip Scheltens, Professor, CEO Alzheimer Center Amsterdam, The Netherland
- Andrea Slachevsky, Memory and Neuropsychiatric Clinic, Santiago, Chile.
- Antonio L. Yaakov Stern, Professor, Chief Cognitive Neuroscience Division, New York, USA
- Antonio L. Teixeira, Professor of Psychiatry and Neurology, Houston, USA
- Nicolas Villain, Neurologist, Cognitive and Behavioural Neurology, Paris, France

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CDCIG response - 18 February 2021

Dear Professor Cappa and colleagues
Thank you for your further communication regarding our test accuracy reviews.
We apologise if we misinterpreted your original letter; thank you for the clarification. We are pleased that your expert group and our Cochrane group agree on key points regarding cognitive screening tests, namely that short screening tests have utility in practice and research, and that reviews of the accuracy of these tests have value, but that a screening test in isolation is not sufficient to phenotype a specific dementia

syndrome, nor indeed to make a general dementia diagnosis. Throughout our test accuracy reviews we discuss this important point.
We agree that when taken out of context of the complete review, the wording of some of our titles may suggest that authors were reviewing the accuracy of screening tests for diagnosis of specific dementia types. As we discussed in our previous response, this is an issue of semantics and highlights the differences in terminology between the test accuracy and dementia research community. Titles that refer to 'Alzheimer's disease and other dementias' use the phrase as an umbrella term for undifferentiated dementia, recognising that in a particular healthcare setting Alzheimer's dementia is likely to be the predominant pathology.
The same argument applies to review objectives as the statement of the objectives of a Cochrane review repeats, in slightly expanded form, the wording of the title. Cochrane reviews are dynamic and updated as new evidence becomes available. We reached out to the authors of the reviews you mentioned and they are happy for the reviews to be updated. Taking on board your useful comments we will ensure that the updated objective text makes it clear that we are not proposing screening tests as diagnostic instruments.
It is heartening that through this correspondence we have found that we agree on the fundamental concepts around dementia assessment. We will post all the correspondence, including these final comments, on our Review Group website and we are happy that the complete correspondence be shared with any interested stakeholders.
Sincerely
Terry Quinn

Joint Co-ordinating Editor

Jenny McCleery
Joint Coordinating Editor

Cochrane Dementia and Cognitive Improvement Group
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Acceptance of response - 20 February 2021

From: Stefano Cappa <stefano.cappa@iusspavia.it>
Sent: 20 February 2021 17:04
To: Sue Marcus <sue.marcus@rdm.ox.ac.uk>
Subject: Re: Response to rejoinder - CDCIG DTA reviews

thank you very much!
Stefano

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