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<table>
<thead>
<tr>
<th>Rounds</th>
<th>Number of Participants</th>
<th>Clinical</th>
<th>Non-clinical</th>
<th>Continent</th>
<th>Area of interest</th>
<th>Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>153</td>
<td>109 (71%)</td>
<td>44 (29%)</td>
<td>Africa 1%; Australia 1%; Asia 9%; Europe 62%; North America 23%; South America 4%</td>
<td>Clinical trials 12% Diagnostics 35% Epidemiology 12% Rehabilitation 12% R&amp;D 29%</td>
<td></td>
</tr>
<tr>
<td>R2</td>
<td>119</td>
<td>89 (75%)</td>
<td>30 (25%)</td>
<td>Africa 2%; Australia 2%; Asia 13%; Europe 59%; North America 17%; South America 7%</td>
<td>Clinical trials 9% Diagnostics 42% Epidemiology 18% Rehabilitation 10% R&amp;D 21%</td>
<td>81 (68%)</td>
</tr>
<tr>
<td>R3</td>
<td>119</td>
<td>90 (76%)</td>
<td>29 (24%)</td>
<td>Africa 2%; Australia 1%; Asia 10%; Europe 63%; North America 18%; South America 6%</td>
<td>Clinical trials 12% Diagnostics 39% Epidemiology 17% Rehabilitation 9% R&amp;D 23%</td>
<td>100 (84%)</td>
</tr>
<tr>
<td>R4</td>
<td>115</td>
<td>85 (74%)</td>
<td>30 (26%)</td>
<td>Africa 2%; Australia 0%; Asia 8%; Europe 65%; North America 18%; South America 7%</td>
<td>Clinical trials 14% Diagnostics 40% Epidemiology 19% Rehabilitation 6% R&amp;D 21%</td>
<td>100 (87%)</td>
</tr>
<tr>
<td>R5</td>
<td>98</td>
<td>65 (66%)</td>
<td>33 (34%)</td>
<td>Africa 1%; Australia 0%; Asia 8%; Europe 62%; North America 24%; South America 5%</td>
<td>Clinical trials 9% Diagnostics 35% Epidemiology 21% Rehabilitation 9% R&amp;D 26%</td>
<td>84 (86%)</td>
</tr>
<tr>
<td>R6</td>
<td>125</td>
<td>87 (70%)</td>
<td>38 (30%)</td>
<td>Africa 2%; Australia 1%; Asia 8%; Europe 66%; North America 17%; South America 6%</td>
<td>Clinical trials 9% Diagnostics 44% Epidemiology 17% Rehabilitation 7% R&amp;D 23%</td>
<td>116 (93%)</td>
</tr>
</tbody>
</table>

Supplementary Table 1: Participants in each Delphi round. Surveys were answered anonymously. The data presented is from participant selection of the provided ‘login’ options for each survey; whether their work is predominantly clinical or non-clinical, in which continent they reside, and selected area of interest from the five provided
options. As part of the login participants also provided a memorable date and first initial. Participant overlap between rounds has been estimated from the login data and may therefore be higher due to possible login selection variance from the same participant.
Supplementary Figure 1: Authors professions and affiliations. Data taken from the invitation survey prior to the Delphi surveys. Note that more than one profession could be selected or provided per respondent (for example one respondent selected; neuropathologist, cell biologist and biochemist). Authors selected/provided one affiliation. Data shown as percentage of the number of authors (n=153).
First preference (N)

- VCI - O'Brien et al., 2003: 64
- VCI subtypes - Zhao et al., 2010: 12
- VCI - Hachinski & Bowler 1993: 8
- VCI-ND subtypes - Cao et al., 2010: 5
- VCD - Roman et al., 2004: 4
- VCI-ND - Rockwood et al., 2000: 4
- Subcortical VaD - Erkinjuntti et al., 2000: 4
- Mixed Dementia - Rockwood et al., 2000: 3
- IVD - Chui et al., 1992: 2
- VaD - Roman et al., 1993: 1
- VCD - Sachdev et al., 1999: 0
- VaD Subtypes - Kalaria et al., 2004: 0
Supplementary Figure 2: Delphi round 2 first preference vote for which paper could form the basis of a more widely accepted model of VCI conceptualisation.

Supplementary text 1: A summary of the aims and topics addressed in each VICCCS Delphi round

Round 1: The aim was to gather baseline data of views; firstly, regarding perceptions of the different ways of conceptualising vascular impairment of cognition and subsequently about the operational diagnostic criteria (e.g. ICD-10, DSM) currently available. Participants were specifically asked not to read up on all the options provided as the aim was initially to survey current use and familiarity.

Round 2: Summary responses from Round 1 regarding perceptions of the different ways of conceptualising vascular impairment of cognition and the operational diagnostic criteria (e.g. ICD-10, DSM) currently available were presented. The aim of this round was to gather opinions on these results and also delve deeper on some of the issues the current data presented, including a critique of the usefulness of the criteria. Participants were then asked to familiarise themselves with all papers (where relevant) and vote for which concepts could act as foundations for a more widely accepted future concept, which would be developed in the remainder of the study.

Round 3: The focus was to develop a consensus conceptual framework of vascular cognitive impairment (VCI). The results from the Round 2 vote on which existing concepts to develop and the areas of improvement necessary to enable this were fed back. Views were sought on proposed guiding principles for this revised concept, as well as opinion on the scope and certain terminologies to be taken forward.

Round 4: Results from Round 3 were presented. In some areas there were high levels of agreement but there were also some areas highlighted by respondents that were necessary to be revisited in Round 4 in order to try to come to a greater level of consensus. Areas discussed included: guiding principles of the revised concept; scope; terminology and subtypes.
Round 5: The excellent progress made in Round 4 in which consensus guiding principles for the revised VCI concept and some terminologies were agreed were reported. As the penultimate round, the intention of Round 5 was to resolve remaining issues using a cut-off percentage to mark the consensus view of our participants and anything failing below this was not taken forward. Issues regarded certain terminologies, subtypes and the scope of the revised concept.

Round 6: A short final round of the study intended to attain greater level of consensus on outstanding issues including; “stand alone” subtypes and a definition for post-stroke dementia and "mixed dementia".
Supplementary text 2: Further detail of discussions regarding further sub-typing of mild forms of VCI

Subtyping of Mild forms of VCI was addressed in rounds 3-6. We initially asked participants to state whether or not there should be subtypes of the mild form of VCI. There was almost a three-fold preference in favour of having subtypes (68%) over not having subtypes (26%). 68% of respondents remained in favour of sub-classifying mild VCI into one of two options, each that involved a choice of 4 subtypes of mild VCI. The next most preferred option, sub-classified into two sub-types, was only supported by 11% of respondents showing that 4 sub-types was the clear preference. There was less clarity on preferences from the two options that allowed categorisation of mild VCI into 4 sub-types:

(A) A separation based on amnestic/non-amnestic characteristics combined with the breadth of domains: (I) isolated memory impairment, (II) multiple cognitive domain impairment (including memory and one or more of language, executive function), AND 2 Non-amnestic; (III) single non-memory domain impairment (language, executive function) or (IV) multiple non-memory domain impairment

or

(B) A separation based on executive/non-executive characteristics combined with the breadth of domains affected (i.e. executive function the focus instead of memory to encapsulate the broader aspects of VCI). These were proposed to include (i) single domain executive function, (ii) multiple domain executive function, (iii) non-executive function single domain, or (iv) non-executive function multiple domains.

There was no overall majority (i.e. not ≥67%) support for either of the 4 sub-type options. Subsequently, respondents were asked to indicate support for various proposed reasons for their chosen preference to gain insights on what aspects appeared to impede the reaching of a consensus. A near consensus 66% acknowledged and saw benefit in the amnestic/non-amnestic separation option as it allowed better alignment to sub-typing formats that are applied by
some researchers to mild cognitive impairment (MCI) as a precursor to more severe forms of impairment. However this was closely followed by 52% of respondents suggesting that the executive/non-executive separation option was more relevant to VCI as it lessened an over-emphasis on memory impairment (i.e. what some described as an “Alzheimerization” of VCI). A modest (30%) of respondents stated that the executive/non-executive separation option (option (B)) is more relevant to VCI.
**O’Brien concept** classification and causes of sporadic VCI:

<table>
<thead>
<tr>
<th>O'Brien concept classification and causes of sporadic VCI:</th>
<th>Percentage support as a subtype in Round 4</th>
<th>Percentage support as a descriptive term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post stroke dementia</td>
<td>68%</td>
<td></td>
</tr>
<tr>
<td>Mixed AD and VaD*</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td><strong>Multi-infarct (cortical)</strong></td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Strategic infarct</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td><strong>Subcortical ischaemic</strong></td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Hypoperfusion</td>
<td>50%</td>
<td>70%</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>50%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Specific arteriopathies†</strong></td>
<td>55%</td>
<td>68%</td>
</tr>
</tbody>
</table>

**Subtypes suggested by VICCCS participant:**

<table>
<thead>
<tr>
<th>Subtypes suggested by VICCCS participant:</th>
<th>36%</th>
<th>69%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small and large vessel</td>
<td>37%</td>
<td>48%</td>
</tr>
<tr>
<td>Mixed types of vascular pathologies (e.g., large vessel and small vessel forms)</td>
<td>53%</td>
<td>46%</td>
</tr>
<tr>
<td>Fronto-temporal type of VCI with predominating changes in personality &amp; behaviour</td>
<td>21%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Mixed other neurodegenerative dementias with CVD†</strong></td>
<td>65%</td>
<td></td>
</tr>
</tbody>
</table>

Supplementary Table 2: Details percentage support of the *O’Brien concept*[1] classification and causes of sporadic VCI. Those in bold italics were agreed as subtypes in the revised concept. Those in italics were agreed descriptive terms. Subtypes that were suggested by certain VICCCS participants to be additional.
subtypes of Major forms of VCI are listed. The percentage support show none received majority support as subtypes and only vasculitis achieved consensus support (69%) as a descriptive term. **“Mixed other neurodegenerative dementias with CVD” and “Mixed AD and VaD” were enveloped into the new VICCCS subtype “Mixed dementias”. Specific arteriopathies† was agreed in a separate question over two rounds to include; genetic, hereditary and developmental anomalies (e.g. Fabry's disease, sickle cell disease, CADASIL, CARASIL), small vessel disease from chronic hypertension and/or diabetes, inflammatory/immunological vasculitis, Moyamoya disease, and intracranial atherosclerosis. In Round 3, we asked whether it would be helpful to try and assign different types of Major VCI (VaD) i.e. dementia into "large vessel" and "small vessel" forms of VCI. A total of 76% of participants thought such a separation would be helpful. In Round 4, participants were then asked to clarify the context in which this should be applied; (i) as a descriptive term, to help provide information on the location of pathology or (ii) as a collective term, to help group some causes of VCI. In this round, 92% percent of respondents were in favour of this form of subgrouping; however 55% preferred (i) and 37% of respondents preferred (ii). After feedback of these results, there was no clear majority for the context of use again in Round 5. A final attempt was made in Round 6 to achieve consensus on this issue, particularly since there was originally such a high level of support consensus (76%) from all respondents as to this idea of separation. In this attempt we posed the question on whether there was any further support for this mode of separation to be used as a descriptive term to provide supportive information on the location in pathology and that in the absence of a (67%) consensus it would not be taken any further forward. In this final round there was a surprising reversal in the level of support with only 48% of respondents showing support for the use of “large vessel" and "small vessel" forms of VCI as a descriptive term and therefore it is not recommended.
Supplementary text 3: Further detail of discussions regarding clear definitions for “Mixed dementia” and Post-stroke dementia (PSD)

“Mixed dementia”

The sub-type of “mixed dementia” and how it is generally defined in clinical practice and research was identified in the earliest VICCCS rounds to be an area that many participants felt needed elucidation. Indeed its conceptualisation and how mixed AD with cerebrovascular disease (or VaD) fitted within the VCI construct was not explored in depth by O’Brien and colleagues. VICCCS attempted to build on this and sought to obtain a consensus definition from one of six proposed definitions of mixed dementia taken from the literature (see supplementary Box 1), or to propose an alternative or composite definition. There was no overall consensus for any one of the provided definitions. The most popular by Dubois and colleagues [13] achieved only 27% support, while a number of respondents expressed dissatisfaction that previous definitions have over emphasis on AD and VaD (i.e. another facet of the “Alzheimerization” of VCI as expressed by some respondents) particularly when VaD also co-existed with other forms of dementia.

Due to this lack of agreement, participants were then asked to select their top 3 preferences from a new list of definitions (including the original 6 definitions alongside either newly suggested definitions or modified versions to existing ones) attempting to capture concerns given as part of free text feedback. Again there was no clearly supported definition. However the most widely supported definition at this stage (25% of first choice votes from 10 options) was again the Dubois [13] description. Yet, since none achieved our pre-specified consensus level of acceptance, it was subsequently proposed and agreed by participants that amendments to the term “mixed dementia” was necessary for the revised concept, to better describe the symptomatology and co-morbidities involved. This was also intended to overcome what traditionally had become regular use of the term to describe co-morbidity of AD and VaD, and sometimes other forms of mixed dementias that did not necessarily have a vascular component. Participants were thus asked to vote on the usefulness to differentiate through better elaboration between contributing dementias by either; adding "mixed dementia - vascular" and "mixed dementia - non-
vascular", or replace the term "mixed dementia" in the name with an abbreviated specification of the representative phenotypes e.g. "VCI-AD", "VCI-LBD". Participants were also asked if they thought there was any need for change.

A clear and overwhelming consensus view (97% of respondents) favoured change to the traditional imprecise usage of the term mixed dementia. In the final Delphi Round 6, a solution to the continual differences in opinion regarding mixed dementia throughout VICCCS rounds was proposed and accepted by 95% of respondents. The proposed solution was that the term "mixed dementias" would serve only as an “umbrella” term to capture this as a heterogeneous sub-type of Major VCI (VaD) under which all of the phenotypes that were present would then be further specified as separate additional sub-groups e.g. patients would be referred to as having VCI-AD, VCI-LBD etc. as appropriate. A strong 81% of respondents also endorsed the use of this approach in both research AND clinical applications, whilst there was also consensus (68% support), for the suggestion that the order of terms should reflect the relative contributions of the co-occurring pathology, e.g. AD-VCI, or VCI-AD (as far as their discrimination allowed). It was acknowledged however that although naming according to perceived relative contribution is supported as a concept, it may be difficult to determine in practice. Further elucidation of this and strategies to try and overcome this would be important aspects of any future operational diagnostic protocols to try and improve phenotyping for future research and clinical management (see Box 3 for a summary of areas of future research either proposed or reflected in responses from the VICCCS).

“Post-stroke dementia”

Although there was consensus that the term post-stroke dementia (PSD) was useful for both research purposes (73%) and clinical diagnosis (86%), a lower sub-consensus 63% of participants were happy with the description of PSD originally proposed by O’Brien and colleagues. In Rounds 5 and 6 we attempted to address what were possible shortcomings with the previous definition of PSD.
Evidence of cognitive impairment prior to stroke

Whether a person with PSD should or should not have cognitive impairment prior to a stroke was not detailed previously. After two iterative VICCCS rounds, the following inclusive definition was supported by a two thirds majority (75%) of Round 6 respondents: “A patient described as having PSD may or may not have presented evidence of cognitive impairment prior to stroke”. Of those respondents that supported the statement, mild cognitive impairment was the most favoured (84%) regarding what level of cognitive impairment could be present in a patient prior to stroke for this to be classified as PSD, from the options given (mild, major, or either level). All but one of that minority of respondents that did not agree with this statement, supported a proposed alternative statement that a patient described as having PSD should not have any cognitive impairment prior to stroke.

From questions posed in Round 5, it also became apparent that participants deemed the following issues to require some modification:

Time-frames and the emergence of PSD

Collective views on the time-frame in which PSD manifests after an initial stroke was highly variable in Round 5. The majority of responses (95%) from our initial question including suggested and invited answers on time frames showed an agreement that no longer than one year was deemed most appropriate. The largest proportion of responses supported the option for an emergence of dementia within 3 months of a stroke (53%). In a subsequent Delphi round, a summary of these results were presented back to participants and they were again asked to make a preference from the list of options provided that would help to differentiate PSD from other forms of major VCI (VaD). There was no consensus obtained across the options that included: 1 month (11%); 3 months (36%); 6 months (28%) and 12 months (22%). A small proportion of respondents (3%) did not agree with differentiating between PSD and major VCI (VaD).
While no consensus was obtained for the time interval options provided, it was clear that a combined majority of responses (75%) were based around a time-interval of 6 months or less.

In Round 6 participants were also asked for their views on a further elaboration on the previously supported definition of PSD that was prompted by some additional responses received to questions about either immediate or delayed PSD (i.e. intended to differentiate with more acute forms of PSD). A more detailed definition was proposed and viewpoints invited in Round 6 on the following: Immediate AND/OR delayed cognitive decline that begins after stroke and that does not recover and within a specified time-frame. There was 83% agreement with this statement. However, there was equally divided opinion (50% each) on whether differentiation of immediate and delayed PSD should be specified by a time-frame. Furthermore, there was no clear majority amongst the 50% who did support the use for a particular immediate time-frame when various time intervals were proposed i.e. within 1 month (45%), within 3 months (35%), within 6 months (6%), within 12 months (8%) with 5% of respondents stating they were unable to comment. Yet, amongst those that supported time-frame based differentiations of immediate and delayed PSD, it was clear that the greatest preference amongst these supporters (80%) was that less than 3 months would be an appropriate time-frame to identify cases of immediate PSD. However, since there was still a lack of majority consensus across all respondents in this round (i.e. 50% were not in support of the use of time-frames), this will not be taken forward as a recommendation.

(C) Alzheimer’s disease (AD) and PSD

The inclusion of AD in the description of PSD as described by O’Brien and colleagues was an area of disagreement amongst respondents. This was reinforced by the responses received to a question posed about how participants would classify a hypothetical patient with a recent history of stroke (within the time-frame of choice specified for PSD) who had no prior history of dementia or cognitive impairment, but subsequently had an otherwise typical clinical
presentation of AD. A minority of respondents (19%) stated they would classify this hypothetical patient as PSD. The most supported classification (58%) for this hypothetical, albeit less than our consensus level, was "Mixed AD and VCI/VaD".

In light of these results, where only a minority would classify this hypothetical patient befitting the definition of PSD, as PSD, in the following round we asked participants if the level of support towards a “Mixed” classification indicated a necessary removal of AD from the description of PSD in the revised VCI concept. Only 54% of respondents were in favour of the removal. Yet, when then asked as to possible reasons for the lack of support for the removal of AD from the PSD classification, 78% of respondents agreed with the structured questions that the lack of support for the inclusion of AD in Round 5 was because AD is but one of a number of forms of dementia that could be present. In a subsequent related question, we also asked that if there were another hypothetical case that presented with another neurodegenerative disease such as DLB, instead of AD, would they classify this as VCI-DLB, i.e."mixed". A definitive 93% of respondents stated they would.

The responses to these two questions indicated that while participants were reluctant to remove AD or other forms of dementia from the description of PSD, in practice the majority of participants would not classify these patients as PSD, rather they would classify them as a specified “mixed” category.

There were also numerous respondents who thought subcortical ischaemic vascular dementia (SIVaD) should be distinguished (unlike its inclusion in the O’Brien proposal) from PSD. This was consistent with the prior agreement for SIVaD to be used as a standalone subgroup in VICCCS. However, a suggestion to remove SIVaD from the description of PSD was subsequently put to all participants but there was only 52% support for this.

To attempt to resolve the apparent overlap between how ‘Mixed Dementia”, PSD and other subgroups of VCI could be described it was further re-visited in VICCCS *Diagnosis* Round 2. A consensus (72%) thought a diagnostic category of PSD was still valid to include in the VICCCS diagnostic criterion, and 66% would
use this term in clinical diagnosis. A consensus (85%) still supported the VICCCS definition that a patient described as having PSD may or may not have presented evidence of mild cognitive impairment prior to stroke.

However, of the 72% in favour of having a PSD category, only 53% supported keeping PSD inclusive of neurodegenerative pathology separate from mixed dementia while 45% supported PSD without any other evidence of co-occurring neurodegenerative pathology. Of the 53% who supported PSD inclusive of neurodegenerative pathology, 85% thought it would be helpful to have further descriptive information, as with a "mixed" classification, describing the contributing phenotypes e.g. PSD-AD, or PSD-DLB. 67% of all respondents stated they would specify phenotype terms in clinical diagnosis.

Possible ways to delineate PSD and the occurrence of neurodegenerative pathology were later proposed, detailed in Box 3 and Figure 3, received consensus support (78%). The apparent conflict to the desired retention of SIVaD within the classification of PSD and desires elsewhere for SIVaD to be a separate subtype of Major VCI (VaD) can be differentiated by the consideration of time, i.e. whereby appearance within 6 months of having a stroke would be the determining factor for a diagnosis of PSD. This temporal basis for cognitive decline after stroke differentiates PSD from other forms of major VCI (VaD).
Round 3 question: Mixed AD with cerebrovascular disease (or vascular dementia) was not dealt with in depth in the O'Brien et al., 2003 concept and from comments received in both Round 1 and 2 of this study, it serves as an area which people feel is very important to elucidate. With this in mind, which one of the following definitions of mixed dementia should be adopted for the VICCCS concept? If you cannot choose one but would prefer a composite definition, please state this in the "Other" category.

Mixed dementia should be defined as:

1. "Dementia with major disturbance in memory, an atypical course and a more rapid cognitive impairment than those of VCI or AD alone."[2]

2. "Dementia with otherwise typical clinical presentation of AD with one of the following; past or recent history of stroke, presence of gait disturbances, hallucination/delusions, cognitive fluctuations and evidence of significant levels of small vessel ischaemic changes, strategic lacunar infarcts or large vessel infarcts on brain imaging. Both clinical features and diagnostic markers must be apparent. The evidence of low CSF amyloid beta or positive amyloid-ligand PET imaging can support a mixed dementia diagnosis."[13]

3. "Dementia with a course suggestive of AD and focal neurological symptoms or brain imaging suggestive of ischaemia. The presence of vascular risk factors alone in a patient with otherwise clinically typical AD is not enough to support the diagnosis of mixed dementia." [8]

4. "Dementia consisting of pre-existing AD that has been worsened by stroke."[5]

5. "Dementia where there are patterns fulfilling the clinical criteria for possible AD with clinical and imaging signs of relevant CVD."[10]

6. "If a patient demonstrates typical clinical history with supportive imaging and/or biomarker evidence of AD, but there is also evidence of CVD, the classification should be that of a diagnosis of AD with an appropriate description or assigned category (to be defined) of the level of co-morbid CVD
severity" ["VICCCS derived composite definition based on definitions 1-5 and attempting incorporate feedback comments raised elsewhere in VICCCS"]

Supplementary Box 1: Definitions of mixed dementia provided in round 3

Supplementary references


