**The Vascular Impairment of Cognition Classification Consensus Study (VICCCS)**

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**Abstract**

INTRODUCTION: Numerous diagnostic criteria have tried to tackle the variability in clinical manifestations and problematic diagnosis of vascular cognitive impairment but none have been universally accepted. These criteria have not been readily comparable, impacting on clinical diagnosis rates and in turn prevalence estimates, research and treatment.

METHODS: The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) involved participants (81% academic researchers) from 27 countries in an online Delphi consensus study. Participants reviewed previously proposed concepts to develop new guidelines.

RESULTS: VICCCS had a mean of 122 (98-153) respondents across the study and a 67% threshold to represent consensus. VICCCS redefined vascular cognitive impairment (VCI) including classification of Mild and Major forms of VCI and sub-types. It proposes new standardised VCI-associated terminology and future research priorities to address gaps in current knowledge.

DISCUSSION: VICCCS proposes a consensus-based updated conceptualisation of VCI intended to facilitate standardisation in research.

## 1. Introduction

Cerebrovascular pathology including; microinfarcts, lacunar infarcts, larger infarcts (of embolic or thrombotic origin) and white matter lesions, is moderately to strongly associated with cognitive decline[1-4]. Risk factors include hypertension, diabetes mellitus, smoking, atrial fibrillation, positive family history, age and hypercholesterolaemia[5-7], with some risk from *APOE* (epsilon 4 allele) and *MTHFR* variants[8]. Since Hachinski et al[9] proposed the term multi-infarct dementia, numerous subsequent proposals have tried to capture the clinical and aetiological complexity of cognitive impairment caused by heterogeneous cerebrovascular disease (CVD) and pathologies[10-21] . These

include: vascular dementia (VaD), vascular cognitive impairment (VCI), subcortical (ischaemic) vascular dementia and vascular cognitive disorder, which have given rise to multiple criteria and research guidelines[13, 17, 19, 21] that are not readily interchangeable[22, 23]. These factors contribute to variable prevalence estimates in the literature, as do descriptions of clinical manifestations. However, VaD, used to describe a severe form in the continuum of VCI, is probably the second commonest cause of dementia after Alzheimer's disease (AD), although as populations age this is likely to increase[13, 17, 21, 24]. Yet, incidence of dementia is now decreasing in high-income countries, which may partly relate to better CVD management[25]. CVD commonly contributes to many forms of dementia, including AD[26-28], and may be targeted with some success [29], although further research into possible associations and causal relationships is needed. Studies into causes and treatments of AD have greatly outnumbered those for VaD, partly by the availability of widely used diagnostic criteria that continue to evolve[30], and partly because of relatively more funding opportunities.

The lack of consensus criteria for diagnosis of VaD and VCI has impeded sharing and comparison of data on a larger scale, together with different specialties conducting narrow focused research[31]. Greater harmony of approach within the research community is needed[23, 32]. A workgroup convened by the NINDS-CSN made some progress [33], producing detailed research recommendations for VCI. However, their subsequent implementation and adoption remains unclear.

The vascular impairment of cognition classification consensus study (VICCCS) was designed to achieve a broader consensus on the conceptualisation of impairment in cognition contributed to by vascular pathology, for clinical diagnosis and research. The aim was to provide criteria that could be widely adopted within the field, to underpin future research. VICCCS elaborated previous work to

inform the way forward, with input from a broad spectrum of participants from the international research community.

## 2. Methodology

### 2.1 Participant selection

Previous attempts to develop consensus criteria were largely based on comparatively smaller pools of opinion leaders as part of organised meetings, conferences or symposia[33]. The intention for VICCCS was to draw upon the expertise of as many participants from as wide an array of disciplines as possible. Participants for VICCCS were identified through unbiased review of published articles relating to the concept or diagnosis of VaD/VCI in Pubmed, up to August 2010. Several relevant research networks, including the British Association for Stroke Physicians, Alzheimer's Disease Neuroimaging Initiative (ADNI) and the European Alzheimer's Disease Consortium (EADC) were also invited.

Nine hundred and five individuals were initially identified although it was not possible to find the contact details of all of these most likely due to the fact that some of the source studies were published over 20 years previously. Further efforts to source these missing contacts details were made by inviting all potential participants who were contacted to nominate and provide contact details for potentially interested colleagues. This lead to 789 invitations initially sent that generated a potential 367 (46%) initially interested pool of international participants. Unlike previous endeavours, VICCCS used periodic internet-based surveys to facilitate greater involvement and promote contributions through providing sufficient time for reflection and responses that were given with anonymity and parity. The study required considerable relevant clinical and research knowledge, and time commitment to complete multiple surveys. Nonetheless, on average 122 participants contributed to each round (range 98-153). Of these, a mean of 72% (range 66-76%)

were clinicians with direct involvement in clinical decision-making. The remainder were non-clinical researchers. Average continental distribution: Europe 63%, North America 19%, South America 6%, Asia 9%, Africa 2%, Australia 1%. Representation in each round is detailed in Supplementary Table 1. Bar graphs summarising the professions and affiliations of the authors are also provided in Supplementary Figure 1. The most common profession was Neurologist (46%) and the most common affiliation was academic researcher (68%).

### 2.2 VICCCS Delphi process

We used a Delphi approach, an iterative structured process involving a series of questionnaires with progressive refinement of questions, to achieve consensus amongst respondents[34]. Only the independent moderator (OAS, who did not herself participate in the survey) had access to identification details of the respondents. The anonymity of responses facilitated free expression of opinion throughout the study. Structured feedback of responses after each round, informed the nature of subsequent questions, allowing unbiased evolution of group judgements that may be difficult face-to-face. A threshold of two-thirds agreement was chosen to represent consensus [35] for issues refined through multiple iterative rounds. Overall, six rounds of web-based surveys were administered, approximately one every 2 months, to maintain engagement. In the first two rounds, opinion was canvassed on published criteria, their utility and weaknesses. The remaining 4 rounds focused on addressing weaknesses and standardisation of terminology. A summary of the topics addressed in each round is provided as supplementary information.

## 3. Results

### 3.1 VICCCS Rounds 1 and 2: critical appraisal of existing proposals

In the first round, views were sought on the most important issues to be resolved. The extent of use of existing criteria and guidance, identified through literature review, were assessed. We separated questions on 'concept' papers such as those concerning the scope and definitions (n=12), from those proposing diagnostic criteria (n=15). Four papers covered both aspects and were included in both sections. Round 1 gathered participants' views on these papers, but also invited additional suggestions for relevant manuscripts that should be considered. Participants were asked to indicate their familiarity with the papers and score their usefulness, from "*no longer relevant*" to "*useful in all cases*", and to select 3 concepts that could form the basis for wider acceptance. To reduce bias in selection that might have been caused by definitions that were older and perhaps more familiar, those selected that scored "*useful in most" or "useful in all cases"* were ranked to represent what was a 'considered useful vote'. The ranking showed that more recently published concepts, even if not widely known, were better regarded as a foundation for future use. The collated scores, were fed back to participants in Round 2. Participants were then asked to reconsider all papers, including those that might be less familiar, before again ranking the criteria, after which low-ranking criteria would be eliminated from further consideration.

Almost 60% of respondents ranked the VCI construct of O'Brien and colleagues [36], representing a broad continuum from mild impairment to dementia, as the preferred conceptual basis. The second and third ranked definitions, which obtained 11% and 7% first-preference votes, also encompassed VCI and associated concepts (Supplementary Figure 2).

In addition, 78% of respondents felt that the definition of VCI needed to be broader in scope. Therefore, the remaining VICCCS rounds focused on obtaining consensus on a revised conceptual model for VCI. The content of the subsequent rounds was based on responses to early-round questions on definition, scope, sensitivity to subtypes of VCI and clinical utility.

### 3.2 Rounds 3 – 6: formulation of a revised VCI concept

In Round 3, participants were asked to state their agreement or disagreement with proposed guiding principles for refinement of the concept of VCI. These had over 94% agreement; amendments proposed by some participants were reported for comment in Round 4. Consensus guiding principles are listed in Box 1.

Round 3 addressed *three areas* identified in Round 2 as meriting clarification or modification. While 29% of respondents thought the O'Brien construct did not need any major improvement, a percentage of respondents felt changes were desirable to its *scope* (13%), *sensitivity to subtypes* (31%) and *descriptiveness* (39%). The subsequent rounds worked towards improving these perceived limitations. Forty two percent of respondents thought the O'Brien construct was not well aligned with clinical operational criteria. These limitations were subsequently addressed in a focussed follow-on Delphi (VICCCS *diagnosis*) to develop operational criteria (in preparation, however see Box 2 and supplementary text for some reported findings).

#### 3.2.1 Scope

Approximately one third (34%) of Round 3 participants suggested that other potential mechanisms of VCI should be included in the revised concept. In Round 4 participants were asked to vote on inclusion of the suggested mechanisms. There was consensus that the additional mechanisms listed in Table 1 should be included within the revised concept of VCI. Over Rounds 4-6, there was also agreement as to what should constitute the arteriopathies subgroup (proposed in the O'Brien construct), however, in VICCCS, specific arteriopathies are a descriptive term of cause rather than a subgroup (Table 2).

### 3.2.2 Sensitivity to subtypes

The O'Brien construct was thought by 31% of respondents to be limited in capturing subtypes of VCI. Whilst it acknowledged rare hereditary disorders cause VCI, the construct focused mainly on sporadic forms of VCI. 78% of VICCCS respondents suggested that both hereditary (i.e. "Type I" or "familial" VCI) and sporadic (i.e. "Type II") should be encompassed within VCI. In Round 4, most (85%) respondents preferred the terms *sporadic* and *familial* to be used as *descriptive information* for various forms of VCI rather than to define separate categories.

The proposed subtypes of the revised concept of VCI according to VICCCS are depicted in Figure 1.

#### 3.2.2.1 Mild and Major VCI (VaD)

In the O'Brien construct, VaD was used as an umbrella term for subgroups of severe forms of VCI. Round 3 participants were asked whether the term VaD was still useful. No clear consensus emerged, although a small majority (56%) favoured its continued use. However, the timing of this VICCCS round coincided with the drafting of the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), widely used by clinicians world-wide. The draft DSM-5 proposal was that VaD or major vascular cognitive disorders (VCD)[37] be shown in parentheses with the description "major neurocognitive impairment due to vascular disease" as a classification group for severe forms of impairment heretofore referred to as VaD[38]. We therefore sought VICCCS participants' views on the use of the terms "Mild" and "Major" in relation to VCI. Although only 39% of Round 4 respondents were aware of the draft DSM-5, 71% agreed that the revised VCI concept should use the terms "Mild" and "Major" to align VICCCS recommendations with DSM-5. In Round 5, a 71% majority supported the terminology "Mild forms of VCI" and "Major forms of VCI (VaD)".

3.2.2.2 Further sub-typing of Mild forms of VCI

Subtyping of Mild forms of VCI was addressed in rounds 3-6. Most respondents (68%) were in favour of specifying subtypes. However, in response to a separate question 63% thought that this separation lacked supporting evidence and was premature, and no subtype option could be agreed. Further detail of this is provided in the supplementary information. VICCCS propose that Mild VCI is not sub-typed at this time until research provides better justification.

3.2.2.3 Further sub-typing of Major forms of VCI (VaD)

In Round 3, respondents were asked to decide which subtypes of dementia proposed by O'Brien and colleagues should be recognised in VICCCS. Variable levels (81-50%) of agreement were found. In Round 4 most respondents (94%) agreed that this lack of consensus might be overcome if it were possible to avoid mixing site, severity and mechanism. 96% supported an effort to develop a more systematic step-wise approach towards sub-typing based on VICCCS proposed categories of **L**ocation, a**E**tiology, **D**omains (affected) and **S**everity, provisionally named "LEDS" criteria. With this in mind, participants were asked which of the O'Brien sub-types allowed for more mutually exclusive grouping of patients or might be considered better suited as *descriptive terms* for either the 'mechanism' or 'location' of damage. The sub-types; "Specific arteriopathies", "Haemorrhagic" and "Hypoperfusion" were not supported as standalone sub-types (13-18%) and thus are recommended as descriptive terms of causal mechanisms in VCI. The remaining sub-type terms received variable support between rounds. Round 6 collected a definitive decision, with terms that did not achieve majority (67%) support to be descriptors. "Subcortical ischaemic" (83%) and "Multi-infarct (cortical)" (74%) were supported as sub-types of Major VCI (VaD). As in earlier rounds, post-stroke dementia (PSD) was supported (73%) as a sub-group and 86% thought it also helpful for clinical diagnosis. In contrast, despite near threshold support (66%), for consistency "Strategic infarct dementia" will also

be proposed as a descriptive term for VCI. Additional suggestions for standalone sub-types of VCI were also invited. None of these were supported but “Vasculitis” was agreed (69%) as a helpful descriptive term of cause (Supplementary table 2). The resultant VICCCS recommended sub-types and descriptive terms are presented in Table 2.

### 3.2.3 Descriptiveness - clear definitions

#### 3.2.3.1 “Mixed dementias”

Mixed dementia and it’s definition in clinical practice and research were identified as needing elucidation from the earliest rounds, with 97% of respondents favouring change to the traditional imprecise usage. In the final Delphi Round, 95% of respondents agreed with a proposed solution to the differences in opinion on the term (detailed in supplementary information). “Mixed dementias” was proposed should serve only as an “umbrella” term for sub-types of Major VCI (VaD) under which all phenotypes present would be specified. Patients would be referred to as having for example; VCI-AD, VCI-DLB etc. according to whatever dementia co-morbidities presented. A large number of respondents (81%) endorsed this approach for both research and clinical applications, and consensus (68%) was that the order of abbreviations should reflect the relative contributions of the co-morbidities, as far as practicable.

#### 3.2.3.2 **“**Post-stroke dementia**”**

There was consensus for the term “post-stroke dementia” (PSD) to be used in research (73%) and clinical (86%) contexts, but no consensus (63%) around how PSD was previously described, which we had tried to address in later rounds and continued to do in VICCCS *diagnosis*. Related issues thought necessary to clarify PSD, including evidence of cognitive impairment prior to stroke and timeframes for the emergence of PSD, are detailed in supplementary information. VICCCS consensus (78%) views

on delineation of PSD are detailed in Box 2 and Figure 1. Of note is the temporal association between cognitive decline and stroke differentiates PSD from other forms of major VCI (VaD), i.e. cognitive impairment within 6 months of having a stroke would be the determining factor for a diagnosis of PSD.

Consensus proposed definitions for Major VCI (VaD) subtypes (PSD, Mixed dementias, Subcortical ischaemic vascular dementia, Multi-infarct dementia) are presented in Box 2.

**4. Discussion**

VICCCS has provided revision and consensus-based elaboration of the construct of VCI in the majority of areas addressed. Lack of consensus in some areas was mainly due to little research data available at the time, for example, the sub-categorisation of Mild forms of VCI. VICCCS showed that although half of the respondents wanted to lessen the over-emphasis on memory-impairment in the conceptualisation of VCI, two-thirds acknowledged the benefit in the amnestic separation to facilitate alignment with current formats used for AD and mild cognitive impairment (MCI). Thus subtypes of VCI require more research-based justification.

Definition of more homogeneous groups was supported for Major VCI - also important for clinical trial design. Clinical diagnosis of coexisting pathologies remains a challenge. Previous definitions of mixed dementia were not greatly supported in VICCCS, partly due to dissatisfaction with the over emphasis of AD (see supplementary information). Since the study concluded, a revised concept of the most favoured definition (25% support) has been published for “mixed AD”[30] that does provide separate criteria for coexisting CVD and Lewy body pathology, however does not differentiate these by terminology. VICCCS proposes in mixed dementias and PSD that all phenotypes identified should be specified, depending on whatever dementia-related co-morbidities are present, wherein the order of abbreviations reflects the perceived relative contributions.

Improvements to the practicalities and accuracy of this would be important aspects of any future operational diagnostic protocols, whilst ongoing research in biomarkers may be helpful. Recent evidence lends weight to this approach, where subcortical vascular dementia can be identified in an outpatient memory clinic setting according neuropsychological features and CSF-biochemical markers distinct from those of AD[39]. Box 3 summarises this and other areas for future research either proposed or reflected in responses from VICCCS.

VICCCS was conducted between 2010 and 2013 that coincided with the development of DSM-5[40] and VASCOG criteria for VCD[37]. VICCCS participants were given the opportunity to provide collective feedback on draft DSM-5 proposals that were made available prior to its finalisation. This was enabled through a tailored survey developed (by OAS) in consultation with Perminder Sachdev acting on behalf of the DSM-5 Neurocognitive Disorders Work Group and was prompted by their online request for input from the clinical research community into the refinement process. Awareness amongst VICCCS participants of this request was relatively modest, demonstrating a need for wider advertisement of such consultations in future. VICCCS participants agreed that the *Mild* and *Major* terminologies proposed in DSM-5 were helpful and similarly should be adopted in VICCCS.

In relation to the subsequent published criteria (in 2014) for vascular cognitive disorders, VICCCS had previously explored but was not supportive of this concept and the use of this term vascular cognitive disorder[11, 17]. However, the VASCOG criteria are also reported to be aligned to DSM-5[37].

### 4.1 Considerations of the Delphi process on VICCCS outcomes

A key principle of the Delphi method is that decisions from a structured specialist group of individuals are more accurate. The use of online surveys in VICCCS, to avoid scheduling constraints of

a physical meeting, facilitated the inclusion of an unprecedented large number of international participants who have enriched discussions. The anonymity offered by Delphi reduced the potential for any individuals to dominate direction of discussions. Furthermore, in combination with the repeated group feedback, the anonymity allowed contemplation, review of initial judgments and scope for participants to freely change opinions, all of which promoted the generation of consensus[34, 41]. The use of specific published papers helped to focus the discussion points and in some cases, increased awareness of previous studies, aiding more-informed decision making. After the initial rounds, structured, mostly closed questions were mainly employed to ensure continued focus whilst some feedback was possible, in the primary discussion of topics. This sometimes extended the duration of the study and complexity of the arguments, such as the discussion of mixed dementias and PSD. Yet the extended debate was useful but increased risk of participant attrition, and variation in respondent numbers in each round did variably impact on the relative contribution of each respondent towards consensus. However, most topics were dealt with over multiple rounds giving many opportunities to confirm the consensus view. The maintenance of a high number of participants throughout the study provides assurance that a consensus concept of VCI has been realised, although by definition the consensus was based on a majority view.

## 5. Conclusions

VICCCS presents a new consensus based set of guidelines supported by a large international pool of researchers. These guidelines have drawn upon, expanded and refined previous efforts to improve and clarify the conceptualisation of VCI. It is anticipated that VICCCS guidelines will be widely adopted in the community to increase the levels of consistency and standardisation in undertaking VCI research. This should significantly enhance the interpretation and comparison of findings across studies and support the likelihood of more large-scale collaborative research that will be vital to help overcome historical limitations posed by the prevalence of VCI.

## 6. Acknowledgements

### 6.1 Contributors

OAS was the study coordinator, analysed the data, formulated the questionnaires and wrote the manuscript. PGK was Chief investigator, conceived and designed the study, obtained the necessary funding, reviewed each round data, formulated the questionnaires and wrote the manuscript. YB-S, APP, SL were Co-investigators and members of the Steering Group. Other listed authors were members of the Steering Group who reviewed the content of the pilot questionnaires, draft and final manuscript and were participants in the study. Authors listed under the banner of VICCCS groups contributed to data gathering in multiple survey rounds and approved the final submitted version of the paper.

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Legends:

Figure 1: Revised conceptualisation of VCI in VICCCS. Subtypes of VCI are divided according to level of VCI impairment into Mild VCI and Major VCI (VaD). Mild VCI is not further sub-divided at this time. Major VCI (VaD) is classified into 4 main subtypes as depicted. The 6 month temporal basis (denoted by the hashed box) for cognitive decline after stroke differentiates PSD from other forms of major VCI (VaD). Post stroke dementia (PSD) and Mixed dementias are further delineated if a comorbid neuropathology is present (N.B. AD and Dementia with Lewy bodies (DLB) are given as examples, with # denoting other possible combinations). Subcortical ischaemic vascular dementia or Multi-infarct (cortical) dementia subtype cases with these specific types of dementia alone, however cases also presenting with any other neurodegenerative pathology would then be categorised as Mixed dementias (dashed arrows) according to the comorbidities present.

Key words: vascular cognitive impairment, vascular dementia, guidelines, criteria, consensus, Delphi

Abbreviations:

Alzheimer's disease (AD)

Cerebrovascular disease (CVD)

Dementia with Lewy bodies (DLB)

Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

Mild cognitive impairment (MCI)

Post-stroke dementia (PSD)

Vascular cognitive disorders (VCD)

Vascular cognitive impairment (VCI)

Vascular dementia (VaD)

The Vascular Impairment of Cognition Classification Consensus Study (VICCCS)