Priorities for research into cavernoma

Final Report of the James Lind Alliance Cavernoma Priority Setting Partnership

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on behalf of the Cavernoma PSP

www.cavernoma.org.uk/psp
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Cavernoma Alliance UK
Helping the Cavernoma Community

James Lind Alliance
Priority Setting Partnerships

Brain & Spine Foundation

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Abbreviations

CAUK	Cavernoma Alliance UK
CCM	Cerebral Cavernous Malformation
UKDUETS	UK Database of Uncertainties about the Effects of Treatments
JLA	James Lind Alliance
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NHNN	National Hospital for Neurology and Neurosurgery
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PSP	Priority Setting Partnership

Supporting Documents

Supporting documents in the report, shown in the document as **[WebXX]**, can be found collectively at: URL – www.cavernoma.org.uk/our-projects-and-campaigns/support-files

References to academic articles appear in the text as [RefN] and are found in Section 8.

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- The Lothian Health Board Endowment Fund
- The National Hospital Development Foundation
- The reserves and members of CAUK.

We also wish to acknowledge the input from David Crowe, whose attention to detail and understanding of the process of running a PSP were vital and from Robin Harbour, whose massive input and skill in organising the input, sifting this into appropriate categories, proposing the wording of the questions and providing all the necessary information to ensure that our questions were suitable for UKDUETS went on largely behind the scenes.
He provided much of the quality of what we have been able to achieve.

1. EXECUTIVE SUMMARY

Cavernous malformations – also known as cavernomas – affect people at any age and occur throughout the central nervous system including the brain (where they may cause haemorrhagic stroke and epileptic seizures) and the spinal cord (where they may bleed and cause myelopathy).

Despite the availability of microsurgical excision and stereotactic radiosurgery for cavernoma treatment, and known genetic causes of most familial forms of cavernoma, uncertainties about cause, diagnosis, prognosis, treatment and care remain.

Therefore, in order to prioritise these uncertainties about brain and spine cavernomas for researchers and funding agencies, we undertook a James Lind Alliance (JLA) Priority Setting Partnership (PSP). This PSP was conducted by a multidisciplinary steering group of patients, carers, healthcare professionals, representatives of patient support organisations, an information specialist, a JLA adviser, and an administrator according to a protocol developed in August 2014 and approved in January 2015. The methods and outcomes of the PSP are described in detail in this report with additional information available online.

In January-March 2015, we gathered uncertainties using a web-based survey that was distributed by professional and support organisations in the UK via email, post and social media to patients, carers, and healthcare professionals. We received 2,268 uncertainties from 299 respondents (63% patients, 18% healthcare professionals, and 19% others), and identified a further 34 uncertainties from literature searches. An information specialist subsequently: de-duplicated these submissions; rejected submissions that were out of the scope of the PSP; rejected uncertainties if there was evidence in published systematic reviews that they had been answered; and added uncertainties identified by these systematic reviews, resulting in a long list of 79 unique uncertainties. The Steering Group worked in pairs to further shorten the long list to 54 uncertainties, which we circulated to 246 survey respondents who had volunteered to prioritise the long list of uncertainties. 136 (55%) of these respondents participated in the web-based prioritisation exercise, in which we used the rank order technique to generate a short list of 31 uncertainties. At a final in-person workshop involving 29 participants (41% patients, 31% healthcare professionals, and 28% others), facilitated by three JLA advisers, we achieved consensus on a final prioritised list of 27 uncertainties (listed in the UK Database of Uncertainties about the Effects of Treatments [UKDUETS]), of which the 'top ten' shown in the panel below are immediate priorities for future research.

The top ten uncertainties reflect the concerns of patients, carers and healthcare professionals in the UK: five concerned prognosis, three concerned treatment/care, and two concerned cause. The JLA process assures the internal validity and reliability of these priorities, but their generalisability to other populations is unknown. The 27 uncertainties identified by this JLA PSP, and in particular the top ten, can now inform the projects that the research community pursue and that funding bodies support in the UK and perhaps other parts of the world.

Top Ten Research Priorities for Cavernomas

1. Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with brain or spine cavernoma?
2. How do brain and spine cavernomas start and develop?
3. What is the risk of brain or spine cavernomas bleeding for the first and subsequent times?
4. Could drugs targeted at cavernomas improve outcome for people with brain or spine cavernomas compared to no drug treatment?
5. What mechanisms trigger bleeding or epileptic seizures in people with brain or spine cavernomas?
6. Are any features of brain or spine cavernoma on imaging associated with a higher or lower risk of bleeding?
7. Does the use of anti-coagulant drugs increase the risk of bleeding from brain or spine cavernoma?
8. Does regular monitoring of brain or spine cavernoma improve outcome compared to no monitoring?
9. What features of brain cavernoma lead to the development of epilepsy, or influence the severity of existing epilepsy?
10. Do any specific activities undertaken by people with brain or spine cavernomas provoke bleeds or other symptoms?

2. CAVERNOMA

2.1 THE CONDITION

Cavernoma (also known as a 'cavernous angioma', 'cavernous haemangioma', or 'cerebral cavernous malformation' [CCM]) are abnormal developments of blood vessels in the brain, brainstem or spinal cord that result in the formation of 'caverns': a nexus of blood capillaries surrounded by a sheath of connective tissue. Blood can leak internally, causing them to enlarge, and can also leak externally.

Most frequently they cause no medical problems and are said to be asymptomatic; it is estimated that about 1:625 people have asymptomatic cavernoma in the brain [Ref01]. However, annually, about 1:400,000 of the population (i.e. 160 per annum from a UK population of 64 million) are diagnosed with symptomatic cavernoma [Ref02], being diagnosed by MRI scans following an epileptic seizure or stroke. They are diagnosed in people of all ages. The average age of first diagnosis is 43 years [Ref02].

Treatment of cavernoma most often deals with the symptoms, e.g. antiepileptic drugs for epilepsy, but there are two direct treatments of cavernoma: excision by microsurgery or stereotactic radiosurgery of the cavernoma. The dangers of microsurgery are dependent on location, and an individual together with their medical advisors has to weigh the benefit of excision against the risk of damage to nervous tissue. Gamma-knife surgery is non-invasive, but it is far less clear that there are beneficial effects. There are as yet no drugs for treatment of cavernoma.

Management of cavernoma involves treatment of the symptoms, information about the future risks of haemorrhage and epileptic seizure [Ref03], and considering the possibility and advisability of direct treatment.

The proportion of people with cavernomas who have inherited a gene that causes multiple cavernomas is estimated to be 10-40% [Ref04]. There are three known 'cavernoma' genes CCM1, CCM2 and CCM3. People with a mutation in one of these genes are much more likely to develop multiple cavernomas than those without a mutation [Ref05]. For those with a mutation in one of these genes, each of their children has a 50% chance of inheriting the mutation.

2.2 EVIDENCE-BASED TREATMENT

In 2012, Cavernoma Alliance UK and Genetic Alliance UK jointly sponsored a study of the known evidence-base for the treatment and management of brain cavernoma [Ref06] in adults. This guideline and a subsequent review [Ref07], **[Web01]** did not find randomised trials or 'observational studies with dramatic effects' specific to adults with brain cavernoma, allowing the authors to make few specific recommendations for the clinical investigation and management of adults with CCMs. This absence of evidence prompted the need to determine what are the most important uncertainties for the treatment and management of cavernoma.

2.3 UKDUETS, JLA AND PSPs

The National Institute for Health and Care Excellence (NICE) has created a database of treatment uncertainties for afflictions and diseases: the "UK Database of Uncertainties about the Effects of Treatments" (UKDUETS[1]). The gateway to entries onto UKDUETS is well controlled, requiring potential uncertainties to meet a number of criteria: they must be shown to be genuinely uncertain, and (i) that no up-to-date, reliable systematic reviews of research evidence addressing the uncertainty about the effects of treatment exists or (ii) an existing up-to-date systematic review of research evidence shows that uncertainty does exist.

One high-quality route to meeting the criteria for populating UKDUETS with a range and prioritisation of uncertainties relating to any particular affliction or disease, is promoted by the James Lind Alliance (JLA), now part of NICE. JLA have a rigorous protocol for identifying and prioritising potential uncertainties[2], and the cavernoma community elected to take this route.

The essence of the JLA approach is to create a Priority Setting Partnership (PSP). This is a partnership of equals of all those with a direct interest in the outcome, including clinicians, patients, carers and organisations such as Cavernoma Alliance UK (CAUK[3]) and the Brain & Spine Foundation[4].

David White and Ian Stuart with the JLA Team: L to R – David White, Amy Street, Katherine Cowan, Caroline Whiting, Beccy Maeso, Ian Stuart.

1. www.library.nhs.uk/duets
2. www.jlaguidebook.org/
3. www.cavernoma.org.uk/
4. www.brainandspine.org.uk/

3. PSP INITIATION

3.1 ORIGIN OF THE CAVERNOMA PSP

The initiative for starting the Cavernoma PSP came from those who had developed the 2012 guidelines for CAUK, in particular Professor Rustam Al-Shahi Salman (a neurologist from the University of Edinburgh and NHS Lothian), Mr Neil Kitchen (a consultant neurosurgeon from the National Hospital for Neurology and Neurosurgery - NHNN) and Dr Ian Stuart (the founder and co-ordinator of CAUK), with David White (Chair of Trustees of CAUK) taking on much of the organisation. Together, this group undertook the preparatory work for creating the Cavernoma PSP.

JLA were first approached in April 2013. They asked if we were convinced that the full PSP route to identifying cavernoma uncertainties was optimal for us, pointing out simpler and cheaper alternatives. We decided that we wished to create a Cavernoma PSP for two main reasons: the quality of the output which would be important in applying for funding for the required research subsequently, and for the opportunity of patients and clinicians to work together and raise the profile of cavernoma. JLA advised that before the Cavernoma PSP started, we needed to raise about £25k. This took time, but generous funding to this total was received from The Hospital Saturday Fund, the Lothian Health Board Endowment Fund, the National Hospital Development Foundation and the reserves and members of CAUK in a special appeal for this PSP.

3.2 THE STEERING GROUP

JLA assigned David Crowe as our project manager. We then approached those who were to form our Steering Group, the body which takes on the responsibility for the conduct of the PSP. We felt that a Steering Group of 10-12 people would enable us to include patients and carers (including carers/parents of children with cavernoma) and clinicians covering the main disciplines and specialising in both adults and paediatric issues. We included a representative from both CAUK and the Brain & Spine Foundation. Vital support for the work came from an information specialist (Robin Harbour) and an administrator (Francesca Howarth).

Steering Group Members

Patients and Carers

- Ian Stuart (Patient and Founder and Co-ordinator, Cavernoma Alliance UK [CAUK])
- David White (Carer and Chair of the Trustees of CAUK)
- Simon Temple (Patient)
- Paula Wheeler (mother of son with cavernoma)

Clinicians

- Professor Rustam Al-Shahi Salman (Neurologist, University of Edinburgh and NHS Lothian)
- Mr Neil Kitchen (Consultant Neurosurgeon, National Hospital for Neurology & Neurosurgery)
- Dr Jenny Thomson (Clinical Geneticist, Leeds Teaching Hospitals NHS Trust)
- Dr Vijeya Ganesan (Consultant Paediatric neurologist, Great Ormond Street Hospital)
- Mr Connor Mallucci (Consultant Paediatric neurosurgeon, Alder Hey Children's Hospital)
- Mr Matthias Radatz (Consultant in stereotactic neurosurgery, Clinical Director of the National Centre for Stereotactic Radiosurgery, Sheffield Teaching Hospitals)

Other Organisations

- Angela Collett (Brain & Spine Foundation)

The Support team

- David Crowe (JLA)
- Robin Harbour (Information Specialist, until recently Lead Methodologist. Healthcare Improvement Scotland)
- Francesca Howarth (Administrator)

The Steering Group meeting at NHNN: Angela Collett, Francesca Howarth, Ian Stuart, Robin Harbour, Paula Wheeler, Rustam Al-Shahi Salman, Neil Kitchen, Jenny Thomson, David Crowe, with David White behind the camera.

3.3 PROTOCOL

One of the first responsibilities of the Steering Group was to agree the framework for our work: the Protocol **[Web02]**. This was structured along JLA guidelines and included our Aims and Objectives, set out below.

We opted to have a broad scope, in particular including uncertainties relating to all ages of patient from babies to adults, and by including questions relating to a broader set of topics than just treatment.

3.4 AIMS AND OBJECTIVES OF THE CAVERNOMA PSP

The overall aim of the Cavernoma PSP is to identify unanswered questions about the management of brain and spine cavernomas affecting adults, children and babies, from patient, carer, family and clinical perspectives and then prioritise these treatment uncertainties.

The objectives of the Cavernoma PSP are to:

- Work with patients, carers, clinicians and others to identify uncertainties about the effects of cavernoma diagnosis, prognosis, treatments and care
- Agree by consensus a prioritised list of those uncertainties, for research
- Publicise the results of the PSP and process
- Take the results to research commissioning bodies to be considered for funding.

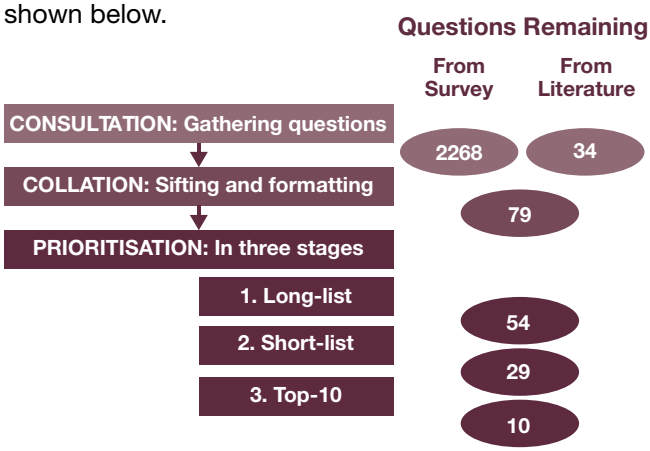
The PSP process is phrased in terms of determining the 'treatment uncertainties' that need resolving for an affliction, not least because the prime output of the PSP is to add to UKDUETS.

The Cavernoma PSP often used the phrase 'Research Questions' or 'Unanswered Questions' in its deliberations, partly because we had a scope broader than just treatments and partly because we thought in terms of 'questions to which we want/need answers'.

4. PROCESS

4.1 OVERVIEW

The PSP was undertaken in three main phases as shown below.



4.2 STEP 1: CONSULTATION - GATHERING QUESTIONS/UNCERTAINTIES

Survey 1

The first stage in identifying uncertainties is to obtain individuals' views as to the unanswered questions that concern them about cavernoma. We aimed to gather as many ideas as possible from as large a body of opinion as possible. We opted to do this by means of a survey and to make this available widely. The core of the survey asked one question for each of the broad topics of our scope plus an open question, and encouraged respondents to propose as many questions as they wished within each topic:

Table 1: Survey 1 topics		
Causes	Diagnosis	Treatment
Care & support	Prognosis	Open question

In addition, we asked respondents to provide demographic and other information about themselves.

We used 'Lime Survey[5]' as the vehicle for this survey, and did a pilot run in December 2014 with members of the Steering Group to iron out any problems. The survey itself went live at the end of January 2015 and ran until the end of March. The survey used is available on the Cavernoma PSP Resource site **[Web03]**.

Dedicated pages within the CAUK website gave details of the PSP. Access to the survey from clinicians was primarily through their professional societies and for patients and carers primarily from members of CAUK and related support charities (see Table 2). Links to the survey was prominent on the CAUK home page and the survey was frequently promoted on the CAUK social media (Facebook and Twitter) sites. Paper copies of the survey were also available on request.

5. www.limesurvey.org/en/

Table 2: Organisations approached for uncertainties	
Association of British Neurologists	Cavernoma Alliance UK
Society of British Neurological Surgeons	Brain & Spine Foundation
British Association of Neuroscience Nurses	Epilepsy Society
British Association of Stroke Physicians	Findacure
British Neurovascular Group	Genetic Alliance UK
British Paediatric Neurology Association	Headway
British Society for Genetic Medicine	Neurological Alliance
Contact a Family	Stroke Association

Survey Output

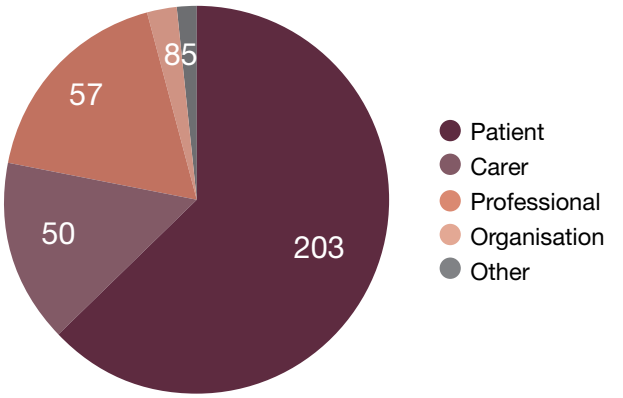
There were 299 respondents to the survey **[Web03]**, profiled in Figures 1a and 1b and Annex A. Many respondents provided multiple responses within one or more of the categories in Table 1, and these were organised into separate questions by Robin Harbour, our information specialist. This produced 2,268 responses.

4.3 STEP 2: COLLATION - SIFTING AND FORMATTING

Preliminary Sift

A preliminary sift of the responses was undertaken by Robin Harbour and reviewed by the Steering Group. Although all the input to Survey 1 was important to the respondent, it was not always relevant to the aims of the PSP. The purpose of the sift was to remove irrelevant material, to group the remainder where appropriate and to format the wording into an appropriate form for UKDUETS. However, nothing was disposed of, and the responses that were discarded during the PSP process will be used outside the PSP as the basis of an information paper targeted primarily at patients and their carers.

Figure 1a
RESPONSES BY CATEGORY OF RESPONDENT



The questions asked by survey respondents did not rigidly follow the categories laid out in the questionnaire. Responses were therefore categorised along the lines of the research activity codes used by the UK Clinical Research Collaboration in their Health Research Classification System[6] . These categories are set out in Table 3.

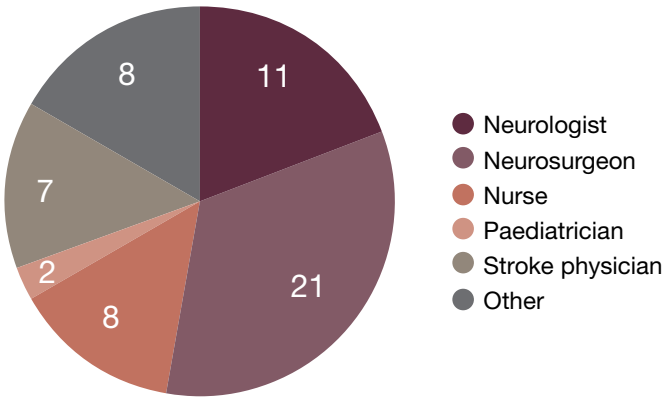
Table 3: Categories		
i) Aetiology / causes (A)	ii) Diagnosis (D)	iii) Treatments (T)
iv) Self-management (S)	v) Care & support (C)	vi) Prognosis (P)
vii) General questions (GQ)	viii) Genetics (G)	ix) Non-questions
The letter(s) in brackets are used as a short code in some later listings.		

Questions that were outwith the scope of the PSP were initially identified by Robin Harbour, and subsequently reviewed and agreed by members of the Steering Group (SG). Other out-of-scope questions were identified as the SG worked through the process and considered questions in more detail.

Some of the survey responses took the form of general statements rather than questions. These were included in a separate category labelled 'Non-questions'. This was reviewed by two members of the SG to ensure that any important issues not addressed by direct questions were not omitted from the later stages of the process.

In addition, 34 questions/uncertainties were identified in the literature, thereby giving a total of 2,302 questions/uncertainties to be categorised. The output of this initial categorisation is given in **[Web04]**. Within each category, responses are grouped, and responses that were deemed to be out-of-scope for the PSP are also given. A summary table showing the numbers of questions at different stages of the prioritisation process is given in Table 4.

Figure 1b
RESPONSES OF CLINICIANS BY DISCIPLINE



The total is more than the number of respondents because those who were in more than one category (e.g. clinicians with Cavernoma) were double counted.

6. www.hrcsonline.net/sites/default/files/HRCS_Document.pdf

Grouping Questions

The 2,302 questions were not unique: many questions were asked by many more than one respondent. In saying this, the wording was seldom identical, but many groupings could be phrased by means of a common wording capturing the essence of the origin. For example, at this sifting stage, 142 responses were grouped under "Is there any evidence that specific physical activities can trigger cavernoma symptoms?", embracing such original wordings as "Are there any activities to be avoided?", "Am I able to lead a normal life?", "What activities should my son/daughter avoid at school if s/he has a cavernoma?".

At this sifting stage, of the original 2,302 questions from Survey 1 and the Literature:

- 1056 were asked by two or more people and were merged into 39 grouped questions in Robin Harbour's original sift
- 34 were derived from the literature
- 75 were non-questions, and
- The remaining 1,137 ungrouped questions were asked by just one person. The assignment of this set was considerably refined in Step 3 below.

4.4 STEP 3: PRIORITISATION

Prioritisation Stage 1: The Long List

Each of the above categories was reviewed by two members of the Steering Group in order to agree whether the sets of grouped questions were appropriately grouped, and to assign the questions into three lists:

1. **Uncertainties:** questions that reviewers are confident should be included in the list for final prioritisation.

2. **Possible uncertainties:** research questions that could be considered for the final prioritisation list, but where reviewers are uncertain or unable to agree on their relevance.

3. **Out of Scope.** Questions that were either placed in the wrong category or were not within the scope defined in the protocol defined for this PSP.

The output from the above review provided the main input to a Steering Group meeting on 29th April 2015, for which Robin Harbour had prepared three lists **[Web05]**:

a. A first draft of a 'Long-List' of potential Research Questions, grouped by the categories of Stage 2. This contained 79 questions. The number of respondents from Survey 1 who had proposed that question was indicated for each question.
b. A list of 12 potential research questions that had been wrongly categorised in the original sort, and which had therefore not been properly scrutinised (from list 3 above).
c. A list of those questions that he deemed 'out-of-scope', numbering 346.

Table 4:
Summary of the Numbers of Questions/Uncertainties Considered at Each Stage of the Process

CONSULTATION				COLLATION	PRIORITISATION					
Catergory	Sifted Responses			RQ's	STEP 1	LONG LIST		STEP 2	SHORT LIST	STEP 3	TOP 10
	Surv'y	Lit	Total								
Aetiology/ Cause	358	0	358	9	Each category edited by two members of the Steering Group to check assignations and wording, and then the whole considered in a Steering Group meeting to agree Long-List	6	54	Each question in the Long-List scored on 5-point scale by Survey 2 (Prioritisation Survey) and ranked Short-List calculated from ratings.	29	Workshop of 30 determine Top-10 and ranking of the final list, down to 27 following some merging of questions	Top-10 and 11-27
Diagnosis	284	2	286	7		4					
Treatment	388	26	414	11		12					
Self-Manage-ment	317	0	317	8		2					
Care & Support	105	2	107	3		3					
Prognosis	492	4	496	11		12					
Genetics	179	0	179	19		5					
General Qs	70	0	70	11		10					
	2193	32	2227	**79**		**54**			**29**		**10 (27)**
Non-Questions	75		75	**Non-Questions - discarded**							
TOTAL	**2268**		**2302**								

The Steering Group reviewed the three lists, and considered that none of the questions in lists (b) or (c) should be added to the long-list.

There was concern that the breadth of the questions was uneven. In particular the genetics questions were considered to be more specific than many others, and it was felt that this would count against these questions in the later prioritisation; broad questions would tend to be favoured by covering many possible situations.

A number of questions were merged at the meeting, and subsequent reconsideration of the genetics questions resulted in some of these being merged and expressed more broadly. The outcome agreed by the Steering Group was a long list of 54 questions **[Web06 and Annex B]**. Note that each question was given a short code and the number of respondents asking that question was also recorded.

Prioritisation Stage 2: the Short-List

The second stage in the prioritisation process by the JLA procedures is to generate a shortlist of about 30 research questions from the long-list.

The Steering Group decided that it would undertake the long list to shortlist prioritisation via a survey asking respondents to score each of the 54 long list questions on a five-point scale headed "Not a priority, Low priority, Medium priority, High priority, Very high priority", and to use the output to generate an overall ranking to the 54 questions. We asked all 246 people who had expressed a willingness to contribute to the prioritisation from Survey 1 to take part. The profile of this set is shown in Table 5.

We used Survey Monkey[7] to undertake this survey, and used its facility to randomise the order of the unanswered questions given to each respondent to prevent bias. For the survey, the questions were not categorised, see Step 2 (A), and no indication of the number of Survey 1 responses that had been grouped to form that question was given.

It became apparent during testing the survey with members of the Steering Group that the wording of some of the questions proved problematic for the non-clinicians. For this reason we converted the questions into "plain English". Robin Harbour prepared a first draft, which was subsequently reviewed and edited by SG member Jenny Thomson.

The survey form is available on the Cavernoma PSP Resource site **[Web07].**

Replies were received from 136 respondents, all but one of whom scored at least 50 of the RQs (the exception ranked only 17). One person gave every question a Very High Priority score. The respondents were broken down as shown in Table 5.

Table 5: Profile of respondents to Survey 2

	Asked	Answered
Patients	172	91
Clinicians	42	28
Carers/Others	56	22
TOTAL	**270**	**141**
Some respondents fitted more than one category.		

The scores were weighted 1-5 for "Not a priority, Low priority, Medium priority, High priority, Very high priority". The average score for each question was calculated for (a) all returns, (b) Patients, (c) Clinicians and (d) Carers/Others and the average score and variance was also calculated for each respondent **[Web08]**.

Further analysis of the outputs from the survey is provided in Annex C.

Creation of short-list from the rankings of the Prioritisation Survey.

We rejected simply ranking the overall score of each question on the grounds that the result would be dominated by the views of patients due to the much larger number of patients responding. We also rejected the 'best-score' method used by some PSPs which uses the best average score from patients, clinicians and carers/others for each question. The problem with this method is that if one group scores consistently higher than another group, then that group will dominate. To take the extreme example: if group A score everything greater than 'x' and Group B score everything less than 'x', then the outcome is that of Group A alone.

We considered two potential options for using the rankings to prioritising the long-list.

1. Take the mean score for each question from each of the three categories (patients, clinicians, carers/others) and use the average of these three scores

2. Use the three rank-order lists (clinicians, patients and carers/others) and determine how many questions/uncertainties were required to populate each point on the combined rank-order lists. Further detail of this method is given in Annex D.

We opted to use the rank-order method. 28 questions were required to populate all three rank-order lists down to rank-order 20, and 31 questions were required to populate the three lists down to rank-order 21. A subgroup consisting of Robin Harbour, Rustam Al-Shahi Salman, and Simon Temple reviewed and refined the original shortlist, merging two pairs resulting in a final Short-List of 29 questions.

7. www.surveymonkey.com/

Delegates at the Final Workshop

Prioritisation Stage 3: the Workshop

The final prioritisation of the shortlist **[Web09]** was designed to establish the top ten uncertainties. This was undertaken in a full-day workshop on 23rd September 2015 with 29 participants (9 Clinicians, 12 Patients and 8 Carers/Others – see Table 6) chosen to provide representation of the major clinical areas treating cavernoma patients (adult and paediatric neurologists and neurosurgeons, clinical geneticists), the major types of cavernoma (symptomatic and asymptomatic, brain, brainstem, spinal cord) and carers (of both adults and children) together with Angela Collett from the Brain & Spine Foundation.

The day was co-ordinated and run by three JLA Advisers (David Crowe [Cavernoma PSP Project Manager], Richard Morley and Sally Crowe).

Table 6: Participants in final workshop

Clinicians	Patients	Carers/Others
Grace Vassallo	Ian Stuart (SG)	Clare O'Dea
Rustam Al-Shahi Salman (SG)	Roxanna Dixon	Anna Farrar
Neil Kitchen (SG)	Simon Temple (SG)	Paula Wheeler (SG)
Owen Sparrow	David Scott	David White (SG)
Vijeya Ganesan (SG)	Pat Spallone	Barry Gifford
Jennifer Thomson (SG)	Emma Tait	Angela Collett (SG)
Jonathan Berg	Margie Foxton	Julie Manning
Ian Kamaly	Emily Fletcher	Dianne Harniess
Conor Mallucci (SG)	David Pena	
	Abi Rawlins	
	Alice Joy	
	Lottie Gazzard	
Observers:	Neil Henderson (NETSCC) and Amy Street (JLA)	
SG = Steering Group		

The prioritisation was undertaken in three sessions illustrated below. The cards prepared for the workshop are given in **[Web10]**.

The final, plenary, session concentrated on the top 10 questions/uncertainties and their rank order. However, the Workshop recommended that all of the questions remaining after the day's discussions and subsequent resolution of outstanding issues (27 in total) should be added to UKDUETS, with the PSP emphasising the top-10.

5. THE PRIORITISED LIST OF CAVERNOMA UNCERTAINTIES

Delegates at the Workshop pondering the priority to be given to questions laid out on cards **[Web10]**

David Crowe addressing the Workshop

Sally Crowe helping delegates prioritise questions during the first session at the Workshop. LtoR: Sally Crowe, Neil Henderson, Roxanna Dixon, Anna Farrar, Emily Fletcher and Grace Vassallo

The Cavernoma PSP opted to incorporate the full set of 27 prioritised unanswered questions (uncertainties) that were the culmination of the final Workshop onto the "UK Database of Uncertainties about the Effects of Treatments" (UKDUETS[8]), but also to emphasise the Top 10 in relevant publications in the medical literature [Ref08]. The full list of research priorities is set out below split between the Top 10 priorities and priorities 11 to 27.

Top 10 Research Priorities

1. Does treatment (with neurosurgery or stereotactic radiosurgery) or no treatment improve outcome for people diagnosed with brain or spine cavernoma?
2. How do brain or spine cavernomas start and develop?
3. What is the risk of brain or spine cavernomas bleeding for the first and subsequent times?
4. Could drugs targeted at cavernomas improve outcome for people with brain or spine cavernomas compared to no drug treatment?
5. What mechanisms trigger bleeding or epileptic seizures in people with brain or spine cavernomas?
6. Are any features of brain or spine cavernoma on imaging associated with a higher or lower risk of bleeding?
7. Does the use of anticoagulant drugs increase the risk of bleeding from brain or spine cavernoma?
8. Does regular monitoring of brain or spine cavernoma improve outcome compared to no monitoring?
9. What features of brain cavernoma lead to the development of epilepsy, or influence the severity of existing epilepsy?
10. Do any specific activities undertaken by people with brain or spine cavernomas provoke bleeds or other symptoms?

8. http://www.library.nhs.uk/duets/SearchResults.aspx?tabID=294&catID=15622

9. www.jla.nihr.ac.uk/priority-setting- partnerships/cavernoma

Priorities 11-27

11. Is stereotactic radiosurgery or neurosurgery for brain or spine cavernomas better for improving outcome?

12. What is the impact of brain or spine cavernomas on life expectancy?

13. When is the optimum time to start treatment of a brain or spine cavernoma diagnosed in an infant?

14. Why do only around half of people with a cavernoma gene mutation develop symptoms?

15. What causes brain or spine cavernomas arising following radiotherapy for brain tumours?

16. What causes single brain or spine cavernomas?

17. Why do some patients develop multiple cavernomas even though they do not have any of the known genetic variations that can cause them?

18. What are the non-genetic causes of brain or spine cavernomas?

19. Which behavioural or psychological therapies are effective in treating patients following neurosurgery for brain or spine cavernomas?

20. Which symptoms indicate that a brain or spine cavernoma is bleeding?

21. Can a care pathway improve outcome for patients with brain or spine cavernomas?

22. Which brain or spine cavernoma sites carry the highest risk of symptoms that impact on the life of patients?

23. What kind of rehabilitation and support services have been shown to be effective for patients and their families / carers following diagnosis of, or treatment of, brain or spine cavernomas?

24. What are the long-term effects of stereotactic radiosurgery for people with brain or spine cavernomas?

25. What proportion of brain or spine cavernoma bleeds are non-symptomatic?

26. Is it possible to identify signs and symptoms that are unique to brain or spine cavernomas?

27. What is the optimum radiation dose for use in stereotactic radiosurgery of brain or spine cavernomas?

COMMENTARY

Although JLA PSPs are principally concerned with the treatment and management of a particular condition, we chose to broaden the scope to a wider range of topics including cause, diagnosis and prognosis. This allows the wider concerns of patients, their carers and healthcare professionals to be considered, and is reflected in the final list of research priorities.

The top priority concerned the only two available direct treatments of cavernoma, as distinct from treatments of the symptoms: microsurgery and stereotactic radiosurgery (done with gamma knife or linear accelerator techniques). Logically there are four uncertainties concerning the two treatments: their relative effectiveness to each other, their individual efficacies compared to no treatment, or whether no treatment is better than either. All four were in the short list of 31 questions considered at the workshop, the final stage in the prioritisation. The final wording of the top priority is broad and in practical terms embraces three of the four uncertainties. The fourth, the direct comparison between the two treatments, appears outside the top-10 as number 11.

The top-10 uncertainties also include the two most frequently asked questions of the originating survey: one concerning lifestyle, and the other concerning the origins and development of cavernoma. Half of the top-10 questions concern prognosis.

6. SUBMISSION TO UKDUETS

The Workshop itself did not address the full set of data required for submission to UKDUETS. This was completed by Robin Harbour in consultation with Professor Rustam Al-Shahi Salman and Mark Fenton from UKDUETS, and the outcome was then approved by the Steering Group **[Web11].**

The main steps involved in preparation for adding the uncertainties to UKDUETS were:

- Preparation of the questions in PICO (Patients, Intervention, Comparison, Outcome) format
- Carrying out a literature search and identifying existing systematic reviews or guidelines relevant to each question. (This search covered the Cochrane Controlled Trials Register, DARE, Embase, International Controlled Trials Register, Medline, Orphanet)
- Identifying the source of each question (patients, carers, clinicians, published source).

The JLA Website has an excellent summary of the Cavernoma PSP[9] (footnote on page 12).

7. NEXT STEPS AND LESSONS LEARNED

7.1 NEXT STEPS

The PSP represents only the start of the exercise of obtaining good evidence for the management of cavernoma. It is now necessary to promote research to address the identified uncertainties, in the first place by publicising the findings of the PSP, not only on UKDUETS, but also widely in the research literature and elsewhere amongst all those who might undertake the necessary research.

Answering Uncertainties

Finding answers to the uncertainties will require a range of different approaches. What is vital to answering the treatment uncertainties is that the shortcomings brought out in the *Guidelines for the management of cerebral cavernous malformations in adults* **[Web01]** ("the absence of randomised controlled trials and the large number of observational studies of CCM treatment (a) without a comparison group, or (b) not showing a dramatic effect in an observational study, or (c) at high risk of bias") are avoided, and that randomised controlled trials are undertaken where feasible, and where not feasible that attention is paid to how observational studies will be undertaken to be of value to improving the treatment and management of cavernoma.

It is probable that the most rapid improvement in the treatment and management of cavernoma will be from randomised clinical trials and well-conducted observational studies. These improvements will be incremental, and can be disseminated to enable best-practice to be understood by all clinicians. What is also highly desirable is that a cohort of clinicians be established to ensure that these benefits are realised. These approaches from clinicians will provide answers to many of the treatment, prognosis and lifestyle and self-support uncertainties. It is particularly important that that good evidence is obtained for whether, and in what circumstances, gamma-knife surgery is the most effective treatment.

Providing answers to many of the other uncertainties, especially those of cause and genetics, will require basic research, not necessarily by clinicians. It will be from such studies that new forms of treatment, for example the potential for new medication to reduce the development or haemorrhage of cavernoma, will arise. This requires generating knowledge and excitement within the communities of cell biologists and molecular biologists. Such research is taking place. For example, a recent paper [Ref09] describes the molecular causes of cavernoma, working both on mouse models of cavernoma (i.e. mice that generate cavernoma-like structures) and on cavernomas from human patients who have undergone microsurgery for their removal. The UK has very well-established communities capable of taking these approaches in all leading Universities and Research Institutes.

Such studies will not produce therapies in the short term, but there are plausible routes from the basic research to the development of new types of treatment.

The need for a comprehensive database/register

Since the numbers of those diagnosed with cavernoma are relatively small, and the symptoms and appropriate interventions so dependent on the location of the cavernoma, it is highly desirable that a representative database/register of information on the outcomes for cavernoma patients is developed and maintained. Since this database needs to be future-proof and of value to all those who might use it, including for example not just clinicians and research natural scientists, but also social scientists and health economists, it is important that all such research communities have a voice in its design. The database should include information on the lifestyles and treatment of those patients, and needs to follow their future health over their lifetime. It needs to be UK-wide and it is highly desirable that there is co-ordination between clinicians across the UK, so that the high investment in the clinical work undertaken routinely by clinicians is maximized.

Patients' understanding

Further, the responses to the first survey showed that many patients were unaware of a considerable body of evidence familiar to the clinicians, asking questions that were rejected on the basis that the answers were known. We intend to generate a set of what will probably be called 'Frequently Asked Questions' (FAQs) and publicise these more widely on the CAUK website and elsewhere.

7.2 LESSONS LEARNED

Overall, the PSP process was successful in creating a genuine partnership between clinicians, patients and carers to determine the key uncertainties and research issues relating to cavernoma. We were able to address the different emphases given to uncertainties by healthcare professionals and patients that became apparent, and to recognise their importance in our prioritisation. As stated in the section above, one output from this was to highlight the importance of research at all levels. Improvement of preventative, therapeutic and rehabilitative treatments will require a mix of basic and applied research as well as requiring clinical trials.

From the survey responses that were not uncertainties, it became apparent that patients and carers still need good information about what is and what is not known about cavernoma, and to be able to keep this up-to-date as best practice evolves.

However a number of issues and challenges became apparent during the PSP process. Some of these relate to the PSP process itself whilst others relate to the research that will be required to resolve the uncertainties.

Throughout the prioritisation process there was a tension between defining specific questions, which would be directly amenable to research, and broader questions, which were more likely to achieve widespread support and a high ranking during prioritisation. The focus on identifying a list of only 10 high priority questions led towards broader questions. Whilst valid and important topics for research, some of them will inevitably need to be disaggregated into a number of more specific questions for research.

The representation of healthcare professionals in the prioritisation process was uneven, with neurosurgeons, neurologists, stroke physicians and nurses relatively well represented, but with much less representation from other relevant medical specialities. The social care professions were not represented at all. To some extent this is inevitable given that the best-represented specialities are those that are probably most likely to come into contact with patients with cavernoma on a regular basis. This is an issue that future PSPs may wish to consider at an early stage.

It is believed that broadly equal numbers of men and women are affected by cavernoma. However men were significantly under-represented among the survey respondents and this may have had an effect on the outcome. It should be noted that there is a similar gender bias among the members of CAUK, who were the main source of patient and carer recruits for the survey.

During the PSP, it became clear that clinicians, patients and carers had somewhat different priorities. Broadly, the clinicians tended to prioritise treatment uncertainties while patients gave a high priority to self-management and prognosis questions. Some of the issues prioritised by patients and carers may be very hard to answer or may require fundamental research.

Cavernomas occur in a wide range of locations in the brain and spine, have both genetic and non-genetic causes, and become symptomatic at very different ages. In order to develop robust statistical conclusions from research it will be necessary to study large numbers of patients or to study specific sub-groups (e.g. people with the familial form of the condition). It will be challenging to obtain adequate sample sizes for a relatively rare condition.

The results of the PSP are specific to the UK and its healthcare system. It is possible that clinicians, patients and carers in other countries would have different priorities. The UK prioritisation should be valuable to those involved with cavernoma in other countries and may help to promote international collaboration in cavernoma research. This would be helpful in broadening the pool of patients who could participate in research.

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ANNEX A

FURTHER ANALYSIS OF SURVEY 1

Total number of Respondents = 299

A. Respondent profiles for Survey 1

Respondents by category		
	N	%
Patient	203	62.8
Professional	57	17.6
Carer	50	15.5
Organisation	8	2.5
Other	5	1.5
TOTAL	**323**	**100.0**

Other
- I am post op cavernoma
- I have an interest in brain diseases and conditions; a family member had Parkinson's disease
- Mother of son with AVM treated by Gamma Knife
- I have two grandchildren, brother and sister with this condition
- Both my children have multiple cavernomas.

The total is more than the number of respondents because those who were in more than one category (e.g. clinicians with Cavernoma) were double counted.

Analysis of Clinical Respondents	
General Practitioner	1
Medical geneticist	1
Neurologist	11
Neurosurgeon	21
Neurophysiologist	1
Stroke physician	7
Nurse	8
Specialist Stop Smoking Advisor NHS	1
Art Psychotherapist	1
Neurological Rehabilitation (doctor)	1
Neuroradiologist	1
Paediatric neurologist	1
Paediatrician	2
TOTAL	**57**

Location of Cavernoma		
	N	%
Spine	20	8.6
Brain	213	91.4
TOTAL	**233**	**100.0**

More analysis is needed of this table. The greater total of 233 than the number of patients is only very partially explained by 4 declaring cavernoma in both spine and brain.

Relationship of carers to person with cavernoma		
	N	%
Parent	33	62.3
Partner	12	22.6
Child	4	7.5
Sibling	0	0.0
Friend	1	1.9
Colleague	0	0.0
Other	3	5.7
TOTAL	**53**	**100.0**

Other
- I have the Cavernoma
- Grandparent
- Cousin, niece

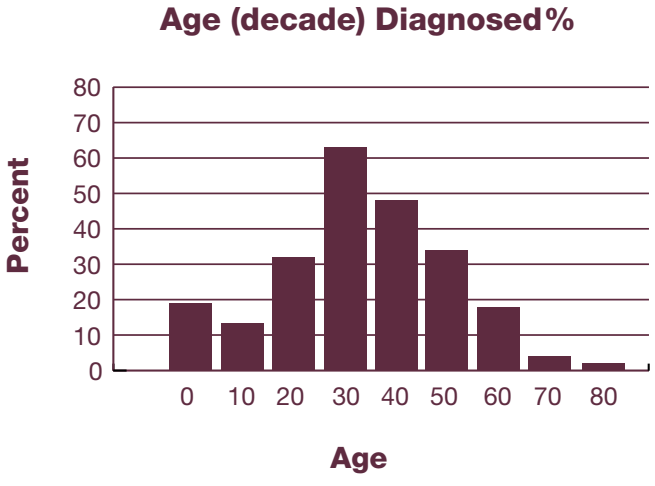
Ethnicity of Respondents		
	N	%
White	250	88.7
Black or Black British	3	1.1
Asian or Asian British	15	5.3
Chinese	2	0.7
Hispanic	4	1.4
Mixed	6	2.1
Any other ethnic group	2	0.7
Subtotal	**282**	**100.0**
Prefer not to say	1	
No Entry	16	
	299	

ANNEX B

Gender of respondents		
	N	%
Male	93	32.6
Female	192	67.4
Subtotal	**285**	**100.0**
No Entry	14	
TOTAL	**299**	

Note that the majority of the patients responding to the survey will have been members of CAUK. The gender imbalance shown here is a feature of CAUK's membership.

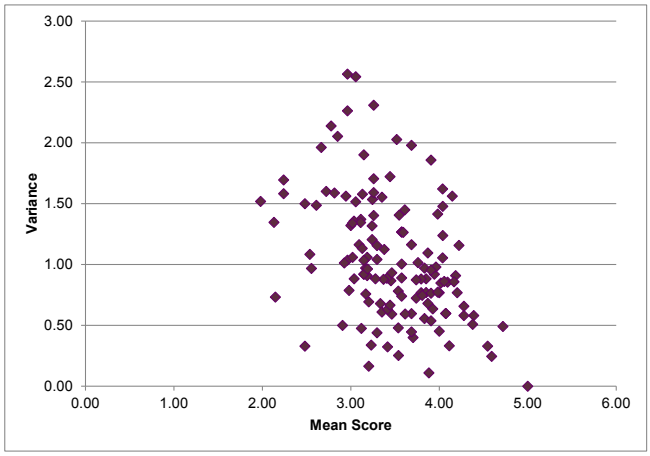
Age Diagnosed by Decade		
Age	N	%
0	17	7.4
10	12	5.2
20	32	14.0
30	63	27.5
40	49	21.4
50	34	14.8
60	19	8.3
70	2	0.9
80	1	0.4
Subtotal	**229**	**100.0**
Not given	70	
Total	**299**	



Note that the average age at diagnosis in this survey was 33.2 years, to be compared to the literature value of 43.2 years (see page 5 and [Ref02]).

VARIATION OF INDIVIDUAL'S RESPONSES

The Figure plots the variance against the mean score for each individual. It is apparent that respondents behaved very differently in their interpretation of importance and in their use of the range of ranking.



ANNEX C

THE LONG-LIST

Table A2 is the Long-List of 54 Unanswered Questions. Each question was assigned a short code in which the alphabetic component indicates the category of origin (see Table 3). “Resp” indicates the number of respondents from Survey 1 who asked this question. ‘Qry’ in this column occurs when the question is the merger of two or more questions.

Table A2: The Long-List ranked by code		
Code	Research Question / Uncertainty	Resp
A1	What is the evidence for non-genetic causes of cavernoma (e.g. age, brain/head injury, high blood pressure, radiation exposure, stress)?	111
A2	What do we know about the ways in which cavernomas can cause or affect epilepsy? (Take into account lobar localization; size of cavernoma; number of cavernomas.)	4
A4	Is the risk of developing a cavernoma affected by gender or ethnic group?	5
A5	Some people develop a single cavernoma for no apparent reason. Others develop more than one cavernoma because of something in their genes. Why does this happen and do these cavernomas develop in different ways?	10
A6	Why do some people develop cavernomas after having radiotherapy for brain tumours? Is it related to the type of brain tumour, the dose of radiotherapy, something in their genes, or some other factor?	2
A7	Would knowing how radiation causes cavernomas help to understand how other cavernomas arise? Could that help find ways of preventing cavernomas?	2
C1	What is the best way to treat emotional and psychological symptoms in patients who have had surgery?	17
C2	What kind of rehabilitation and support works best for patients and their families after they have been diagnosed with or treated for cavernoma?	19
C3	What is the psychological effect on patients or their families of gene testing or genetic counselling?	4
D1	What is the best test for diagnosing cavernomas?	73
D2	If healthcare staff working in primary care were better informed about cavernoma, would they be more likely to diagnose and start treatment more quickly?	16
D3	How can symptoms due to cavernoma be recognised and lead to cavernoma diagnosis?	3
D4	How can patients tell if their symptoms are due to the cavernoma or not?	20
G1	Can we find better ways of telling the difference between hereditary and non-hereditary cavernomas?	60
G2	Does genetic testing in someone with cavernomas improve their medical care and outcome?	39
G3	Does genetic testing in a child of someone with cavernomas, improve their medical care and outcome?	42
G4	Is there an underlying genetic cause of cavernomas and are there any additional genetic or non-genetic factors that trigger their development?	8
G5	How many patients with multiple cavernomas have gene mutations just in their cavernoma cells rather than all their body cells? If the mutations are just in their cavernoma cells, does this mean their relatives are less likely to develop cavernomas?	9
G6	Is it better to analyse DNA from cavernomas removed during surgery or to analyse DNA from blood samples?	2
G7	Why do only 50-60% of people with a cavernoma gene mutation develop symptoms?	2
G8	What other genes cause cavernomas and do different genes lead to different outcomes?	6
G9	Is there a genetic cause of cavernomas that occur alongside other brain blood vessel abnormalities?	2
G10	How likely is it that a mutation that increases the risk of developing a cavernoma will appear in the three known genes (known as CCM1, CCM2 or CCM3)?	Qry
GQ1	How do cavernomas start and develop?	7
GQ3	What proportion of bleeds correlate with a clinical symptom/sign?	1
GQ4	Cavernomas can appear in different locations. Do we know which carry the highest risk?	1
GQ5	Would there be any benefit in establishing a database of all patient reported symptoms and how often they occur?	3
GQ6	Does menopause affect symptoms/signs and follow up?	1
P1	Do we know what factors increase the development of cavernomas and symptoms?	237

P2	What is the risk of a Cavernoma bleeding for the first and subsequent times?	142
P3	Do we know what impact pregnancy and type of childbirth has on cavernomas?	27
P4	Does having a cavernoma affect life expectancy?	31
P5	Is it possible to tell from a scan when a cavernoma is (a) leaking, (b) worsening or (c) about to burst?	1
P6	Is there a list of common symptoms that could alert people with incidental cavernomas to a possible bleed?	1
P7	Does regular monitoring of cavernomas help reduce bleeding and anxiety?	69
P8	Does age make a difference to the severity of symptoms from cavernoma?	2
P9	Is it safe to take blood thinning medicines if a patient has cavernomas?	2
P10	Can someone have a cavernoma without having any symptoms?	1
P11	Are there any conditions other than epilepsy that regularly occur with cavernoma?	5
P12	Is it worth screening children thought to be at high risk of a cavernoma if they are not showing any symptoms?	5
S1	Can special diets or dietary supplements reduce the risk or severity of cavernoma symptoms?	14
S2	Are there any activities cavernoma patients should avoid or take up to reduce the risk of symptoms recurring?	254
T1	Is it better to treat cavernoma with stereotactic radiosurgery (gamma knife) or to have no treatment?	64
T2	Is it better to treat cavernoma with stereotactic radiosurgery (gamma knife) or to have an operation to remove it?	13
T3	Which healthcare specialists should look after patients with cavernomas?	19
T4	Is it better to treat cavernoma with an operation to remove it or to have no treatment?	109
T5	Are there any drug treatments for cavernomas?	59
T6	Is there any evidence that alternative therapies are effective in the treatment of cavernoma?	18
T7	Could the introduction of a care pathway for cavernoma improve outcome for patients?	3
T8	When an infant is diagnosed with a cavernoma, is it better to start treatment early or to wait until later in life?	4
T9	Do the risks of cavernoma treatment outweigh the risks of recurrent haemorrhage from cavernoma?	11
T10	Do we know if nervous tissue interacts differently to cavernoma than normal blood vessels, thereby indicating a possible target of treatment?	1
T11	What is the appropriate radiation dose for use in radiosurgery (gamma knife) of cavernomas?	Qry
T12	What are the long-term effects of stereotactic radiosurgery (gamma knife)?	Qry

Qry = Number of respondents uncertain due to merger of questions.

ANNEX D

FURTHER ANALYSIS OF THE PRIORITISATION SURVEY

Table A3(A) shows the average score for each Research Question (RQ) / Uncertainty from the Clinicians. 'No' is the number who scored that RQ, 'Ave' is the average score, 'C' is the short code for that question and 'R' the number of respondents in Survey 1 who asked that RQ.
Similar Tables were recorded for 'Patients', for 'Carers/Others' and for 'All'. These are available in **[Web08]**

Table A3(A): CLINICIANS

No	Ave	RQ	C	R
28	4.64	Do the risks of cavernoma treatment outweigh the risks of recurrent haemorrhage from cavernoma?	T9	11
28	4.61	Is it better to treat cavernoma with stereotactic radiosurgery (gamma knife) or to have an operation to remove it?	T2	13
27	4.56	Is it better to treat cavernoma with an operation to remove it or to have no treatment?	T4	109
28	4.32	Is it better to treat cavernoma with stereotactic radiosurgery (gamma knife) or to have no treatment?	T1	64
28	4.25	Is it safe to take blood thinning medicines if a patient has cavernomas?	P9	2
28	4.11	What is the risk of a Cavernoma bleeding for the first and subsequent times?	P2	142
28	4.00	What are the long-term effects of stereotactic radiosurgery (gamma knife)?	T12	Qry
27	3.85	Cavernomas can appear in different locations. Do we know which carry the highest risk?	GQ4	1
28	3.82	Why do some people develop cavernomas after having radiotherapy for brain tumours? Is it related to the type of brain tumour, the dose of radiotherapy, something in their genes, or some other factor?	A6	2
28	3.75	Is it possible to tell from a scan when a cavernoma is (a) leaking, (b) worsening or (c) about to burst?	P5	1
26	3.73	When an infant is diagnosed with a cavernoma, is it better to start treatment early or to wait until later in life?	T8	4
28	3.68	Would knowing how radiation causes cavernomas help to understand how other cavernomas arise? Could that help find ways of preventing cavernomas?	A7	2
28	3.68	Do we know what factors increase the development of cavernomas and symptoms?	P1	237
28	3.61	How do cavernomas start and develop?	GQ1	7
28	3.61	Does regular monitoring of cavernomas help reduce bleeding and anxiety?	P7	69
28	3.61	What is the appropriate radiation dose for use in radiosurgery (gamma knife) of cavernomas?	T11	Qry
27	3.59	Why do only 50-60% of people with a cavernoma gene mutation develop symptoms?	G7	2
26	3.54	What proportion of bleeds correlate with a clinical symptom/sign?	GQ3	1
27	3.48	Is there an underlying genetic cause of cavernomas and are there any additional genetic or non-genetic factors that trigger their development?	G4	8
27	3.44	Some people develop a single cavernoma for no apparent reason. Others develop more than one cavernoma because of something in their genes. Why does this happen and do these cavernomas develop in different ways?	A5	10
27	3.44	Does having a cavernoma affect life expectancy?	P4	31
27	3.41	Would there be any benefit in establishing a database of all patient reported symptoms and how often they occur?	GQ5	3
28	3.39	What do we know about the ways in which cavernomas can cause or affect epilepsy? (Take into account lobar localization; size of cavernoma; number of cavernomas.)	A2	4
28	3.39	Do we know what impact pregnancy and type of childbirth has on cavernomas?	P3	27
27	3.33	Are there any drug treatments for cavernomas?	T5	59
28	3.32	What other genes cause cavernomas and do different genes lead to different outcomes?	G8	6
26	3.31	Is it better to analyse DNA from cavernomas removed during surgery or to analyse DNA from blood samples?	G6	2
27	3.30	Does genetic testing in someone with cavernomas improve their medical care and outcome?	G2	39
27	3.26	Can we find better ways of telling the difference between hereditary and non-hereditary cavernomas?	G1	60

27	3.26	Does genetic testing in a child of someone with cavernomas, improve their medical care and outcome?	G3	42
27	3.26	Is there a genetic cause of cavernomas that occur alongside other brain blood vessel abnormalities?	G9	2
27	3.26	Could the introduction of a care pathway for cavernoma improve outcome for patients?	T7	3
27	3.22	How many patients with multiple cavernomas have gene mutations just in their cavernoma cells rather than all their body cells? If the mutations are just in their cavernoma cells, does this mean their relatives are less likely to develop cavernomas?	G5	9
27	3.19	Is it worth screening children thought to be at high risk of a cavernoma if they are not showing any symptoms?	P12	5
27	3.11	How likely is it that a mutation that increases the risk of developing a cavernoma will appear in the three known genes (known as CCM1, CCM2 or CCM3)?	G10	Qry
27	3.07	What is the psychological effect on patients or their families of gene testing or genetic counselling?	C3	4
28	3.04	What is the evidence for non-genetic causes of cavernoma (e.g. age, brain/head injury, high blood pressure, radiation exposure, stress)?	A1	111
27	3.00	What is the best way to treat emotional and psychological symptoms in patients who have had surgery?	C1	17
27	3.00	Do we know if nervous tissue interacts differently to cavernoma than normal blood vessels, thereby indicating a possible target of treatment?	T10	1
27	2.96	Are there any activities cavernoma patients should avoid or take up to reduce the risk of symptoms recurring?	S2	254
26	2.96	How can symptoms due to cavernoma be recognised and lead to cavernoma diagnosis?	D3	3
27	2.93	Which healthcare specialists should look after patients with cavernomas?	T3	19
26	2.92	Is there a list of common symptoms that could alert people with incidental cavernomas to a possible bleed?	P6	1
26	2.92	Does age make a difference to the severity of symptoms from cavernoma?	P8	2
27	2.85	Is the risk of developing a cavernoma affected by gender or ethnic group?	A4	5
26	2.85	How can patients tell if their symptoms are due to the cavernoma or not?	D4	20
27	2.81	What kind of rehabilitation and support works best for patients and their families after they have been diagnosed with or treated for cavernoma?	C2	19
26	2.81	What is the best test for diagnosing cavernomas?	D1	73
27	2.59	Does menopause affect symptoms/signs and follow up?	GQ6	1
27	2.52	Are there any conditions other than epilepsy that regularly occur with cavernoma?	P11	5
27	2.37	Is there any evidence that alternative therapies are effective in the treatment of cavernoma?	T6	18
27	2.30	If healthcare staff working in primary care were better informed about cavernoma, would they be more likely to diagnose and start treatment more quickly?	D2	16
27	2.04	Can special diets or dietary supplements reduce the risk or severity of cavernoma symptoms?	S1	14
26	1.88	Can someone have a cavernoma without having any symptoms?	P10	1

Table A3(B) Shows the rank scored by the Clinicians, Patients and Carers/Others for each question.
Table A3(C) is the same data analysed to show the Research Question by Rank for Clinicians, Patients and Carer/Others.
"BOX A – 21" lists the RQs that are contained at least once in Table A3(C) down to Rank 21; there are 31 RQs in "BOX A – 21"

TABLE A3(B)

Code	RANK		
	Clinician	Patient	Carer
A1	37	9	14
A2	23	16	17
A4	45	53	53
A5	20	21	6
A6	9	38	34
A7	12	33	22
C1	38	32	19
C2	47	29	7
C3	36	51	44
D1	48	27	39
D2	52	25	25
D3	41	11	18
D4	46	6	29
G1	29	44	38
G10	35	42	46
G2	28	52	52
G3	30	49	45
G4	19	28	11
G5	33	45	33
G6	27	50	50
G7	17	47	49
G8	26	46	26
G9	31	40	27
GQ1	14	12	1
GQ3	18	19	23
GQ4	8	20	9
GQ5	22	22	35
GQ6	49	35	51
P1.	13	2	4
P10	54	54	54
P11	50	24	24
P12	34	48	43
P2.	6	8	21
P3.	24	39	40
P4.	21	18	13
P5	10	1	20
P6	43	5	8
P7	15	15	31
P8	44	41	41
P9	5	13	12
S1	53	37	48
S2	40	4	16
T1	4	14	28
T10	39	34	47
T11	16	36	36
T12	7	23	30
T2	2	10	32
T3	42	26	37
T4	3	7	3
T5	25	17	5
T6	51	43	42
T7	32	30	10
T8	11	31	15
T9	1	3	2

TABLE A3(C)

Rank	RANK		
	Clinician	Patient	Carer
1	T9	P5	GQ1
2	T2	P1.	T9
3	T4	T9	T4
4	T1	S2	P1.
5	P9	P6	T5
6	P2.	D4	A5
7	T12	T4	C2
8	GQ4	P2.	P6
9	A6	A1	GQ4
10	P5	T2	T7
11	T8	D3	G4
12	A7	GQ1	P9
13	P1.	T1	A1
14	GQ1	P9	P4.
15	P7	A2	S2
16	T11	P7	T8
17	G7	T5	A2
18	GQ3	P4.	D3
19	G4	GQ3	C1
20	A5	GQ4	P5
21	P4.	A5	P2.
22	GQ5	GQ5	A7
23	A2	T12	GQ3
24	P3.	P11	P11
25	T5	D2	D2
26	G8	T3	G8
27	G6	D1	G9
28	G2	G4	T1
29	G1	C2	D4
30	G3	T7	T12
31	G9	T8	P7
32	T7	C1	T2
33	G5	A7	G5
34	P12	GQ6	GQ5
35	G10	T10	A6
36	C3	S1	T3
37	A1	T11	T11
38	C1	A6	G1
39	T10	P3.	D1
40	S2	G9	P3.
41	D3	P8	P8
42	T3	G10	T6
43	P6	T6	P12
44	P8	G1	C3
45	A4	G5	G3
46	D4	G8	G10
47	C2	G7	T10
48	D1	P12	S1
49	GQ6	G3	G7
50	P11	G6	G6
51	T6	C3	GQ6
52	D2	G2	G2
53	S1	A4	A4
54	P10	P10	P10

BOX A - 21

A1	P4.
A2	P5
A5	P6
A6	P7
A7	P9
C1	S2
C2	T1
D3	T11
D4	T12
G4	T2
G7	T4
GQ1	T5
GQ3	T7
GQ4	T8
P1.	T9
P2.	

This report is dedicated to Ian Stuart

Ian Stuart was diagnosed with a brainstem cavernoma in 1987. On returning to England from California, he realised that others with cavernoma felt isolated and had difficulty in learning about their condition and, in 2005, he founded the patient support group now known as Cavernoma Alliance UK (CAUK). This became a charity in 2006, so this report is published in CAUK's Tenth Anniversary Year.

CAUK is a membership organisation, and as one of the founder members said on Facebook in April this year (2016) "If it wasn't for Ian and his determination and drive then CAUK wouldn't exist. When I was diagnosed there was nothing in the UK and Ian started the charity himself from his bedroom. There are not many people who have a symptomatic cavernoma who would have the energy to do what he does."

CAUK now has 1200 members and is a thriving charity providing support to all with cavernoma, their relatives, friends and carers, and to the professional healthcare community.

Ian also realised from the outset that it was vital that the treatment of cavernoma be put on a firmer foundation. He was instrumental with a small group of others, notably Professor Rustam Al-Shahi Salman and Mr Neil Kitchen, in realising the necessity of having a good evidence base for the treatment and management of cavernoma, and that the JLA PSP would enable the identification and prioritisation of the research questions that need answering.

This report is dedicated to Ian in recognition of his continuing leadership and care for the cavernoma community.

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