SUGGESTED RESPONSES TO FAQs

GENERAL

Q1 I don't want my management approach to be decided by chance, this is far too important a decision for that. I want my surgeon or neurologist to suggest what they recommend in my case.

For some people with at least one symptomatic brain cavernoma it will not be clear what is best: treatment including surgery or treatment without surgery.

At the moment, there is no reliable evidence to recommend which of these approaches to take for some people with a symptomatic brain cavernoma and this is why the CARE Study has been set up.

Currently what happens is that these people are faced with one of the following scenarios:

1. Their doctor may recommend treatment without surgery on the one hand, or on the other they may recommend treatment including surgery. This recommendation is based on the doctor's knowledge, experience and personal opinion. A doctor in another hospital might recommend the same person not to have surgery. That's because we do not have reliable evidence to indicate that either approach is best.

2. The doctor may explain that they are unable to make a recommendation and suggest that you make a decision between treatment including surgery and treatment without surgery. You may find that decision very difficult to make.

The CARE Study has been set up, to compare treatment including surgery and treatment without surgery for symptomatic brain cavernoma and determine whether one results in better outcomes than the other. It is the same type of study (a randomised controlled trial) as the studies which have found out how we can best treat COVID-19. The aim is to provide reliable evidence for doctors to be able to make clear recommendations for treatment to people in your position in future.

Q2 So I understand that you are comparing these two approaches to managing a symptomatic brain cavernoma. But if you need 2 groups to compare, why can't you just let patients choose? Some will choose treatment including surgery and some will choose treatment without surgery and surely you can then compare the two groups?

To make a fair and reliable comparison between treatment including surgery and treatment without surgery, we need two groups of people who are similar to start with in all ways, apart from which treatment approach they get. Then if one group does better than the other, we'll be able to conclude this was because of the treatment approach which that group received and not due to anything else.

The only way to ensure the groups are similar is to assign people to groups by chance or at random – a process known as 'randomisation'.

If doctors or patients decide which group each patient should join, this allows bias to creep in. For example, the group whose treatment includes surgery would be more likely to include younger and fitter people, reflecting surgeons' and patients' beliefs that these people are more likely to benefit from surgery.

The only reliable method of ensuring the groups are similar, is to assign people to groups by chance, using randomisation. These studies are called 'randomised controlled trials' and they are the fairest way of comparing treatments. For example, they have taught us which drugs do and which drugs don't help to prevent or treat COVID-19.

For this reason, neither you, nor your neurologist or neurosurgeon, can decide whether you receive treatment with surgery or treatment without surgery in the CARE Study.

If you feel strongly you do want to decide what treatment approach you have, then you should not enrol in the CARE Study and you can choose what to do outside of the CARE Study.

There's more information about the benefits of randomised controlled trials, to individuals and the public, on our website.

Q3 In the patient information leaflets 2 types of surgery are described. I don't understand who will decide if I get brain surgery (referred to in the patient information leaflet as neurosurgery and involving removal of the cavernoma) or focussed radiation treatment (referred to as stereotactic radiosurgery). Is this something the doctor will decide, or can I decide?

For some people either treatment including surgery or treatment without surgery will be suitable and this is the first question that your doctor will advise you on. If both are suitable options for you, then you may be eligible to take part in the CARE Study, if you choose.

Having made this clear, the next question for your doctor to answer will be: if you join the CARE Study and find yourself allocated to treatment including surgery, would they recommend brain surgery (referred to as neurosurgery and including removal of the cavernoma) or focussed radiation treatment (referred to as stereotactic radiosurgery). Doctors may recommend either brain surgery or focussed radiation treatment depending on where the cavernoma is located in the brain. These decisions are often made by 'multidisciplinary teams' of doctors including neurosurgeons, neurologists, and radiologists. The most suitable type of treatment is then proposed to the patient.

If your doctor decides that both brain surgery and focussed radiation treatment are options for you, then you may be asked whether you prefer one or the other. If you have no strong preference, then the type of treatment you would get if allocated to 'Treatment including Surgery' by the CARE Study can be decided by chance (randomisation) in the same way that treatment including surgery or treatment without surgery will be decided by chance (randomisation).

Q4 This is a really hard decision to make, whether to participate in this study. I don't know what to do.

We understand that this can be a very difficult decision to make, and we are here to support you in making it We recommend that you would take time to reflect on the options available and discuss these with your family, friend and doctors. You will find lots of helpful information on our website about the CARE Study and the value of randomised controlled trials. The specialist who you have seen about your cavernoma is likely to be willing to discuss the treatment options with you again. They understand that these decisions are difficult for patients and are usually happy to follow-up their conversation with you to help you come to a decision. You are also welcome to call our helpline, to talk through your options.

Q5 There has been a lot of publicity recently about the development of drugs to reduce the risks of bleeds. Won't such drugs make it better to wait if we are undecided about surgery?

Currently, brain surgery (referred to in the patient information leaflet for the CARE Study as neurosurgery and also known as neurosurgical excision) and focussed radiation treatment (referred to in the patient information leaflet as stereotactic radiosurgery) are the two treatments used for cavernomas in standard clinical practice around the world. That is reflected in current guidelines for clinical practice[1].

But we don't know for sure that these forms of treatment including surgery are more effective than treatment without surgery. At the moment, we are many years away from knowing whether drugs might or might not work and for whom. Most drug treatments for cavernoma have been tested in animals only, and the few that are being tested in humans are at a very early stage in clinical trials. So, the priority is to evaluate the treatments that are already being used and will likely remain options, whilst awaiting the results of the drug trials.

Q6 What are the long- and short-term side effects of the treatment approaches in the CARE Study?

The possible benefits and side effects of all treatment approaches in the CARE Study are described in a table in the CARE Study supplementary Patient Information Leaflet. You can also read more about these standard treatments for cavernoma in our Information booklet: symptomatic brain cavernomas.

[1] 1. https://cavernoma.org.uk/wp-content/uploads/2021/05/Guidelines-for-CCM-Management-in-Adults.pdf
2. https://cavernoma.org.uk/wp-content/uploads/2020/09/Kelly-Fleming-What-a-practicing-clinician-should-know.pdf

If you have further questions, not answered by this information, we suggest you note these down and discuss them with your doctors.

Q7 What is the recovery time from surgery?

The recovery time depends on the type of treatment with surgery.

- **Brain surgery (Neurosurgery)** – several days in hospital and then, provided there are no complications, several weeks recovering at home. Timings vary depending on what type of surgery is done, the site of the cavernoma, complications etc, so you should ask your neurosurgeon how long they expect your recovery to take in your case.

  You may not drive for at least six months after the operation.

- **Radiation treatment (stereotactic radiosurgery)** – day case procedure. A few days feeling headachy and a bit off does happen.

There are also specific considerations about driving, which are described:

- for the UK on the DVLA's website: https://www.gov.uk/guidance/neurological-disorders-assessing-fitness-to-drive#cavernous-malformation

  Note that on the DVLA list of conditions website page it lists Angioma but not cavernoma. On the Angioma page, the heading is 'Angioma or cavernoma' so with cavernoma you should follow the guidelines for Angioma.

- for the Republic of Ireland on the RSA (Road Safety Authority) website: https://www.rsa.ie/docs/default-source/services/s2-licensed-drivers/slainte-agus-tiomaint-medical-fitness-to-drive-guidelines-2021.pdf

Q8 What are the Pros and Cons of taking part in the CARE Study?

Pros

There are various benefits to taking part in this research study:

- You may find it a relief to have the decision about whether to have surgery taken out of your hands.
- Your health in this study will be under review with the possibility of an additional brain MRI scan. You may feel supported by this.
- The results of this study will help doctors to improve the healthcare of patients in the future.

Your participation in the CARE Study will help doctors to work out if it will be possible to determine whether treatment without surgery or treatment including surgery is best in a larger study in the future. Your participation will allow us to design future studies with patients, carers and families at the forefront.

Cons

If you take part in the CARE Study, you will not be able to choose whether you/your child has treatment including surgery or treatment without surgery as this will be determined by chance (randomisation).

The risks associated with treatment without surgery and treatment including surgery are summarised in the table in the CARE Study supplementary patient information leaflet with more detail in the section entitled **What are the possible disadvantages of taking part?**

Attending research appointments at the hospital and completing the 6-month follow up questionnaires at home will take up some of your time. The researchers involved in the study will do their best to work around you when organising appointments and calls. Taking a blood sample for DNA may cause discomfort or bruising.

Q9 What does joining the study involve and how long will I be involved?

If you participate in the CARE Study, you will receive all the normal care and support that would be given in standard NHS care outside the study. In addition, the research team at your hospital will support you to understand the CARE Study and enrol, if you choose.

If you decide to take part, you will first be asked to complete a questionnaire and invited to give a small blood sample. You will be told whether you have been allocated to treatment without surgery or treatment including surgery.

If you are allocated to treatment including surgery, you will receive the relevant surgical treatment, usually within around 3 months. If you are allocated to treatment without surgery, you will be offered all the usual care that this involves.

Whichever treatment you receive, you will be invited to one extra visit to the hospital 6 months after you join the study and will be asked to have a brain MRI scan at this time to assess the cavernoma and whether it has changed. This scan will be in addition to your normal clinical care, if you are treated without surgery and will take 20-30 minutes. The whole appointment should last around 3 hours.

A member of the central research team (based within the Trial Coordinating Centre at the Edinburgh Clinical Trials Unit) will get in touch with you by telephone or email every 6 months until the end of the study to check how you are doing. They will send you some questionnaires by post for you to post back to them by freepost.

The CARE Study team currently plan to finish the study around May 2023, but it may be later if further funding is obtained to continue, in which case they will let you know.

The CARE Study Short patient information leaflet and CARE Study Supplementary patient information leaflet contains more details about what taking part in the study involves.

Q10 What does it mean that to be eligible a person must have a "Clinical history attributable to a brain cavernoma of symptomatic stroke due to ICH or FND or epileptic seizure(s)"

The CARE Study requires that there is certainty that the diagnosed cavernoma is the cause of the symptoms. It is very difficult to prove a link between some symptoms and a cavernoma (for example headaches, migraine, memory loss) and different doctors are not always consistent in this. This inconsistency complicates the CARE Study. The reason why the symptoms are limited to 'symptomatic stroke due to ICH, FND or epileptic seizure(s)' is so that a link between the cavernoma and these symptoms can be agreed and applied consistently by all the Study Teams. This definition will be clear to the doctors in the Study Team but may be less clear to people with cavernoma and their families.

We can try to help you determine whether you are eligible. The CARE Study requires that there is certainty about the diagnosis of a cavernoma, and this it has caused symptoms. People are eligible if they have had symptoms due to either bleeding in the brain (known as brain haemorrhage), a 'focal neurological deficit' or epileptic seizure now, or at some point in the past. Study Teams will ask about your symptoms to confirm that they are due to the cavernoma. This will be best understood by the doctors in the Study Team.

- Intracranial haemorrhage is often called a haemorrhagic stroke.
- A Focal Neurological Deficit (FND) is a symptom or problem with the function of your body that can be clearly linked to the location of the cavernoma in your brain. Examples are muscle weakness in a specific part of the body e.g. drooping of the left side of the face, partial paralysis of the right arm. Speech, vision, and hearing problems are also considered focal neurological deficits.
- Epileptic seizures can affect people in different ways, but usually involve a loss of awareness of your surroundings or jerking of one of your limbs.

It can be difficult to prove a link between some symptoms and a cavernoma (for example headaches). Different doctors are not always consistent in this, and the decision of the specialist you see in the CARE Study is final.

CAUK Helpline colleagues are here to guide you, but are not able to deal with the detail of what defines a symptomatic cavernoma. They must leave the final decision about eligibility to doctors in the CARE Study team at participating hospitals. So, if you think you have or have been diagnosed with a symptomatic cavernoma, you will be advised to speak to a doctor in the CARE Study team.

CHILDREN, YOUNG PEOPLE AND CAVERFAMILIES

Q11 How will my child and family be followed up and supported? Short and long term?

If you participate in the CARE Study, you will receive all the normal care and support that would be given in standard clinical practice. In addition, the research team at your hospital will support you to understand the CARE Study and enrol, if you choose.

If you decide you want your child to take part, you will first be asked to complete a questionnaire about your child. Your child will also be invited to give a small blood sample, which is optional. You will be told whether your child has been allocated to treatment without surgery or treatment including surgery.

If your child is allocated to treatment including surgery, they will receive the relevant surgical treatment, usually within around 3 months. Your child will also receive any medical treatment that they would receive in their usual care if they were not in the study. Likewise, if you are allocated to treatment without surgery, you will be offered all the usual care that this involves.

You and your child will be invited to one extra visit to the hospital 6 months after they join the study, and your child will be asked to have a brain MRI scan at this time to assess the cavernoma and whether it has changed. This scan may or may not be extra to your child's normal clinical care if they are treated without surgery, because normal practice varies as to whether this is offered. It will take 20-30 minutes. The whole appointment should last around 3 hours.

A member of the central research team (based within the Trial Coordinating Centre at the Edinburgh Clinical Trials Unit) will get in touch with you and your child by telephone or email every 6 months until the end of the study to check how they are doing. They will send you some questionnaires by post for you to post back to them by freepost. The study team currently plan to finish the study around May 2023, but it may be later if further funding is obtained to continue, in which case the team will let you know.

Q12 How will taking part in the trial affect school absence and what support will there be during this time?

If your child joins the CARE Study and is allocated to have neurosurgery, they will need to take time off to have the surgery and recover from it. Your neurosurgeon will be able to advise on how long this will be in your child's case, but it is likely to involve a few days in hospital then a period of weeks until fully recovered.

If your child joins the CARE Study and is allocated to have treatment without surgery, they will need to continue to attend for their usual appointments as advised by your multidisciplinary team.

Your child will be invited to attend for a 6-month check-up, which includes an MRI scan (which takes about 20-30 minutes) and the whole appointment usually lasts around 3 hours. Reviews after that will depend on your child's symptoms and your neurologist or neurosurgeon will be able to advise.

Q13 What are the risks to the child?

The risks and benefits of both treatment approaches in the CARE Study are described in a table in the Supplementary Patient Information Leaflet, reproduced in Annex 1. Specific additional considerations for children are:

- there is reluctance to use radiation in very young children due to the potential effects on the developing brain, so a very young child taking part in the CARE Study would usually either have treatment including brain surgery (neurosurgery) or treatment without surgery.

Q14 Can we as parents choose or my child's Neurologist/Neurosurgeon make the decision as to whether it's a good idea for my child to take part in the trial?

Your doctors will help you and your family in your decision-making by explaining the different treatment options and providing information about the risks and benefits of each. Decision-making should be an inclusive process, taking into account the wishes of those involved.

- If you're based in England, Wales or Northern Ireland and your child is 15 years of age or younger, you will need to provide your consent as parent/guardian to your child's participation in the CARE Study. This is the same in Scotland, unless your child has been deemed to have capacity by a clinician, in which case they may consent for themselves to take part.
- If you're based in England, Wales, Northern Ireland or Scotland and your child is 16 years old or older, they will be given the same information leaflet as an adult and be able to provide consent to the study themselves.
- If you're based in the Republic of Ireland and your child is under 18 years of age, you will need to provide your consent as parent/guardian to your child's participation in the CARE Study.

ANNEX 1: TABLE COMPARING TREATMENT INCLUDING SURGERY AND TREATMENT WITHOUT SURGERY

Reproduced from the Supplementary Leaflet for Adults[2]

	Treatment without surgery	Treatment including surgery	
		Neurosurgery	Stereotactic radiosurgery
What may be involved?	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan	• Treat symptoms • Prevent seizures • Rehabilitation • Brain scan
		• Hospital admission for days • General anaesthetic • Opening in the skull • Operation to remove cavernoma • Follow-up brain scan • Must not drive for 6 months	• Hospital attendance for a day • Anaesthetic not needed • Head fixed in a temporary frame • Focussed radiation given once • Follow-up brain scans
What are the possible benefits?	• Bleed/stroke risk reduces as time passes • Avoids risks of neurosurgery or radiosurgery	• Risk of bleed/stroke lower if cavernoma removed • Less worry about symptoms returning	• Risk of bleed/stroke may be lower if cavernoma stabilised, but these benefits are uncertain • Less worry about symptoms returning

[2] https://www.ed.ac.uk/files/atoms/files/care_-_supplementary_pil_adult_v2.0_22mar2021.pdf

	Treatment without surgery	Treatment including surgery	
		Neurosurgery	Stereotactic radiosurgery
What are the possible risks?	• Future bleed/stroke due to cavernoma o Can be mild o May be disabling o Rarely be fatal o Risk higher for cavernoma in brainstem	• Bleed/stroke due to neurosurgery o Can be mild o May be disabling o Rarely be fatal o Risk higher for cavernoma in brainstem	• Bleed/stroke despite radiosurgery o Can be mild o May be disabling o Rarely be fatal o Risk higher for cavernoma in brainstem
	• Epileptic seizures, which may be difficult to control	• Epileptic seizures may not go away	• Epileptic seizures may not go away
	• Cavernoma remains in the brain, so the risks of stroke and seizure may never go away	• Cavernoma may come back	• Cavernoma not removed
	• Worry about symptoms returning	• Complications of treatment (e.g. infection or damage to brain around the cavernoma)	• Complications of treatment (e.g. damage to brain around the cavernoma)