Ensuring your trial is designed for all who could benefit

Trial teams need to do everything possible to make their trial relevant to the people to whom the results are intended to apply (often patients) and those expected to apply them (often healthcare professionals). The four questions below are intended to prompt trial teams to think about who should be involved as participants, and how to facilitate their involvement as much as possible. These questions should be considered by trial teams in partnership with patient and public partners, including individuals from, or representing, groups identified in Question 1. Note that:

* *‘Intervention*’ means the treatment, initiative or service being evaluated.
* ‘*Comparator*’ means the what the intervention is being compared to.
* ‘*Effective*’ means the intervention provides important benefits for people with the disease or condition that is the focus of the trial.

We recommend that trial teams use the worksheets to help them think through their answers to the four key questions.

**1.** Who should my trial results apply to?

Which groups in the community could benefit from the intervention if it was found effective, or benefit from not having it if it was found ineffective and/or harmful?

**2.** Are the groups identified in Question 1 likely to respond to the treatment in different ways?

How might the disease or cultural factors mean that some groups in the community respond to, or engage with, the treatment(s) being tested in different ways?

**3.** Will my trial intervention and/or comparator make it harder for any of the groups identified in Question 1 to engage with the intervention and/or comparator?

How might the intervention and/or comparator, including how they are provided, make it harder for some groups in the community to take part in the trial?

**4.** Will the way I have planned and designed my trial make it harder for any of the groups identified in Question 1 to consider taking part?

How might elements of trial design, such as eligibility criteria or the recruitment and consent process, make it harder for some groups in the community to take part?

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| **1. Who should my trial results apply to?** |
| **[NB. Completed by Sarah Prowse, University of Aberdeen. We were not involved in this trial,** **we did not discuss the information on the worksheets with the trial team, and the worksheets were completed retrospectively rather than at trial design, none of which is ideal.**  **The key documents we used regarding the trial were the final report sent to the funder (NIHR)** [**https://doi.org/10.3310/eme08080**](https://doi.org/10.3310/eme08080) **and the registration document** [**https://www.isrctn.com/ISRCTN15960635**](https://www.isrctn.com/ISRCTN15960635)**.**  **Given the above, the information in the worksheets may not be a proper reflection of the trial because we did not have access to all the trial materials. The information is therefore intended to be illustrative, not definitive.]**  TOPSAT 2 was a UK and European trial to establish the efficacy of a strategy of early aneurysm treatment (within 72h of ictus) in a population of World Federation of Neurosurgical Societies grade 4-5 (WFNS high grade) aneurysmal subarachnoid haemorrhage (aSAH) patients in comparison with the conventional strategy of treatment of aneurysm after neurological improvement (to WFNS grade 1-3). The [NHS describes SAH](https://www.nhs.uk/conditions/subarachnoid-haemorrhage/) as an uncommon type of stroke caused by bleeding on the surface of the brain, often caused by a burst blood vessel (a ruptured brain aneurysm).  Patients with WFNS grade 1-3 usually recover well, but patients with high WFNS grade (4-5) often end up with a bad outcome such as death or severe disability. Grade 1-3 patients are treated early, based on high quality evidence from studies. However, there is no good evidence base for determining the best way of treating those with grade 4-5 SAH. The trial was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health and Care Research (NIHR) partnership.  The [National Study of Subarachnoid Haemorrhage](https://www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwj0j7O-wt6GAxWPTEEAHTHgCvAQFnoECBgQAQ&url=https%3A%2F%2Fwww.rcseng.ac.uk%2F-%2Fmedia%2Ffiles%2Frcs%2Fstandards-and-research%2Fresearch%2Fnational-study-of-subarahnoid-haemorrhage-final-report-2006.pdf&usg=AOvVaw2bYvO05yKJhz7bteTy8EyN&opi=89978449) carried out in 34 Neurosurgical Units in the UK and Ireland from 2001-2002 found the estimated the prevalence of SAH at approximately 8 per 100,000. As this type of stroke is less common, the prevalence of SAH by ethnicity is unclear. [Previous research](https://pubmed.ncbi.nlm.nih.gov/16426989/) has shown that ethnic disparities in the rates of stroke types could be due to substantial differences found in risk factor profiles between ethnic groups (such as age, sex, hypertension, cardiac disease, diabetes, smoking status, and obesity among others).  SAH are most common in people aged 45 and 70 and may be more common in those from Black ethnicities than other ethnic groups. The [NHS](https://www.nhs.uk/conditions/subarachnoid-haemorrhage/) notes this may be because those from Black ethnicities are more likely to have high blood pressure, although disparities exist between the UK and country of origin. For example, [research has shown](https://www.ahajournals.org/doi/full/10.1161/STROKEAHA.108.518852) the risk of stroke is higher in Black Caribbeans in the UK compared with Black Caribbeans in their country of origin which may be caused by factors such as a higher prevalence of stroke risk factors, differences in treatment plans for co-morbid conditions, and less healthy lifestyle practices compared with indigenous Black Caribbean populations.  Thinking of stroke more broadly, the [NHS](https://www.nhs.uk/conditions/stroke/causes/) describes ethnicity as a contributing risk factor to stroke particularly for those who are South Asian (Bangladeshi, Indian, Sri Lankan or Pakistani), African, or Caribbean as rates of diabetes and high blood pressure are more often seen in these groups. South Asians in particular account for approximately [40% of global stroke deaths](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10098949/), and are the largest ethnic minority group in the UK with over three million individuals.  The [Office for National Statistics](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/mortalityfromleadingcausesofdeathbyethnicgroupenglandandwales/2012to2019) found that for both sexes, from 2012 to 2014, the Bangladeshi group had the highest rate of death from cerebrovascular diseases including stroke. In 2017 to 2019 the male and female rates for the Bangladeshi group (112.6 deaths per 100,000 males; 80.4 deaths per 100,000 females) were statistically significantly higher than the rates seen in all other ethnic groups of the same sex, except for females in the Mixed and Pakistani ethnic groups.  A 2021 report from the [UK Government](https://www.gov.uk/government/publications/the-report-of-the-commission-on-race-and-ethnic-disparities-supporting-research/ethnic-disparities-in-the-major-causes-of-mortality-and-their-risk-factors-by-dr-raghib-ali-et-al) on ethnic disparities in health also noted that people from African or Caribbean ethnicities have a 1.5-2.5x greater risk of having a stroke than people who are White European. This is similar for those from south Asian groups, who have a risk near 1.5x greater than White Europeans (notably, those who are Pakistani and Bangladeshi). Considering other risk factors, data published in 2022 from [Health Survey England](https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-england-additional-analyses/ethnicity-and-health-2011-2019-experimental-statistics/blood-pressure) found hypertension was highest among Black Caribbean, Black African and Pakistani adults.  While data related to ethnicity and SAH is unclear, given the general substantial burden of stroke among South Asian and Black African and Caribbean ethnicities the number of these individuals in the trial should reflect, at minimum, the same proportion as is found in the most recent census data for the geographic area (with an emphasis on the recruitment of Bangladeshi men and women). There is a case for over-sampling South Asian individuals to allow greater certainty regarding conclusions drawn from their participation in the trial. |

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| **2. Are the groups identified in Question 1 likely to respond to the treatment in different ways?** [**( VIEW WORKSHEET )**](#WorksheetONE) |
| **[This question has been answered with a focus on ethnicity for the purposes of this example, though the questions have wider relevance than ethnicity.]**  Analyses on the role of religion and/or spirituality in the United States have shown that African American stroke survivors exhibit more fatalistic beliefs about stroke and stroke recovery than White European stroke survivors ([Ellis and Magwood, 2020](https://www.ahajournals.org/doi/abs/10.1161/str.51.suppl_1.TP308)). This is also true of South Asian groups in the United States, with [some evidence](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7646689/) showing commonly held beliefs among such groups that wider contributors to stroke including heart disease cannot be prevented. In [one comparative study of cancer patients](https://bmjopen.bmj.com/content/3/6/e002650.long), British South Asians more frequently used fatalism as a disease coping strategy than British Whites. This may have relevance for attitudes towards wider indications, such as stroke and other cerebrovascular diseases.  More widely a general distrust in research may reduce the willingness of ethnic minority individuals and their carers to take part in a trial. A [study from the UK](https://www.tandfonline.com/doi/full/10.3109/09638288.2014.904936) exploring self-management and care with minority ethnic stroke survivors found that health, illness and recovery beliefs along with religion and the specific role of the family (or carer) need to be considered to maximize the effectiveness of rehabilitative treatment following a stroke. This includes the role of a healthcare provider or healthcare team that may need to become culturally competent on the preferences of stroke survivors. More generally, a general distrust in research may reduce the willingness of ethnic minority individuals to take part in a trial. |

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| **3. Will my trial intervention and/or comparator make it harder for any of the groups identified in Question 1 to engage with the intervention and/or comparator?** [**( VIEW WORKSHEET )**](#WorksheetTWO) | |
| **[This question has been answered with a focus on ethnicity for the purposes of this example, though the questions have wider relevance than ethnicity.]**  Eligible participants were adults aged 18–80 years and had been diagnosed with aSAH grades 4 or 5 on the WFNS scale. Once a poor-grade SAH patient was admitted to neurocritical care at a trial centre, the patient was stabilised from neurological and cardiorespiratory points of view as per local protocol. Once aSAH was confirmed and the patient was stable, the admitting neurosurgical/anaesthetic team assessed the patient regarding eligibility for the trial.  An appropriate clinician (e.g. an ITU consultant/registrar, neurological consultant/registrar or interventional neuroradiology consultant/registrar) with documented responsibility on the delegation log discussed the trial with the patient’s next of kin and provided them with the participant information sheet. A delegated individual then returned after an appropriate interval (maximum 4 hours) to allow adequate time for reflection and obtained assent for the trial from the appropriate consultee. The principal investigator was responsible for ensuring that informed assent for trial participation was given by each patient’s next of kin or relative, or by a nominated consultee, for patients fulfilling the TOPSAT 2 eligibility criteria.  The trial was developed with patient and public involvement (PPI). Feedback following presentations to the Newcastle SAH survivors’ group fed into the development of the process of obtaining assent from relatives and the way that follow-up would be conducted. The Trial Steering Committee also included two PPI members, an aSAH survivor and a relative, who were involved at every stage of the study, including contributing to the Plain English summary and the final NIHR report. However, the final report does not specify under PPI details any further information regarding ethnicity (either as a component of the PPI group, or as a wider consideration within PPI factors contributing to the design of the trial).  No mention of translation is mentioned in the final report, which could be a problem, particularly for an older South Asian population. Moreover, aspects of the intervention, such as informed consent and the information provided to the participant would need appropriate cultural tailoring. [In a previous study](https://academic.oup.com/fampra/article/21/6/636/508715?login=true) of South Asian patient’s views and experiences of clinical trial participation within the NHS, potential barriers included trial burden (which bears heavily on under-served communities), language, and discriminatory practices in the NHS, which can lead to mistrust of health professionals.  The trial was eventually halted because of difficulties resulting in slow patient recruitment. | |
| 1. **Will the way I have planned and designed my trial make it harder for any of the groups identified in Question 1 to consider taking part?** [**( VIEW WORKSHEET )**](#WorksheetTHREEA) |
| **[This question has been answered with a focus on ethnicity for the purposes of this example, though the questions have wider relevance than ethnicity.]**  The randomised trial approach to investigating whether poor-grade aneurysmal subarachnoid haemorrhage patients should receive emergent treatment or be treated on neurological improvement proved unfeasible. Either many patients were not eligible for the trial or patients’ doctors were uncertain of which approach was better, so were reluctant to enroll them in the trial, mostly choosing to treat them early. Therefore, the trial had to stop early because recruitment would have taken too long.  As the trial’s outcomes relied on both the potential administration of the intervention in a life-threatening situation and subsequent follow-up data, it would have been to the advantage of the trial design to consider relevant issues of communication and language in relation to the geographic areas of the participating locations (particularly, those within the UK).  No data on the ethnicity of participants was presented in the final NIHR report. As translation/interpretation are also not mentioned in the final report, we can assume the trial was conducted in English which may have limited the participation of some ethnic minority individuals and their next of kin. A follow-up questionnaire was also administered by post or online at six and twelve months, which may further disadvantage participants of any ethnic group with lower literacy and above-mentioned language differences. |

Worksheets for thinking through factors that might affect ethnic group involvement in a trial

These worksheets are intended to be used by trial teams in partnership with patient and public partners to ensure that ethnic group involvement is considered at the trial design stage.Before completing the worksheets, the trial team **should have answered Question 1** **of the INCLUDE Key Questions with regard to ethnic group involvement**.

The worksheet may cover issues that some trial teams already think about. The intention is that the worksheet will help to highlight issues consistently across trials for all trial teams, as well as raising some questions that may not be routinely considered at present.

Finally, while the worksheet asks trial teams to think about possible differences between ethnic groups, it is important to remember that there are also differences *within* ethnic groups, especially between generations and between men and women. No ethnic group is homogenous. See [Appendix 1](https://www.trialforge.org/trial-forge-centre/include/) for more on our definition of ethnicity.

**Worksheet 1**

This worksheet provides some questions **to guide your thinking about ethnic group involvement when answering Question 2** of the INCLUDE Key Questions.

**Disease and cultural factors that might influence the effect of treatment for some ethnic groups**

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| **Disease** | How might the prevalence of the disease vary between each ethnic group in the target population? | **Response:** Given the differing causes of stroke, it is useful to consider some of the key risk factors that contribute to the prevalence of the disease between varying at-risk ethnic groups.  For example, the burden of cardiovascular disease (CVD), is significant regardless of ethnicity. Studies have shown that 80 per cent of the global burden of CVD can be attributed to [five coronary risk factors](https://raceequalityfoundation.org.uk/wp-content/uploads/2018/03/health-brief16.pdf), all of which are relevant to the UK. Most are potentially modifiable: these are abnormal concentration of cholesterol (and other related substances found in the body), diabetes mellitus, cigarette smoking, hypertension (or high blood pressure) and lack of physical exercise. There is less evidence to explain differences in the potency of individual risk factors across distinct groups, such as individuals from different ethnic groups or younger or older adults.  South Asians living in the UK have a high rate of CVD compared to the majority population. [Work done in the UK in the 1980s](https://www.bhf.org.uk/what-we-do/our-research/research-successes/ethnicity-and-heart-disease) found that first-generation South Asians living in the UK have a higher rate of coronary heart disease (and diabetes) compared to White Europeans. [More recent data show the same pattern](https://raceequalityfoundation.org.uk/wp-content/uploads/2018/03/health-brief16.pdf) (e.g. South Asians living in Scotland have a 60-70 per cent higher incidence of acute myocardial infarction (heart attack) than the general population. Women of South Asian origin do not seem as protected from CVD as women in the general population. Further, young men of South Asian origin experience a high relative risk, at a younger age, compared to those of the majority population.  The [link between CVD and diabetes is especially strong](https://raceequalityfoundation.org.uk/wp-content/uploads/2018/03/health-brief16.pdf). The prevalence of Type 2 diabetes, for example, shows marked differences among ethnic groups. Almost one in five people of South Asian origin living in the UK develop diabetes, compared to one in twenty-five among the general population. Diabetes onset is earlier in South Asians (46 vs 57 for White individuals), and at a lower BMI than White individuals.  Although heart disease is common among people of South Asian origin, there is uncertainty as to why. [Four interrelated explanations](https://raceequalityfoundation.org.uk/wp-content/uploads/2018/03/health-brief16.pdf) emerge: people of South Asian origin are more susceptible to established CVD risk factors; they are more likely to experience established CVD risk factors; there are more specific risk factors, which are not known about; and there are fewer competing causes of death in middle-aged people of South Asian origin.  In contrast to South Asian groups, [Black groups in the UK have a significantly lower risk of heart disease compared](https://www.kingsfund.org.uk/publications/health-people-ethnic-minority-groups-england#CVD) to the majority of the population, despite having a high prevalence of hypertension and diabetes. Lower cholesterol levels among people of African Caribbean heritage than White Europeans may protect them against heart disease. Heart disease rates are low in geographic sub-Saharan Africa and the Caribbean.  Thinking of stroke more specifically, South Asians in particular account for approximately 40% of global stroke deaths and are the largest ethnic minority group in the UK with over three million individuals ([Aurelius et al; 2023](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10098949/)). The [Office for National Statistics](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/mortalityfromleadingcausesofdeathbyethnicgroupenglandandwales/2012to2019) found that for both sexes, from 2012 to 2014, the Bangladeshi population had the highest rate of death from cerebrovascular diseases including stroke. In 2017 to 2019 the male and female rates for the Bangladeshi population (112.6 deaths per 100,000 males; 80.4 deaths per 100,000 females) were statistically significantly higher than the rates seen in all other ethnic groups of the same sex, except for females in the Mixed and Pakistani ethnic groups.  Despite a lower risk of heart disease, research has shown that those who are Black and of African or Caribbean origin are twice as likely to have a stroke, and at a younger age, than those who are White European. The [UK Stroke Association](https://www.stroke.org.uk/sites/default/files/F21_Information%20for%20black%20African%20and%20black%20Caribbean%20people.pdf) notes the reasons for this are complex and not completely understood but may be reflective of high blood pressure, diabetes, lifestyle factors, and sickle cell disease, which are all stroke risk factors specific to Black ethnic communities.   [One UK study](https://doi.org/10.1186%2Fs12916-016-0618-2) found the type of stroke experienced may be crucial in better understanding and generating prevalence data for Black communities, with unique distinctions among Black Caribbean patients and Black African patients. These differences between Black communities and those who are White European could not be explained by traditional risk factors alone, and more research is needed on aspects such as genetic susceptibility, differing rates of control of vascular risk factors, or as yet undetermined environmental risk factors. |
| How might the severity of the disease vary between each ethnic group? | **Response:** A 2023 [multi-centre registry-based cohort study](https://pubmed.ncbi.nlm.nih.gov/36723729/) of acute stroke outcomes amongst UK ethnic minorities found compared to White Europeans, those from ethnic minorities had earlier onset of an acute stroke by about 5 years and a 2- to fourfold increase in many stroke-related adverse outcomes and death. However, further research is necessary to identify the aetiology of these ethnic differences to improve healthcare inequalities through strategic planning including preventative measures and intervention, including better diversity inclusion and routine documentation of ethnicity.  The [NHS](https://www.nhs.uk/conditions/subarachnoid-haemorrhage/) notes SAH may be more common in those from Black ethnicities as they are more likely to have high blood pressure. However, disparities exist between the UK and country of origin. For example, [research has shown](https://www.ahajournals.org/doi/full/10.1161/STROKEAHA.108.518852) the risk of stroke is higher in Black Caribbeans in the UK compared with Black Caribbeans in their country of origin which may be caused by factors such as a higher prevalence of stroke risk factors, differences in treatment plans for co-morbid conditions, and less healthy lifestyle practices compared with indigenous Black Caribbean populations. |
| How might the disease present in people from each ethnic group (this may include symptoms, type or pattern or rate of disease progression)? | **Response:** As above (see ‘Disease’). Given the differing causes of stroke, it is useful to consider some of the key risk factors that contribute to the prevalence of the disease between varying at-risk ethnic groups. Conditions that may increase the risk of having a stroke include high blood pressure (hypertension), indications of cardiovascular disease including high cholesterol and irregular heartbeats (atrial fibrillation), as well as type 2 diabetes. [Traditional risk factors alone](https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-016-0618-2) cannot account for ethnic differences within stroke, and more research is needed on aspects such as genetic susceptibility, differing rates of control of vascular risk factors, and/or as yet undetermined environmental risk factors. | |
| How close is the match between each ethnic group living with the disease and the ethnic groups living in the areas where the trial is to be run? | **Response:** The lead study centre was noted on the trial registry as Royal Victoria Infirmary (Newcastle Upon Tyne) alongside eight other NHS hospitals in England. None of the listed centres were within Greater London. According to the 2021 Census, [London was the most ethnically diverse region in England and Wales](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/regional-ethnic-diversity/latest) with more people from the black, Asian, mixed and ‘other’ ethnic groups living in London than anywhere else (36.8% White British). The other study areas were much less reflective of ethnic diversity including the lead study centre in the North East (90.6% White British).  It would be sensible to check local site populations against the overall disease burden but given the importance of South Asians and those from Black ethnicities in a trial in which heart disease is a key underpinning factor, these sites may not all be a good match between the ethnic groups needed and where the trial is recruiting. However, recruitment did take place in both the UK and wider Europe, although no data on participant ethnicity are presented within the final NIHR report. | |
| Other factors to consider: As SAH is a less common form of stroke, the above have been provided as relevant in the context of designing wider trials related to cerebrovascular diseases. | | |
| **Cultural** | How might perceptions of the disease and social stigma around it be different for each ethnic group in the target population? | **Response:** Given the differing causes of stroke, it is difficult to assess concisely how perceptions of the disease and social stigma around it are different for each ethnic group in the target population.  Analyses on the role of religion and/or spirituality in the United States have shown that African American stroke survivors exhibit more fatalistic beliefs about stroke and stroke recovery than White European stroke survivors ([Ellis and Magwood, 2020](https://www.ahajournals.org/doi/abs/10.1161/str.51.suppl_1.TP308)). This is also true of South Asian groups in the United States, with [some evidence](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7646689/) showing commonly held beliefs among such groups that wider contributors to stroke including heart disease cannot be prevented. In [one comparative study of cancer patients](https://bmjopen.bmj.com/content/3/6/e002650.long), British South Asians more frequently used fatalism as a disease coping strategy than British Whites. This may have relevance for attitudes towards wider indications, such as stroke and other cerebrovascular diseases.  A [study from the UK](https://www.tandfonline.com/doi/full/10.3109/09638288.2014.904936) exploring self-management and care with minority ethnic stroke survivors found that health, illness and recovery beliefs along with religion and the specific role of the family (or carer) need to be considered to maximize the effectiveness of rehabilitative treatment following a stroke. This includes the role of a healthcare provider or healthcare team that may need to become culturally competent on the preferences of stroke survivors.  In terms of trial participation, generally, trials are known to lack diversity – much of this may be down to lack of trust in the medical and research systems due to historical abuse and exploitation of Black and minority ethnic populations. [Research](https://www.diabetes.org.uk/resources-s3/2017-11/south_asian_report.pdf) has shown that South Asians are often explicitly excluded from research due to perceived cultural and communication difficulties. It has also been shown that many [South Asian people are unwilling to participate](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2571097/) because they accept their illness as an unalterable punishment from God, or have a fear of what research entails. | |
| How might ways of describing the disease be different for each ethnic group? | **Response:** It is uncertain whether terms other than ‘stroke’ may be used by some ethnic groups. | |
| How might cultural practices, beliefs and traditions influence the acceptability of, and adherence to, the treatment(s) for each ethnic group? | **Response:** In the treatment of poor-grade subarachnoid haemorrhage trial 2 (TOPSAT 2), patients with grade 4–5 subarachnoid haemorrhages were randomly assigned to either early treatment, irrespective of condition, or treatment when their condition improved, irrespective of when that happened (so it was treat on improvement, not delayed treatment). The trial report notes that either many patients were not eligible for the trial or patients’ doctors were uncertain of which approach was better, so were reluctant to enroll them in the trial, mostly choosing to treat them early. Therefore, the trial had to stop early because recruitment would have taken too long.  How acceptable, or useful such an intervention might be considered to be by a wide range of ethnic groups is unclear. It would be useful to know to what degree there are differences between ethnic groups in attitudes to this sort of intervention (treating with immediacy, or with delay) for less common types of strokes including SAH. See ‘Cultural’ above for further information. | |
| How or when might people in each ethnic group access healthcare for this disease differently? | **Response:** [Cultural and social norms](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3588185/) strongly influence health-seeking behaviours – research has shown that health promotion activities tend to be based on assumptions of individualism and self-investment, which may need to be re-thought for South Asian groups in particular where community is often more important.  [South Asians](ghttps://www.diabetes.org.uk/resources-s3/2017-11/south_asian_report.pdf) are often explicitly excluded due to perceived cultural and communication difficulties. Language and cultural differences are barriers that impact all minority groups – with people from non-White-European populations seeking healthcare at later stages of their disease than their White counterparts. [Language and literacy factors](https://www.pcdsociety.org/resources/details/living-with-diabetes-a-qualitative-review-of-minority-ethnic-groups-in-a-deprived-london-borough) are also known factors that impact on overall health literacy. Study participants have reported that both the spoken and written health information provided were sometimes meaningless, even when translated into their own language. Their inability to transform information into action was either due to limited health knowledge or limited linguistic proficiency in either their native language or English and they also felt they were unable to maximise their consultation with their healthcare professional.  [Research findings](https://bmjopen.bmj.com/content/6/1/e009498.short) from ethnic minority groups show a strong preference for cultural beliefs surrounding familial relationships and a desire to provide genuine care (e.g., they are the best person to provide care for the stroke survivor, not the healthcare system). This may inherently influence the way in which such communities interact with the healthcare system or participate in trials such as TOPSAT 2. | |
| Other factors to consider: As SAH is a less common form of stroke, the above have been provided as relevant in the context of designing wider trials related to cerebrovascular diseases. | | |

**Worksheet 2**

This this worksheet provides some questions **to guide your thinking about ethnic group involvement when answering Question 3** of the INCLUDE Key Questions.

**Intervention and comparator factors that might affect how some groups engage with the intervention and/or comparator\***

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| **What** | How might the intervention(s) and comparator limit participation of people from each ethnic group in the target population? | **Response:** The intervention randomly assigned patients with grade 4–5 SAHs to either early treatment, irrespective of condition, or treatment when their condition improved, irrespective of when that happened (so it was treat on improvement, not delayed treatment). Treatment is typically aneurysm coiling where a very thin tube is fed inside blood vessels into the aneurysm in the brain and the aneurysm is blocked off by platinum wire coils placed through that tube.   While PPI is mentioned within the final NIHR trial report, to what extent differing ethnicities were represented within the PPI is not stated. No mention of translation is mentioned, which could be a problem, particularly for older South Asian populations. Moreover, the information provided to patients as part of the intervention would likely need further cultural tailoring (particularly, as next of kin were involved in the process of consent).  Material targeting the individual is a strategy that works from a White ethnic group perspective but may be less effective in South Asians (who tend to have more of a sense of community, so appeals to community may be useful) and Black individuals, where appeals to family may be more useful.  How acceptable, or useful such interventions might be considered to be by a wide range of ethnic groups is unclear. It would be useful to know to what degree there are differences between ethnic groups in attitudes to the intervention and associated follow-up as related to stroke occurrence and management. |
| How, and in what way, were people from each ethnic group involved in selecting or designing the trial intervention/comparator? | **Response:** The trial was developed with PPI. Feedback following presentations to the Newcastle SAH survivors’ group fed into the development of the process of obtaining assent from relatives and the way that follow-up would be conducted. The Trial Steering Committee also included two PPI members, an aSAH survivor and a relative, who were involved at every stage of the study, including contributing to the Plain English summary and the final NIHR report. However, the final report does not specify under PPI details any further information regarding ethnicity (either as a component of the PPI group, or as a wider consideration within PPI factors contributing to the design of the trial). Without special efforts, it is reasonable to assume that the PPI will have been from a predominantly White perspective, as it is for most UK trials. |
| Other factors to consider: | |
| **Who** | How might the person delivering the intervention/comparator limit participation of people from each ethnic group in the target population? | **Response:** The randomised trial approach to investigating whether poor grade aSAH patients should receive emergent treatment or be treated on neurological improvement proved unfeasible. Either many patients were not eligible for the trial or patients’ doctors were uncertain of which approach was better, so were reluctant to enroll them in the trial, mostly choosing to treat them early. Therefore, the trial had to stop early because recruitment would have taken too long.  As the trial’s outcomes relied on both the potential administration of the intervention in a life-threatening situation and subsequent follow-up data, it would have been to the advantage of the trial design to consider relevant issues of communication and language in relation to the geographic areas of the participating locations (particularly, those within the UK).  In general, those tasked with screening and recruitment, such as the admitting physician, will need cultural competence training to ensure that people from ethnic groups different to their own are approached, and that both recruiter and potential recruit (in this case, next of kin) feel comfortable about the discussion. Depending on the language requirements of target ethnic groups, this may require interpretation and/or translation.  That said, [NHS staff are a more diverse group](https://www.ethnicity-facts-figures.service.gov.uk/workforce-and-business/workforce-diversity/nhs-workforce/latest) than the wider UK population – of NHS staff whose ethnicity is known, 79.2% are White (including White minorities), and 20.7% are from all other ethnic groups. This contrasts to the wider population – the [2011 Census](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest) showed that 86.0% of the population of England and Wales was White. If the staff conducting the trial with participants are of the same ethnicity, or share a common language, distrust may be reduced. |
| Other factors to consider: | |
| **How** | How might the mode of delivery (e.g. telephone, video-call, face-to-face, in groups) limit participation of people from each of the ethnic groups in the target population? | **Response:** See above (*What/Who*). The trial was eventually halted because of difficulties resulting in slow patient recruitment. |
| Other factors to consider: The trial recruited only 23 patients over 25 months; therefore, feasibility could not be confirmed, and recruitment had to be terminated early. | |
| **Where** | How might where the intervention/comparator is delivered (e.g. hospital, general practice, local library) limit the participation of people from each ethnic group in the target population? | **Response:** See above (*What/Who*). The trial was eventually halted because of difficulties resulting in slow patient recruitment. |
| Other factors to consider: The trial recruited only 23 patients over 25 months; therefore, feasibility could not be confirmed, and recruitment had to be terminated early. | |
| **When & Intensity** | How might when the intervention/comparator is delivered (e.g. during working hours) or the intensity (e.g. number of times it is delivered, over what period, time commitment for each session and overall) limit participation of people from each ethnic group in the target population? | **Response:** See above (*What/Who*). The trial was eventually halted because of difficulties resulting in slow patient recruitment.  A follow-up questionnaire was also administered by post or online to surviving participants (or their carers) in the UK at six and twelve months, which may disadvantage participants of any ethnic group with lower literacy and above-mentioned language differences. |
| Other factors to consider: The trial recruited only 23 patients over 25 months; therefore, feasibility could not be confirmed, and recruitment had to be terminated early. | |

**Worksheet 3a**

This worksheet provides some questions **to guide your thinking about ethnic group involvement when answering Question 4** of the INCLUDE Key Questions.

**Trial eligibility and participation factors that might affect how some groups engage with the trial**

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| --- | --- | --- |
| **Eligibility** | How might eligibility criteria exclude members of each ethnic group in the target population for reasons other than their clinical eligibility for the trial (e.g. availability of medical history, must speak English, location, gender, age, discussing pregnancy, internet/mobile telephone access)? | **Response:** The participant inclusion criteria were as follows:  1. Aged 18-80 years  2. WFNS grade 4 or 5 SAH (grade for trial eligibility purposes is the WFNS grade recorded at first medical assessment following: hospital attendance AND confirmation of the diagnosis of SAH – by CT (or MRI) and/or lumbar puncture)  3. Assent obtained from next of kin, professional consultee or welfare attorney/nearest relative  The need to obtain assent (consent) from next of kin, professional consultee or welfare attorney/nearest relative may lead to some ethnic minority groups being disproportionately affected dependent on the language skills of both potential participants and clinical staff.  As translation/interpretation is not mentioned in the final NIHR report, we can also assume this process is in English. As mentioned above, language issues (both world language and culturally-tailoring) may limit the participation of some ethnic minority individuals. This is particularly important for those from South Asian backgrounds and Black Caribbean backgrounds, where a variety of languages may be spoken in the home or country of origin.  Clinicians with expertise in cerebrovascular care will be able to shed more light on whether any specific clinical criterion may disproportionately impact certain ethnic groups. |
| Other factors to consider: | |
| **Opportunity to participate** | How might the way(s) (and by whom) potential participants are made aware of the trial (e.g. posters in clinic, written letter from a doctor, asked by a nurse) limit the participation of each ethnic group in the target population? | **Response:** Once a poor-grade SAH patient was admitted to neurocritical care at a trial centre, the patient was stabilised from neurological and cardiorespiratory points of view as per local protocol. Once aSAH was confirmed and the patient was stable, the admitting neurosurgical/anaesthetic team assessed the patient regarding eligibility for the trial.  An appropriate clinician (e.g. an ITU consultant/registrar, neurological consultant/registrar or interventional neuroradiology consultant/registrar) with documented responsibility on the delegation log discussed the trial with the patient’s next of kin and provided them with the participant information sheet. A delegated individual then returned after an appropriate interval (maximum 4 hours) to allow adequate time for reflection and obtained assent for the trial from the appropriate consultee. The PI was responsible for ensuring that informed assent for trial participation was given by each patient’s next of kin or relative, or by a nominated consultee, for patients fulfilling the TOPSAT 2 eligibility criteria.  Depending on the language skills of both potential participants and clinical staff, who approaches the potential participant may limit the ability of some ethnic groups (older Pakistani and Bangladeshi women for example) to participate. It is unclear if the trial team explored who should make the initial approach with an ethnically diverse group of patient and public contributors. |
| How might the information that tells potential participants about the trial (e.g. participant information leaflet) limit the participation of each ethnic group? | **Response:** As some ethnic groups including individuals for whom English may not be their first language are a key required group within the trial (e.g. South Asians, Indian subcontinent) then translation of written and oral material into some languages other than English is likely to be essential (see above).  [Other cultural barriers for South Asians](https://onlinelibrary.wiley.com/doi/epdf/10.1111/dme.13895) (e.g. preference for traditional remedies, see earlier) may be as important, or more important, than linguistic barriers so should not be forgotten. [These beliefs, and linguistic issues, are likely to be more relevant among older generations](https://onlinelibrary.wiley.com/doi/epdf/10.1111/dme.13895).  It is unclear if any material was translated into other languages, or culturally modified. A patient information sheet is noted on the trial registry as available on request from the trial team. No further details are supplied on the details of the information sheet via the final NIHR report. |
| How might cultural practices, beliefs and traditions change the way each ethnic group perceives the information they are given? | **Response:** See earlier comments about sociocultural beliefs, self-management and appeals to individualism rather than community and family. |
| Other factors to consider: | |
| **Consent procedures** | How might the way consent is sought (i.e. where, by whom, written vs verbal, verbal translations/multiple languages, access to interpreters) limit the participation of each ethnic group in the target population? | **Response:** Consent is written and since translation/interpretation is not mentioned, we can assume this is in English. As mentioned above, language issues (both world language and culturally-tailoring) may limit the participation of some ethnic minority individuals. The eligibility criteria highlighted above may explicitly exclude some individuals on language grounds linked to consent. | |
| How might the way people would like to discuss participation with family before providing consent differ for each ethnic group? | **Response:** [South Asian women](https://www.researchgate.net/publication/7480322_The_Influence_of_Family_on_Immigrant_South_Asian_Women%27s_Health), particularly older women, are known to make decisions about their healthcare in consultation with members of their community and family. Family is also important to people with Black heritage. In this trial, as consent could be sought from next of kin, it would be useful to consider the role of familial relationships as related to ethnicity and the willingness of others to enrol a family member or other loved one in a clinical trial. | |
| How might the way the research team can check how well consent information is understood differ for each ethnic group? | **Response:** There is no information about how understanding is confirmed as related to ethnicity. It was noted that the individual delegated to discuss the trial with the patient’s next of kin (or other appropriate party) would allow for an appropriate interval (maximum 4 hours) to allow adequate time for reflection. | |
| Other factors to consider: | | |

**Worksheet 3b**

This worksheet provides some questions **to guide your thinking about ethnic group involvement when answering Question 4** of the INCLUDE Key Questions.

**Trial data collection factors that might affect how some groups engage with the trial**

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| **What** | How, and in what way, were people from each ethnic group in the target population involved in selecting the trial outcomes? | **Response:** The trial was developed with PPI. The Trial Steering Committee included an aSAH survivor and a relative who were noted as involved at every stage of the study. The final NIHR report does not specify any further information regarding ethnicity (either as a component of the PPI group, or as a wider consideration within PPI factors contributing to the design of the trial). |
| How might the trial outcomes themselves, or other data being collected (e.g. a patient’s background information) limit the participation of each ethnic group? | **Response:** The primary end point/outcome was a functional outcome at 12 months determined by ordinal analysis of the Modified Rankin Score (mRS). The mRS is a widely used outcome measure in stroke (including aSAH) and is based on the ability to carry out usual day-to-day activities.  The mRS at 6 and 12 months was established using a questionnaire for the participant (or their carer) to complete either by mail or online. The questionnaire is provided in Appendix 1 of the NIHR report and involves three sections with a mix of Yes/No answer boxes and open-ended questions that allow for more detail. It is unclear whether and how the outcomes may limit participation beyond culturally sensitive issues of language, as outlined above. |
| Other factors to consider: | |
| **Who** | How might the people who collect data limit the participation of each ethnic group in the target population? | **Response:** An appropriate clinician (e.g. an ITU consultant/registrar, neurological consultant/registrar or interventional neuroradiology consultant/registrar) made the initial approach and collection of data regarding potential patients for the trial. It is unclear who further facilitated the follow-up questionnaires.  As noted above, [NHS staff are a more diverse group](https://www.ethnicity-facts-figures.service.gov.uk/workforce-and-business/workforce-diversity/nhs-workforce/latest) than the wider UK population – of NHS staff whose ethnicity is known, 79.2% are White (including White minorities), and 20.7% are from all other ethnic groups. This contrasts to the wider population – the [2011 Census](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest) showed that 86.0% of the population of England and Wales was White. If the staff conducting the trial with participants are of the same ethnicity, or share a common language, distrust may be reduced. |
| Other factors to consider: | |
| **How** | How might data collection methods limit the participation of each ethnic group in the target population? | **Response:** See Worksheet 2. |
| Other factors to consider: | |
| **Where** | How might where data are collected limit the participation of each ethnic group in the target population? | **Response:** Given the trial is conducted for those with poor grade aSAH in the hospital setting, it is important to consider the geographic of location sites as related to ethnicity (particularly, within the UK). See Worksheet 1. |
| Other factors to consider: | |

**Worksheet 3c**

This worksheet provides some questions **to guide your thinking about ethnic group involvement when answering Question 4** of the INCLUDE Key Questions.

**Factors that might affect the planned analysis of trial results**

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| **Retention** | How might the trial data available for participants differ between each ethnic group in the target population? | **Response:** See Worksheet 3b. |
| Other factors to consider: | |
| **Benefits** | How might the benefits of the trial intervention(s) differ between each ethnic group in the target population? | **Response:** Some outcomes, most noticeably the ability to carry out usual day-to-day activities as measured by the mRS, could conceivably have a cultural element although this is uncertain. A [UK study](https://bmjopen.bmj.com/content/6/1/e009498.short) investigating the experiences and perspectives of carers from diverse ethnic groups caring for stroke survivors found cultural and language differences created challenges in working with the health system to provide rehabilitative care (notably, for Black and minority ethnic groups including South Asians).  There was also a distinct finding from Black and other minority ethnic groups that carers strongly believed they were typically the best person to provide care for the stroke survivor, a perception often rooted in cultural beliefs surrounding familial relationships and a desire to provide care viewed as genuine. Irrespective of ethnic group, a gap was identified between hospital discharge and home, where carers experienced poor communication between services and felt they were deemed to be a ‘low priority’ within the health system.  It is plausible that people from different ethnic groups may have different perspectives on rehabilitative care that would influence day-to-day activities, who is best suited to deliver this ongoing care, and how information on care is shared with providers given a lack of culturally tailored resources within the healthcare system. |
| Other factors to consider: | |
| **Harms** | How might the possible harms of the trial intervention(s) differ between each ethnic group in the target population? | **Response:** As above. |
| Other factors to consider: | |
| **Subgroup analyses** | How should variation between ethnic groups in the target population be explored– should there be planned subgroup analyses? | **Response:** An exploration of benefits and harms by ethnic group should be pre-planned, especially given the prevalence of stroke for South Asian heritage individuals. The need for this pre-planned subgroup analysis suggests that over-sampling by ethnicity might be useful. This is unlikely to affect the applicability of the evidence to the majority population but will improve the certainty of conclusions coming from the subgroup analysis. The overall sample size does not need to be changed and it is unlikely to be feasible to fully power any subgroup analyses. |
| Other factors to consider: | |
| **Interim analyses** | How should any interim analysis handle variation between ethnic groups in the target population? | **Response:** Any planned interim analysis should look for signals suggesting that benefits or harms were importantly different in one or more ethnic groups. The certainty available for this will be less than for the majority population, although oversampling may help. |
| Other factors to consider: | |
| **Stopping triggers** | How should any rules to stop the trial early on safety or benefit grounds handle variation between ethnic groups in the target population? | **Response:** Any stopping rules should consider the benefits or harms by ethnic group. The certainty available for this will be less than for the majority population, although oversampling may help. |
| Other factors to consider: The trial recruited only 23 patients over 25 months; therefore, feasibility could not be confirmed, and recruitment had to be terminated early. | |

**Worksheet 3d**

This this worksheet provides some questions **to guide your thinking about ethnic group involvement when answering Question 4** of the INCLUDE Key Questions.

**Factors that might affect the planned reporting and dissemination of trial results**

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| **What** | How, and in what way, were people from each ethnic group in the target population involved in planning the reporting and dissemination of the trial results? | **Response:** Public contributors were part of the trial, but it is not clear if or how they were involved in planning the reporting and dissemination of the trial results (although, the Trial Steering Committee included two PPI members, an aSAH survivor and a relative, who were noted as contributing to every stage of the study). There is no suggestion that the PPI was ethnically diverse. |
| Other factors to consider: | |
| **How** | How might planned reporting and dissemination methods limit engagement with each ethnic group in the target population? | **Response:** The planned reporting and dissemination methods were extensive and included scientific conferences, five to six peer-reviewed journal articles, results available via the sponsor/funder website(s), and other more layperson friendly methods including websites, newsletters, and press releases.  More direct personal or small group feedback will be given to the PPI groups involved in developing, contributing to, and supporting TOPSAT 2. Feedback in the form of a lay summary will be provided to participants via the general section of the trial website, participant specific newsletter at the end of trial (if they indicated they wished to receive it) and by wider publicity generated.  The component of ethnicity has not been addressed within the reporting plans. Dissemination materials intended for the public should consider the health beliefs, health literacy and languages of the ethnic groups in the aSAH community and use channels appropriate for the ethnic group. Formal publications should, at minimum, be published as Open Access material. |
| Other factors to consider: | |
| **Where** | How might where trial results are planned to be reported and disseminated limit engagement of each ethnic group in the target population? | **Response:** As above. |
| Other factors to consider: | |

Worksheet for thinking through measures to address factors that might prevent full community involvement

Use this worksheet to list key factors that might affect the involvement of some ethnic groups in the target population of your trial, along with measures to mitigate the effect of those factors and their cost. Add extra rows as needed.

Please remember that there are also differences *within* ethnic groups, especially between generations and between men and women. No ethnic group is homogenous.

|  |  |  |
| --- | --- | --- |
| **Factors that may prevent full community involvement** | **Proposed measures (several options may be needed)\*** | **Cost of measures** |
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\*See https://centreforbmehealth.org.uk/resources/toolkits/ for suggestions for how to address factors that affect community-wide involvement.

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