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 Heidi Gardner (University of Aberdeen) and Declan Devane (NUI Galway). 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 trial registration document:** [**https://www.isrctn.com/ISRCTN20141297**](https://www.isrctn.com/ISRCTN20141297)**, and the trial report which is available here:** [**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7443739/**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7443739/)**.**  **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.]**  Prostate cancer is the most common cancer in men in the UK. Incidence rates have risen over the last 25 years, largely attributable to the introduction of prostate-specific antigen (PSA) testing. In a study looking at incidences of prostate cancer globally, Western countries were found to have higher rates, but it is not known whether this is purely due to higher detection rates rather than higher occurrences.  A UK study of data from Public Health England between 2008 and 2010, showed a man’s lifetime risk of being diagnosed with prostate cancer is 1 in 8; by ethnic group that breaks down as 1 in 8 for white men, 1 in 4 for Black men, 1 in 13 for Asian men. These rates translate to death rates for 1 in 24 for white men, 1 in 12 for Black men, and 1 in 44 for Asian men. Studies suggest that Black men are predisposed to this disease due to several genetic mutations, and environmental factors such as diet and socioeconomic disadvantage are also thought to be contribute too.  A 2006 study found that Black men in the UK had higher prostate-specific antigen expression, and prostate cancer was also found to present in younger African-Caribbean men than European and South Asian men. There were no significant differences in Gleason scores (a histopathological grading system used to help evaluate the prognosis of men with prostate cancer) between African-Caribbean men, and European and South Asian men. Black men were also found to have slightly worse clinical staging of their prostate cancer; T4 and/or M1 was at 26.4% for Black men and 23.0% for white men (T4 represents tumours invading to adjacent structures, and M1 represents distant metastasis). A subsequent study in 2008 found that although men in the UK have different incidence rates across ethnic groups, on average, African-Caribbean men are diagnosed five years earlier than white men, but all ethnic groups included in the study had equal access to diagnostic services. In also revealed that, apart from an increase in presenting PSA level, clinical presentation and management of prostate cancer were similar among men of all ethnicities.  The trial population should look like the population of men that are at highest risk of prostate cancer, in the UK that translate as including Black men as a priority, with a focus on younger Black men, followed by white men, and then Asian men. The current demographics for the UK suggest that 3.3% of the population are from Black ethnicities, and 7.5% of the population are from Asian ethnic groups (including Indian, Pakistani, Bangladeshi, Chinese, and other Asian backgrounds), but the trial should include a population with more than 3.3% Black men based on disease prevalence rates. |

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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.]**  As discussed in question 1, prevalence and deaths due to prostate cancer are increased in Black men in comparison to white men. Due to the increased health demands of these minority groups, they may stand to benefit more to the treatment. It is not clear whether the root cause of these differences is genetic, social, cultural, or a mix of factors, so it is difficult to suggest whether these groups will respond to the treatment in different ways.  There is evidence from a meta-analysis of 7 randomised trials that included 8814 patients, which suggests that Black men may respond better to radiotherapy than white men, radiotherapy is one of three interventions (radiotherapy, surgery, and active monitoring) being tested in this trial. This analysis demonstrated that Black men enrolled in trials presented with more aggressive disease features but had better treatment and disease-specific outcomes with radiotherapy-based therapy compared with white men. It is not known whether the specific type of cancer (i.e., the genetic composition of the tumour) may have an impact, and further research is needed to assess the reasons why Black men respond to this treatment better than white men. |

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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.]**  At the time that the ProtecT study was designed, PPI was not generally integrated in trial designs, but in this study a version of PPI was used to ensure patient voices were integrated into the work. The trial report does not explicitly list PPI representatives or the ethnic backgrounds of those that provided consultation and feedback, but it does discuss the integration of qualitative research methods to integrate PPI into the design and conduct of the study. Specific to the trial interventions, men that had declined randomisation in the feasibility study explained in interviews how the study should be organised, and this feedback was incorporated into the design of the trial. As a result, the conservative study group was called ‘active monitoring’ rather than ‘watchful waiting’, it is not clear if PPI involvement was used at an earlier stage to support selection of the trial interventions themselves.  The trial has three arms: radiotherapy, surgery, and active monitoring. As mentioned in question 2, a 2021 meta-analysis of 7 randomised trials that included 8814 patients, Black and white men with localised prostate cancer and treated with definitive radiotherapy, suggested that Black men enrolled in trials presented with more aggressive disease features, but had better treatment and disease-specific outcomes with radiotherapy-based therapy compared with white men. If Black men are aware of this research, they may be less likely to engage with the trial due to wanting to receive radiotherapy, in this case randomisation and risk of being allocated to either active monitoring or surgery is the problem. Qualitative research also suggests that men, in this case Black men, may tend to favour treatment using herbal medicine that is routinely used in the West Indies (the Caribbean). In the same study, one person that was taking part in a clinical trial for prostate cancer explained that he took herbal medicine in addition to the clinical trial drugs that he was taking. If this is plausible (i.e., no interactions or clinical reasons why participants should not take herbal medicine), then allowing for this may increase interest and/or engage with the trial.  The person delivering the interventions will vary by the intervention type (radiotherapy, surgery, active monitoring), but the trial report suggests that the specialist research nurses will be the point of contact for participants, including meeting. It is not clear whether this team of specialist nurses represent a variety of ethnic backgrounds.  NHS staff are a more diverse group 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 showed that 86.0% of the population of England and Wales was White. If the staff conducting research visits with participants are of the same ethnicity, or share a common language, this distrust may be reduced. It is important to bear in mind for the surgical intervention specifically, that according to an analysis of NHS medics’ careers in England, Black surgeons are far less likely to be promoted than their white colleagues. Black men who were junior surgeons in 2010 were 27% less likely to be promoted to consultant than white men between 2016 and 2020, while Black women were 42% less likely. Senior Black doctors said that the research matched their experiences and warned of a lack of support for minority doctors to pass tests required to reach the best-paid ranks.  As mentioned previously, Black and minority ethnic populations are known to distrust the medical and research systems due to historical abuse and exploitation, so it may be that engaging with research being conducted at an NHS site would limit participation. | |
| 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 eligibility criteria include men aged 50-69 years with localised prostate cancer. Trial exclusion criteria were a previous malignancy (apart from skin cancer), renal transplant or current renal dialysis, major cardiovascular or respiratory comorbidities, bilateral hip replacement or an estimated life expectancy of <10 years. People with African Caribbean heritage have a much higher risk of high blood pressure, type 2 diabetes, and stroke, but a lower risk of coronary heart disease. Normally, high blood pressure and diabetes increase coronary heart disease risk, and the disassociation isn’t yet understood. The causes of excess cardiovascular disease and stroke morbidity and mortality in Black and minority ethnic groups in comparison to white British people are incompletely understood, but socioeconomic factors are thought to play a role. The same can be said of respiratory diseases, COVID-19 for example has disproportionately impacted people with ethnic minority backgrounds, with crowded housing, public facing jobs, and a link to socioeconomic deprivation being to blame. The exclusion criteria of major cardiovascular or respiratory comorbidities have the potential to inadvertently exclude Black men disproportionately, though someone with a more clinical focus may be able to provide information as to the reason for this eligibility criteria – e.g., these conditions may have a contraindication with one or more of the interventions. If this is the case, then this should be noted explicitly. It is not clear how the final exclusion criteria, ‘an estimated life expectancy of <10 years’ will be measured or arrived at, and criteria like this that may be subjective do run the risk of unconscious bias creeping in that may exclude people from ethnic minority backgrounds, particularly with anti-Blackness coming into play.  Recruitment took place mainly at GP surgeries, but on occasions at other venues such as sports centres or church halls, requiring the nurses to be adaptable and autonomous. In addition, the nurses sometimes travelled widely during recruitment, particularly where there were few surgeries near the hospital or if they had taken part early on in recruitment. The feasibility study showed that nurses were as effective as urologists in randomising participants and the trial report notes that they became central to the success of the main trial. It is not clear whether the nurses involved with this trial represented diverse ethnicities. As mentioned previously, Black and minority ethnic populations are known to distrust the medical and research systems due to historical abuse and exploitation, so it may be that being approached by a medical professional would limit participation.  The primary outcome was definite or probably prostate cancer mortality, including intervention-related deaths, evaluated at a median of 10 years’ follow up. Participants were linked to the NHS national registry for vital status information, which was updated quarterly. Secondary outcomes were analysed at a median of 10 years and included overall mortality (from death certificates), metastases, disease progression, treatment complications (including adverse events) and resource use for the cost-effectiveness analysis. Outcomes were collected on case report forms (CRFs) by research nurses annually, based on medical record reviews and participant information gained at an appointment.  Use of medical notes requires the research team to have access to routinely collected participant data. As mentioned previously this may be an uncomfortable scenario for men from ethnic minority participants due to mistrust. Patient-reported quality of life outcomes focused on symptoms, condition-specific and overall quality of life, and psychological status. These questionnaires were completed at recruitment and at first biopsy appointments, then at 6 months after randomisation and yearly thereafter for at least 10 years. If it’s possible for trial data collection processes to be complete within the clinic setting, that would always be preferable as it will avoid missing data that will likely happen once participants are at home and getting on with their day-to-day lives.  It is not clear whether questionnaire completion relies on participants having access to a mobile telephone or device with Wi-Fi, this may be an issue for participants experiencing socioeconomic disadvantage. Ethnic minority populations are known to be at higher risk of socioeconomic disadvantage, so the trial team should think about contributions to WiFi or mobile data costs. |

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:** Prostate cancer is the most common cancer in men in the UK. Incidence rates have risen over the last 25 years, largely attributable to the introduction of prostate-specific antigen (PSA) testing. In [a study](https://pubmed.ncbi.nlm.nih.gov/21829203/) looking at incidences of prostate cancer globally, Western countries were found to have higher rates, but it is not known whether this is purely due to higher detection rates rather than higher occurrences.  A [UK study](https://pubmed.ncbi.nlm.nih.gov/26224061/) of data from Public Health England between 2008 and 2010, showed a man’s lifetime risk of being diagnosed with prostate cancer is 1 in 8; by ethnic group that breaks down as 1 in 8 for white men, 1 in 4 for Black men, 1 in 13 for Asian men. These rates translate to death rates for 1 in 24 for white men, 1 in 12 for Black men, and 1 in 44 for Asian men. [Studies](https://pubmed.ncbi.nlm.nih.gov/21829203/) suggest that Black men are predisposed to this disease due to several genetic mutations, and environmental factors such as diet and socioeconomic disadvantage are also thought to be contribute too. |
| How might the severity of the disease vary between each ethnic group? | **Response:** A [2006 study](https://pubmed.ncbi.nlm.nih.gov/17125479/) found that Black men in the UK had higher prostate-specific antigen expression, and prostate cancer was also found to present in younger African-Caribbean men than European and South Asian men. There were no significant differences in Gleason scores (a histopathological grading system used to help evaluate the prognosis of men with prostate cancer) between African-Caribbean men, and European and South Asian men. Black men were also found to have slightly worse clinical staging of their prostate cancer; T4 and/or M1 was at 26.4% for Black men and 23.0% for white men (T4 represents tumours invading to adjacent structures, and M1 represents distant metastasis). A subsequent [study in 2008](https://pubmed.ncbi.nlm.nih.gov/17368710/) found that although men in the UK have different incidence rates across ethnic groups, on average, African-Caribbean men are diagnosed five years earlier than white men, but all ethnic groups included in the study had equal access to diagnostic services. In also revealed that, apart from an increase in presenting PSA level, clinical presentation and management of prostate cancer were similar among men of all ethnicities. |
| 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. | |
| 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 feasibility study was conducted in 3 English cities (in 24 primary care centres linked to 3 hospitals) from June 1999 to September 2001. The main phase of recruitment was conducted from October 2001 to January 2009 in nine cities (seven in England, one in Scotland, and one in Wales) where around 100,000 men were recruited in primary care. The study centres were in Bristol, Newcastle, Sheffield, Birmingham, Cardiff, Edinburgh, Cambridge, Leicester, and Leeds.  [London is the most ethnically diverse region](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/regional-ethnic-diversity/latest#ethnic-groups-by-area), where 40.2% of residents identified belonged to either the Asian (18.5%), Black (13.3%), Mixed (5.0%), or Other (3.4%) ethnic group, so the trial team may have found It easier to recruit a more diverse sample if they had a recruiting centre in London. The next most diverse region in England and Wales is the [West Midlands](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/regional-ethnic-diversity/latest#ethnic-groups-by-area), the biggest city of which is Birmingham. The trial team have included Birmingham. The one Scottish site included was in Edinburgh; Glasgow may have been a better choice as it is home to the most ethnically diverse population in Scotland. | |
| Other factors to consider: | | |
| **Cultural** | How might perceptions of the disease and social stigma around it be different for each ethnic group in the target population? | **Response:** [Qualitative research](https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-10793-x) conducted [in the US](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5675170/) has demonstrated significant social stigma around prostate cancer, particularly in men self-identifying as Black and Latino. Dominant themes around prostate cancer diagnosis include the stigma surrounding the condition and the perceived role of an ‘unhealthy lifestyle’ and certain sexual behaviours as risk factors for prostate cancer development. Most participants acknowledge the importance of screening and early detection but discussed barriers to both interest in seeking healthcare and the likelihood of securing it. These barriers included misunderstanding of prostate cancer etiology, distrust of the medical profession, and financial/access limitations (these were conducted in the US, so health insurance coverage likely played a part). Men expressed substantial confusion about screening guidelines, and when Black women were asked about prostate cancer the role of faith and religion in the course of disease was a major theme.  A [qualitative study](https://ecancer.org/en/journal/article/695-research-engagement-among-black-men-with-prostate-cancer) with Black men undergoing treatment for prostate cancer at Guys Hospital in London, UK, explored barriers to prostate cancer research studies. Like the US study described above, themes such as mistrust of researchers were common. In addition, lack of understanding of the research process and the mechanisms of prostate cancer, and a reliance on herbal medicine. Some men explained that they were interested in herbal medicine and would use them in addition to clinical trial drugs, but this is something to bear in mind as a potential barrier to recruitment and engagement from this group.  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. | |
| How might ways of describing the disease be different for each ethnic group? | **Response:** We have not found other ways of describing the disease. | |
| How might cultural practices, beliefs and traditions influence the acceptability of, and adherence to, the treatment(s) for each ethnic group? | **Response:** The trial interventions include active monitoring, radical prostatectomy (surgical), and radical radiotherapy.  [Qualitative research](https://pubmed.ncbi.nlm.nih.gov/28101138/) suggests that men, in this case Black men, may tend to favour treatment using herbal medicine that is routinely used in the West Indies (the Caribbean). In the same study, one person that was taking part in a clinical trial for prostate cancer explained that he took herbal medicine in addition to the clinical trial drugs that he was taking. If this is plausible (i.e., no interactions or clinical reasons why participants should not take herbal medicine), then allowing for this may increase interest and/or engage with the trial. | |
| How or when might people in each ethnic group access healthcare for this disease differently? | **Response:** There are a number of factors that should be taken into account when it comes to how or when Black man in particular might access healthcare for prostate cancer treatment.  A [US study](https://journals.lww.com/academicmedicine/Fulltext/2007/02000/Viewpoint__Cultural_Competence_and_the_African.10.aspx) identified key influences to the provision of culturally competent healthcare, all of which could influence the way that Black men access healthcare. These influences were the legacy of slavery, Jim Crow discrimination, the Tuskegee syphilis study, religion’s interaction with healthcare, the use of traditional home remedies, distrust, racial concordance and discordance, and health literacy. The setting clearly has a US slant, but [similar findings](https://raceequalityfoundation.org.uk/health-care/the-health-and-social-care-experiences-of-black-and-minority-ethnic-older-people/) around [racism](https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-10793-x#ref-CR23), [the use of home remedies](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5215282/), [distrust](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5215282/), and health literacy have been found in a UK setting, with older people from Black and minority ethnic groups known to receive poorer treatment from health and social care services.  Research [conducted in the US](https://journals.sagepub.com/doi/10.1177/0898264313490199) highlights that [men from ethnic minority](https://pubmed.ncbi.nlm.nih.gov/16916126/) backgrounds often [do not feel comfortable](https://onlinelibrary.wiley.com/doi/10.1002/pon.4030) speaking with healthcare providers from different racial or ethnic groups. 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.  Feelings or fear and shame associated with a prostate cancer diagnosis further [compound the issue of open communication](https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-10793-x#ref-CR23) with healthcare professionals, especially with a cancer that can affect [physiological and sexual function](https://www.tandfonline.com/doi/full/10.3109/13685538.2010.522277) is involved, as with prostate cancer. | |
| Other factors to consider: | | |

**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:** [A 2021 meta-analysis](https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787591) of 7 randomised trials that included 8814 patients, Black and white men with localised prostate cancer and treated with definitive radiotherapy, suggested that Black men enrolled in trials presented with more aggressive disease features, but had better treatment and disease-specific outcomes with radiotherapy-based therapy compared with white men. If Black men are aware of this research, they may be less likely to engage with the trial due to wanting to receive radiotherapy, in this case randomisation and risk of being allocated to either active monitoring or surgery is the problem.  [Qualitative research](https://pubmed.ncbi.nlm.nih.gov/28101138/) also suggests that men, in this case Black men, may tend to favour treatment using herbal medicine that is routinely used in the West Indies (the Caribbean). In the same study, one person that was taking part in a clinical trial for prostate cancer explained that he took herbal medicine in addition to the clinical trial drugs that he was taking. If this is plausible (i.e., no interactions or clinical reasons why participants should not take herbal medicine), then allowing for this may increase interest and/or engage with the trial. |
| How, and in what way, were people from each ethnic group involved in selecting or designing the trial intervention/comparator? | **Response:** At the time that the ProtecT study was designed, PPI was not generally integrated in trial designs, but in this study a version of PPI was used to ensure patient voices were integrated into the work. The trial report does not explicitly list PPI representatives or the ethnic backgrounds of those that provided consultation and feedback, but it does discuss the integration of qualitative research methods to integrate PPI into the design and conduct of the study. Specific to the trial interventions, men that had declined randomisation in the feasibility study explained in interviews how the study should be organised, and this feedback was incorporated into the design of the trial. As a result, the conservative study group was called ‘active monitoring’ rather than ‘watchful waiting’. |
| 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 person delivering the interventions will vary by the intervention type (radiotherapy, surgery, active monitoring), but the trial report suggests that the specialist research nurses will be the point of contact for participants, including meeting. It is not clear whether this team of specialist nurses represent a variety of ethnic backgrounds. 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 research visits with participants are of the same ethnicity, or share a common language, this distrust may be reduced. It is important to bear in mind for the surgical intervention specifically, that according to [an analysis](https://www.theguardian.com/society/2021/sep/01/black-surgeons-promoted-far-less-than-white-colleagues-in-england) of NHS medics’ careers in England, Black surgeons are far less likely to be promoted than their white colleagues. Black men who were junior surgeons in 2010 were 27% less likely to be promoted to consultant than white men between 2016 and 2020, while Black women were 42% less likely. Senior Black doctors said that the research matched their experiences and warned of a lack of support for minority doctors to pass tests required to reach the best-paid ranks.  As mentioned previously, Black and minority ethnic populations are known to distrust the medical and research systems due to historical abuse and exploitation, so it may be that engaging with research being conducted at an NHS site would limit participation. |
| 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:** Two of the trial’s interventions (radiotherapy and surgery) will be delivered in a hospital setting, but the active monitoring group was also required to attend hospital visits regularly to review disease progression. As mentioned previously, Black and minority ethnic populations are known to distrust medical and research systems, so it may be that attending research visits at an NHS hospital site would limit participation.  In the active monitoring group, the aim was to avoid immediate radical treatment while assessing the disease over time, with radical treatment offered if disease progression was evident. PSA concentrations were reviewed every 3 months in the first year and twice yearly thereafter. The specialist nurses also met with participants yearly to assess their overall health and discuss graphical displays of PSA results and any concerns raised, overseen by each centre’s local clinical investigator. Changes in PSA concentrations were assessed at each visit, and a rise of ≥ 50% during the previous 12 months triggered repeat testing within 6–9 weeks. If the PSA concentrations were persistently raised, or the patient had any other concerns, a review appointment was made with the centre urologist for discussion of further tests including re-biopsy and all relevant management options. A site monitoring and review team comprising trial research nurses and the trial manager visited sites annually; these visits included observation of the nurse-led active monitoring appointments as per the protocol.  In radiotherapy, neoadjuvant androgen suppression was given for 3–6 months before and concomitantly with 3D-conformal radiotherapy delivered at each of the nine centres. PSA concentrations were measured every 6 months for the first year and then yearly after that. The study oncologist held a review appointment with participants if the PSA concentrations rose by ≥ 2.0 μg/l post nadir or if concerns were raised about disease progression. Management options were discussed, including monitoring, tests and salvage, radical or palliative treatments as indicated.  The predominant approach for surgery was open retropubic with individual-level quality assurance to published standards at each of the nine centres. Participants with a baseline PSA concentration of ≥ 10 μg/l or a biopsy Gleason score of at least 7 points received bilateral lymphadenectomy. Postoperatively, PSA concentrations were measured every 3 months for the first year, every 6 months for the subsequent 2 years and then yearly after that. Adjuvant radiotherapy was discussed and offered to patients with positive surgical margins or extracapsular disease. The centre urologist held a review appointment with participants if their postoperative PSA concentrations reached ≥ 0.2 μg/l to discuss adjuvant radiotherapy.  Getting to hospital can be an issue for a variety of reasons including – poor transport links, the timing and length of research visits (i.e. clashing with working hours, childcare or caring responsibilities), financial reasons (time away from work, cost of travel, parking charges). Many of these factors disproportionately impact people from poor socioeconomic backgrounds. People from ethnic minority groups are at higher risk of experiencing socioeconomic disadvantage. |
| Other factors to consider: | |
| **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:** As above. |
| Other factors to consider: | |
| **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:** As above. |
| Other factors to consider: | |

\*These factors are taken from TIDieR ([http://www.equator-network.org/reporting-guidelines/tidier/](about:blank)).

**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 eligibility criteria include men aged 50-69 years with localised prostate cancer. Trial exclusion criteria were a previous malignancy (apart from skin cancer), renal transplant or current renal dialysis, major cardiovascular or respiratory comorbidities, bilateral hip replacement or an estimated life expectancy of <10 years.  People with African Caribbean heritage have a [much higher risk](https://www.bhf.org.uk/informationsupport/heart-matters-magazine/medical/african-caribbean-background-and-heart-health) of high blood pressure, type 2 diabetes, and stroke, but a lower risk of coronary heart disease. Normally, high blood pressure and diabetes increase coronary heart disease risk, and the disassociation isn’t yet understood. The causes of [excess cardiovascular disease and stroke](https://www.nature.com/articles/1002126) morbidity and mortality in Black and minority ethnic groups in comparison to white British people are incompletely understood, but socioeconomic factors are thought to play a role. The same can be said of respiratory diseases, COVID-19 for example has disproportionately impacted people with ethnic minority backgrounds, with crowded housing, public facing jobs, and a link to socioeconomic deprivation being to blame. The exclusion criteria of major cardiovascular or respiratory comorbidities have the potential to inadvertently exclude Black men disproportionately, though someone with a more clinical focus may be able to provide information as to the reason for this eligibility criteria – e.g., these conditions may have a contraindication with one or more of the interventions. If this is the case, then this should be noted explicitly.  It is not clear how the final exclusion criteria, ‘an estimated life expectancy of <10 years’ will be measured or arrived at, and criteria like this that may be subjective do run the risk of unconscious bias creeping in that may exclude people from ethnic minority backgrounds, particularly with anti-Blackness coming into play.  We discussed location in terms of trial sites earlier on, the trial sites selected are conducive to recruiting a diverse participant population. There is no reason to believe that the medical history information taken from participants would disproportionately impact one ethnic group over another. The language used throughout the protocol and trial registration entry is gendered and focussed on men, inadvertently excluding trans, non-binary, and genderfluid people, though this does not disproportionately impact people from any specific ethnic group. |
| 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:** Recruitment took place mainly at GP surgeries, but on occasions at other venues such as sports centres or church halls, requiring the nurses to be adaptable and autonomous. In addition, the nurses sometimes travelled widely during recruitment, particularly where there were few surgeries near the hospital or if they had taken part early on in recruitment. The feasibility study showed that nurses were as effective as urologists in randomising participants and the trial report notes that they became central to the success of the main trial. It is not clear whether the nurses involved with this trial represented diverse ethnicities. As mentioned previously, Black and minority ethnic populations are known to distrust the medical and research systems due to historical abuse and exploitation, so it may be that being approached by a medical professional would limit participation. |
| How might the information that tells potential participants about the trial (e.g. participant information leaflet) limit the participation of each ethnic group? | **Response:** The trial report references a ProtecT patient information sheet, but no detail is given about the information that it contained. It is unclear if the information given to participants was developed together with people from a range of ethnic groups. |
| How might cultural practices, beliefs and traditions change the way each ethnic group perceives the information they are given? | **Response:** We cannot assess the written information given to potential participants as the contents of the ProtecT patient information sheet are not detailed in the trial report. That said, we have mentioned reduced levels of health literacy previously, and the trial team should ensure that this document is written in an accessible way bearing in mind the potential tendency to prefer the use of herbal home remedies in Black men. |
| 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:** The trial report details that written consent will be obtained by a specialist research nurse, as well as providing information on a qualitative analysis of audio-recording of recruiter appointments. The analysis suggested that informed consent was enhanced by tailored information provision including strategic use of open questions, pauses and ceding the floor to participants in the interaction. These techniques facilitated detailed and systematic exploration of each participant’s concerns and facilitated truly informed consent. No detail is provided about translation or interpretation, which may limit participation of people that don’t speak or read English well. This is likely to be an issue for older generations of South Asian communities for example, this group may not be a target group (they are at lower risk of prostate cancer than their white counterparts), but the age group of 50-69 means that translation/interpretation support should be provided by the trial team. | |
| How might the way people would like to discuss participation with family before providing consent differ for each ethnic group? | **Response:** The trial report does not detail if/how people would like to discuss participation with family before providing consent for trial participation. [Research suggests](https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-10793-x#ref-CR23) that there is a secrecy around family death due to prostate cancer due to a cultural reticence to discuss medical problems with the family in the Black/African-American culture, particularly if it was a ‘personal, sexual type situation’ as prostate cancer is perceived. Black men may therefore not want to discuss trial participation with their family, particularly if they are worried that their sex lives may be negatively impacted. | |
| How might the way the research team can check how well consent information is understood differ for each ethnic group? | **Response:** The trial report details a qualitative analysis of audio-recording of recruiter appointments. The analysis suggested that informed consent was enhanced by tailored information provision including strategic use of open questions, pauses and ceding the floor to participants in the interaction. These techniques facilitated detailed and systematic exploration of each participant’s concerns and facilitated truly informed consent. In contrast, interruptions and failing to address participants’ questions were unhelpful. These techniques were presented to recruiters during training and were taken up by many recruiters over time. | |
| 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:** At the time that the ProtecT study was designed, PPI was not generally integrated in trial designs, but in this study a version of PPI was used to ensure patient voices were integrated into the work. The trial report does not explicitly list PPI representatives or the ethnic backgrounds of those that provided consultation and feedback, but it does discuss the integration of qualitative research methods to integrate PPI into the design and conduct of the study. There is no mention in the trial report of the trial outcomes being informed by PPI, but the way that data are collected to support those outcomes is referenced: ‘The participants in the core serial interview study have formed a PPI-like ‘sounding board’ to give views about possible changes to the study, such as e-mail contact would not be acceptable, questionnaires needed to be shorter and that they highly valued the study and contact with research nurses during the follow-up process.’ |
| 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:** There is no evidence to suggest that the specific outcomes or other data being collected will limit participation of any specific ethnic group. |
| Other factors to consider: | |
| **Who** | How might the people who collect data limit the participation of each ethnic group in the target population? | **Response:** The people who collect the data are specialist research nurses, it is not clear whether this team of nurses includes a variety of ethnicities. As mentioned previously, Black and minority ethnic populations are known to distrust the medical and research systems due to historical abuse and exploitation, so it may be that data collection by people working within these systems could limit participation. |
| Other factors to consider: | |
| **How** | How might data collection methods limit the participation of each ethnic group in the target population? | **Response:** The primary outcome was definite or probably prostate cancer mortality, including intervention-related deaths, evaluated at a median of 10 years’ follow up. Participants were linked to the NHS national registry for vital status information, which was updated quarterly. Secondary outcomes were analysed at a median of 10 years and included overall mortality (from death certificates), metastases, disease progression, treatment complications (including adverse events) and resource use for the cost-effectiveness analysis. Outcomes were collected on case report forms (CRFs) by research nurses annually, based on medical record reviews and participant information gained at an appointment.  Use of medical notes requires the research team to have access to routinely collected participant data. As mentioned previously this may be an uncomfortable scenario for men from ethnic minority participants due to mistrust.  Patient-reported quality of life outcomes focused on symptoms, condition-specific and overall quality of life, and psychological status. These questionnaires were completed at recruitment and at first biopsy appointments, then at 6 months after randomisation and yearly thereafter for at least 10 years.  If it’s possible for trial data collection processes to be complete within the clinic setting, that would always be preferable as it will avoid missing data that will likely happen once participants are at home and getting on with their day-to-day lives.  It is not clear whether questionnaire completion relies on participants having access to a mobile telephone or device with Wi-Fi, this may be an issue for participants experiencing socioeconomic disadvantage. Ethnic minority populations are known to be at higher risk of socioeconomic disadvantage, so the trial team should think about contributions to WiFi or mobile data costs. |
| Other factors to consider: | |
| **Where** | How might where data are collected limit the participation of each ethnic group in the target population? | **Response:** As above. |
| 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:** As detailed on worksheet 3b, data are collected through a variety of methods; medical notes being the primary method, along with questionnaires and case report forms.  Use of medical notes requires the research team to have access to routinely collected participant data. As mentioned previously this may be an uncomfortable scenario for men from ethnic minority participants due to mistrust.  If it’s possible for trial data collection processes to be complete within the clinic setting, that would always be preferable as it will avoid missing data that will likely happen once participants are at home and getting on with their day-to-day lives.  It is not clear whether questionnaire completion relies on participants having access to a mobile telephone or device with Wi-Fi, this may be an issue for participants experiencing socioeconomic disadvantage. Ethnic minority populations are known to be at higher risk of socioeconomic disadvantage, so the trial team should think about contributions to WiFi or mobile data costs. |
| Other factors to consider: | |
| **Benefits** | How might the benefits of the trial intervention(s) differ between each ethnic group in the target population? | **Response:** The reasons behind the increased prevalence of prostate cancer in Black men, are not clear, they could be genetic, social, and/or cultural. As mentioned previously, there is some evidence to suggest that Black men may benefit more than white men when receiving radiotherapy for prostate cancer, even when the disease is further advanced in Black men. |
| 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 disproportionate effects of prostate cancer on Black men, young Black men in particular.  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: | |

**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:** At the time that the ProtecT study was designed, PPI was not generally integrated in trial designs, but in this study a version of PPI was used to ensure patient voices were integrated into the work. The trial report does not explicitly list PPI representatives, but it does discuss the integration of qualitative research methods to integrate PPI into the design and conduct of the study. The ProtecT study results newsletter was given to patient advisory group participants (9 ProtecT participants and 3 female partners, and 2 men who were not part of ProtecT that were part of the NIHR Bristol Nutrition Biomedical Research Unit prostate cancer PPI group) to read in advance at group meetings, and participants were then able to comment on study findings. They supported by sharing views on what information should be included and how best to present it. It is not clear whether various ethnicities were represented in these conversations. |
| Other factors to consider: | |
| **How** | How might planned reporting and dissemination methods limit engagement with each ethnic group in the target population? | **Response:** The trial report is open access and lists 44 related scientific publications from the ProtecT study in peer reviewed journals. Using publications as dissemination is not conducive to engaging any ethnic group, or member of the public with the results of this trial.  Dissemination materials intended for the public should consider the health beliefs, health literacy and languages of the ethnic groups in the community and use channels appropriate for the ethnic group. For example, community radio can be a useful tool for some ethnic groups, as can social media.  The trial report does mention that trial participants will be able to access the results of the trial via a newsletter, though there is no mention of how this method was decided on. The patient advisory groups linked to the study supported by sharing views on what information should be included and how best to present it. It is not clear whether various ethnicities were represented in these conversations. |
| 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.

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| **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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[Centre for Black and Minority Ethnic Health](https://centreforbmehealth.org.uk/)

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[Health Research Board Trial Methodology Research](https://www.hrb-tmrn.ie/)

[Network](https://www.hrb-tmrn.ie/)

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