A randomised, double blind, placebo controlled feasibility study to examine the clinical effectiveness of aspirin and/or Vitamin D3 to prevent disease progression in men on active surveillance for prostate cancer.

Part 1

You are being invited to take part in PROVENT, a clinical trial for men diagnosed with prostate cancer. Before you decide whether or not to take part you need to understand why the research is being carried out and what it would involve for you.

If this information sheet and consent form contain words that you don't understand, please ask the study doctor or nurse to explain anything that is unclear. Please take time to read the information carefully. You will be able to take a copy of this sheet home *so* that you can read it again and, if you want to, discuss it with family members or friends before making your decision.

You should not sign the consent form until you have read this information sheet carefully, asked any questions you might have, and received satisfactory answers.

Contents

1 What is the purpose of the study?

This type of trial is called a 'feasibility study', which simply means we want to find out whether a large scale study would be worthwhile.

The larger trial will try to find out whether certain products can prevent prostate cancers that are not high risk, such as yours, from developing into more serious cancers. Before we can run that trial, we need to work out whether the men we would like to take part, actually want to take part. The feasibility study will also help us work out how long it will take for enough men to join, whether the study is practical and if we need to change anything about how the trial is organised.

Knowing the best way to treat this type of cancer can be very difficult, as it is impossible to tell how someone's cancer is going to develop at the time it is diagnosed. Some never progress beyond the stage they are at when they are found, while others develop into a more serious condition

that needs more aggressive treatment. However, with no way of telling which cancer is which, some men decide to have radical treatment early on to prevent their cancer from progressing, even though their disease might never get any worse.

One of the treatment options that has become popular for this type of disease is called active surveillance, and if you have been given this leaflet
it is because your doctor thinks it would be a suitable option for you. Active surveillance means that rather than treat you with one of the more aggressive or radical treatments, such as surgery or radiotherapy, your doctor will keep a very close eye on you and monitor you every three months for signs that your cancer could be changing. That way you would only need more radical treatment if it becomes necessary.

Over recent years there has been a lot of research suggesting that certain commonly used products can prevent cancers from growing and changing, and two of these products are aspirin and Vitamin D3. In this study, men will be selected at random to take either aspirin **or** Vitamin D3, both aspirin **and** Vitamin D3, or dummy medicines called placebos. Neither the men nor their doctors will know which of the treatments they are taking; this is called a double-blind study. Each group (also known as a 'treatment arm') will contain an equal number of men.

The study will run for three years, with patients recruited over a period of 12 months. At present we do not know the best length of treatment; however, for this study each patient will be treated for up to 18 months. We are inviting men whose prostate cancer is managed by active surveillance to join the study, and hope to recruit 102 men within 12months.

2 Why have I been invited?

You are being invited to take part in this clinical trial because your doctor believes your type of prostate cancer and treatment makes you suitable to join in the research.

3 Do I have to take part?

No. It's up to you whether you take part or not. If you decide not to take part, the standard of care you receive will not be affected in any way. However, we may ask you why you decided not to take part, as this will be important for us when planning the larger trial.

4 What will happen to me if I take part?

If you do decide to take part, you will be asked some 'screening' questions to make sure you are suitable for the trial. If, after answering the questions, it turns out that you are not eligible, you will not be able to join the trial. If you are eligible, you will be asked to read and sign the consent form to confirm that you understand the study and that you agree to participate. You will be given this information sheet and a copy of the consent form to keep.

The consent will also allow us to take a small blood sample at this visit to check your calcium levels if it has not been checked recently, (within two months of the date you signed your consent) form. Vitamin D3 can increase the amount of calcium in your blood. If we do take a sample from you, & the result shows that your calcium level is too high to take part in the research, we shall let you know before you are due to attend the next appointment.
If you are suitable for the study, then most of the procedures and tests you will have are exactly the same as you would have if you were not taking part, with one or two exceptions.

Men who choose active surveillance for their treatment are normally seen every three months, and this study is designed so that the research appointments coincide with those regular appointments. If you take part, the only extra visit will be the randomisation visit, when you will be randomly assigned or 'randomised' to one of the 6 treatment arms below, although you will not be told which treatment arm you are in. This will normally take place 1-4 weeks after signing the consent form for the study.

1. Aspirin 300mg + Vitamin D3

2. Aspirin 300mg + Vitamin D3 placebo
3. Aspirin 100mg + Vitamin D3
4. Aspirin 100mg + Vitamin D3 placebo
5. Aspirin placebo + Vitamin D3
6. Aspirin placebo + Vitamin D3 placebo

5 Randomisation Visit

This is the additional appointment that you need to attend if you choose to take part in the research. Unfortunately, as the study is charity funded, there are no resources to reimburse patients' travel expenses or subsistence costs. We will ask you several questions about your health and lifestyle, and we will also take a blood sample to check your hormone and Vitamin D3 levels, plus a small sample for future research. This will only require an extra tablespoon (15ml) of blood.

At this visit, we will carry out a test to make sure you don't have an infection in your stomach called *Helicobacter pylori*. This is a common bacterial infection that affects the stomach lining and causes gastric ulcers, indigestion and bleeding. You will be asked to bring a stool (faeces) sample to this appointment for the test to detect whether or not you have the bacteria. We will want to make sure you don't have this infection, as aspirin can also irritate the stomach lining and cause bleeding in some people, so having the infection might make this more likely. If you already take medication for indigestion or reflux we will check to make sure it is a medicine that won't affect the test result, and if it is, we will provide you with an alternative to take for two weeks before the test. Antibiotics can also affect the result, and so should not be taken in the four weeks before the test. If we find that you do have this infection, we will contact you and arrange for your GP to prescribe some antibiotic treatment for you. If you are not willing to have this treatment you will not be able to continue with the study.

You will also have a routine rectal examination, after which we will ask you to provide us with a urine sample. This is so that we can collect some cells for tests that look at prostate genes, and can help to detect changes in the prostate.

Finally, you will be given your wallet card, a diary card and study prescription, which will allow you to collect the trial medicines from the pharmacy.

6 Follow Up Visits

As part of your routine care on Active Surveillance, you will have a blood test every three months to check for changes in your PSA level, and we will take some extra blood every six months to test your Vitamin D3, calcium and/or hormone levels. At your 18 month visit an additional small blood sample will be taken for future research. Your doctor will also carry out routine rectal examinations to check for changes in your prostate, and at the 12 & 18 month visits, we will collect a further urine sample.

The doctor or nurse will ask you some questions at each visit to see if the medicines have caused you any problems and to make sure you are happy to continue on the study. Every six months you will be given a prescription for your study medicine and every three months a new diary card to record any problems or missed doses.

At 12 months, you will have a routine MRI scan and a prostate biopsy to make sure your prostate cancer is showing no signs of growth or change. These are both normal procedures for someone on active surveillance, so whether you decide to take part in the study or not, you will continue to have these tests.

Unless there has been a reason to withdraw from the study, your final visit will take place 1 month after you have completed 18 months of treatment. If there is an option at that time to continue with further treatment in the main trial, and you would like to continue, then it may be necessary to sign an additional consent form.

With the exception of the randomisation and final visits, the number of appointments you have to attend will be the same as if you were not on the study, but each visit might take a little longer.

7 What are the medicines being tested?

The medicines being tested are aspirin and Vitamin D3, two products that are well known but are not currently used for preventing cancer. Other research studies have suggested that these products may be effective at preventing some types of cancer, and so our aim is to see whether they can stop prostate cancer that is not high risk from developing into higher risk disease.

The aspirin will be in tablet form, taken once a day with water, and will be coated to avoid irritating the stomach lining. It will be given in one of two different doses. Some men will take a low dose aspirin (100mg) and others will take a regular dose aspirin (300mg). In addition, some men will take a dummy tablet (placebo) containing no aspirin at all.
No one will know which tablet you are taking, not even your doctor, as this is what is known as a double blind study. The Vitamin D3 will be given as an oily liquid, and you will need to take the drops (less than a quarter of a teaspoon) daily; the dose is equivalent to 0.1mg or 4,000 International Units (IU). The drops can either be taken on their own from a teaspoon, soaked into bread, or added to a small quantity of fruit juice, whichever you prefer. Like the aspirin, some men will take Vitamin D3 and others will take a dummy liquid (placebo), but you won't be able to tell which is which.

8 Are there any alternative treatments to this study?

For men who have already made the decision to join an active surveillance programme, your alternative to this study is not to take part. There are several alternatives to active surveillance which your doctor will have discussed with you, including surgery. However, if you are unsure what those alternatives are, or you would like to discuss them again, please ask your doctor who will talk you through them in detail.

9 What are the possible side effects of taking part?

Like all medicines, aspirin and Vitamin D3 can cause side effects, although not everyone will get them; however, both of these medicines are well tolerated and do not normally cause serious side effects. The main concern with aspirin, as already mentioned, is that it can irritate the lining of the stomach and cause bleeding in some people. The doses used in this study are very low, however if you unexpectedly develop indigestion or stomach pain it would be best to stop the tablets until you have spoken to your study doctor. Anyone infected with the bacteria *Helicobacter pylori* is already at increased risk of gastric bleeding, which is why we will test you for this when you start the study and arrange treatment through your GP if you need it.

9.1 Aspirin

Aspirin is a common medicine and has been well studied and used for many years around the world. If you have never experienced side effects when taking aspirin in the past, it is unlikely that you will experience side effects from taking aspirin as part of this trial, but please let the doctor or nurse know if you have ever had any unpleasant reaction to aspirin. Due to the slightly increased risk of bleeding, you will be asked to **stop taking the tablets for a week before having your biopsy, and for two days after the procedure,** as a precaution. You should also stop the tablets if you know that you are going to have any sort of surgery or operation, and tell any doctor who is treating you that you might be taking aspirin and

Vitamin D3. We will give you a card to keep in your wallet with our details in case you need to contact us.

If you experience any of the following side effects while taking your medicine, you should stop taking the tablets and tell your doctor straight away:

- Allergic reaction (hypersensitivity) which may include lumpy skin or hives, skin rash, swelling around the face or mouth, sudden wheeziness, coughing, difficulty breathing or worsening of asthma.
- Severe or persistent indigestion, stomach upset or pain. You may develop ulcers or bleeding from the stomach which can cause severe stomach pain, bloody or black tarry stools or vomiting blood.

Other less common side effects of aspirin include:

- Stomach upset and feeling sick
- An increased tendency to bleed
- Anaemia and other blood disorders
- Mouth ulcers
- Ringing in your ears
- You may succumb to infections more easily
- You may bruise more easily
- Slight blood loss may result in iron-deficiency anaemia during long term use
- Diarrhoea
- Blood in urine
- Stevens-Johnson syndrome (fever, rash, sore mouth and eyes, joint and muscle aches)
- Severe skin problem with shedding of upper layer of skin
- Liver problems, particularly at high doses

Due to the slightly increased risk of bleeding with aspirin, we recommend that while you are on the study you **do not take any extra aspirin or medicine in a similar drug group**, such as ibuprofen or naproxen (medicines known as NSAIDs). If you have pain or a temperature while taking part we recommend that you take paracetamol. If you have any doubts about the medication that you are taking, please contact the study doctor or study nurse and they can advise you.

9.2 Vitamin D3

Side effects from Vitamin D3 are very rare. Any side effects that do occur are mostly due to having too much calcium in the blood. If you have not had your calcium levels checked up to two months before the date you signed your consent form, we will be testing your blood prior to you joining the study, and subsequently every 6 months, to make sure your calcium level is not too high. Possible side effects include:

- Excess calcium in the blood or urine - particularly in people suffering from kidney disease, overactive parathyroid gland, lymphoma, sarcoidosis or histoplasmosis.
- Gastro-intestinal disorders: nausea, flatulence, diarrhoea, abdominal pain
- Skin rash

10 What are the other possible disadvantages and risks of taking part?

For someone who has already chosen active surveillance as their form of management, there are few disadvantages to taking part in this study. You will still have a hospital appointment every three months, although some of your appointments might take a little longer than normal. You will need to remember to take a tablet and the oil every day, unless advised otherwise, and keep a diary. As with all medicines, there is a small risk of side effects from the study medication.

11 What are the possible benefits of taking part?

We can't say that there is any direct benefit to you from taking part in the study at this time as we don't yet know whether aspirin or Vitamin D3 will prevent prostate cancer from developing further. It is hoped that the results of this feasibility study, and the larger main study, will benefit future patients with prostate cancer by preventing the development of more aggressive disease.

A possible benefit of the study would be the discovery and subsequent treatment of a *Helicobacter pylori* infection in someone who did not know that he was infected.

12 What happens when the research study stops?

If this feasibility study is successful, it is hoped that the main study will follow on straight after. Men whose prostate cancers have remained unchanged at that point, and who are happy to continue, may be able to transfer directly into the new study for a further 18 months or more of treatment after signing a further consent form. If, for some reason, the main study does not start, then you would continue to be followed up every three months as part of the normal active surveillance programme, but you would no longer take the study medication.

If at any stage your cancer shows signs of change and you need further treatment, then your doctor will advise you to stop the study. Similarly, if you change your mind about active surveillance and decide you would rather have more radical treatment, your doctor will be able to advise you. Any information and samples that we have collected up to that point will remain part of the study.

You are free to leave the study at any time, and for any reason, and return to a normal active surveillance programme. As before, information and samples that have been collected up to that point will remain part of the study. If you would like all information and samples to be removed from the study, you would need to provide us with a written letter detailing your wishes. Please ask the study doctor or study nurse if you have any questions about this.

13 What if something goes wrong?

You should contact your study doctor or nurse if you have a question or a problem while taking part in the research. Their contact details are on the last page of this information sheet.

If you are seen by a doctor outside the study you should remind them that you are taking part in this research. In case of an emergency, you should act in exactly the same way as you would if you were not on the study. It is unlikely that you will need emergency hospital treatment as a result of this trial, however, you should always inform any doctor treating you that that you might be taking aspirin and Vitamin D3. You should be treated as if you were taking the maximum study dose of one 300mg aspirin tablet and 0.1mg vitamin D3 per day. Treatment code breaks will not be available on a 24 hour basis as this should not affect the way you are dealt with in an emergency, but where a treating physician considers this essential, the coordinating centre will confirm the treatment codes during office hours.

Queen Mary University of London has agreed that if you are harmed as a result of your participation in the study, you will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of the intervention or procedures you received during the course of the study. These special compensation arrangements apply where an injury is caused to you that would not have occurred if you were not in the trial. These arrangements do not affect your right to pursue a claim through legal action

14 Will my taking part in the study be kept confidential?

Yes. All the information about your participation in the study will be kept confidential. Further details about this can be found in Part 2.

15 Who should I call if I have problems or questions?

- You can ask more questions about the study at any time and you can contact the following people for more information:
  'local PI name 'and 'research nurse name'– the study doctor and research nurse.

  Telephone: xxxx xxx xxxx local number
  For urgent advice (24 hour): xxxx xxx xxxx

- You can also visit the PROVENT trial website at: http://www.provent.org.uk

- For independent advice on taking part in a clinical trial please contact the 'local' Health Patient Advice and Liaisons Service (PALS) on 'number 'or Email: 'local PALS email'
  The PALS service is available Monday to Friday 9.30am – 4.30pm.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering taking part, please continue to read the additional information in Part 2 before making any decision.

Part 2

16 What if new information becomes available?

Sometimes during the course of a research study, new or important information becomes available about the medicine that is being studied. If this were to happen, the trial staff would let you know and discuss it with you. Depending on what the information is, you may wish to withdraw from the study or your doctor may advise you to withdraw, in which case you would continue to be seen in the normal active surveillance clinics. If you decided to continue in the study you may be asked to sign an updated consent form.

A special group of experts, known as a Data Monitoring Committee, who are independent of the trial staff and doctors, will be set up to oversee the study on a regular basis to make sure any issues are looked into properly and that the men taking part are informed about any relevant new information. The information sheet and other study documents will also be updated with any new details.

17 What will happen if I don't want to carry on in the study?

You are completely free to leave the study any time you wish and for any reason. If you change your mind about taking part in the study, the standard of care you receive will not be affected. It is also possible for you to stop the study medication, and still remain on the study, under follow-up in the clinic, or by telephone. If you decide you would rather have more radical treatment for your cancer than

active surveillance, your study doctor will be able to advise you. Any information and samples that we have collected up to that point will remain part of the study. If for some reason you should decide to completely withdraw the information and samples that have been collected from you, then we would require you to put this in writing to your study doctor.

18 Will my taking part in this study be kept confidential?

If you join the study, you will be given a study number that will be used on all of your study records and samples instead of your name to ensure your information is kept confidential. Your medical records may be looked at by people who are authorised to check that the study is being carried out properly. Representatives of health authorities and the hospital NHS Trust, and auditors from the Trials Unit or the companies supplying the medicines may have access to your medical records, and these people will be required to keep your information confidential. A responsible representative of Queen Mary University of London will also require access to records for the purpose of monitoring and auditing. By signing the consent form you are giving your permission for this to happen.

Your study doctor is responsible for keeping a code list which makes it possible to link your study number to your name. This will be kept in a safe place to ensure that in an emergency you can be identified. The code list will be kept until twenty years after the study has ended. All of your study data will be protected in accordance with the Data Protection Act (1998).

Your contact details and information collected about you will be stored on a secure database, and access will only be available to members of the trial team, and other members of Queen Mary University London, who may wish to monitor the study. These details may be required to enable the trial team to send you study related information.

19 Informing your General Practitioner

With your permission, given when you sign the consent form, the study doctor will inform your family doctor (GP) that you will be taking part in this research. We feel that this is important because your GP should be aware of any treatment or medications that you receive so they have a more complete picture of your health. After you have joined the study, they will receive a letter that will include the result of your H Pylori test, and this information sheet for their records. If your test shows that you do have the infection, you will also receive a copy of the letter to take to your GP. We also encourage you to mention this trial the next time you see your GP.

There are certain medicines that you should not take while on this trial, and these are shown below. Your GP will be able to check these for you, however, if you are unsure whether you take any of the following medicines please be sure to ask your doctor:

You should not take:
Aspirin, or **any** products containing aspirin
Vitamin D supplements containing more than 400IU
NSAIDs e.g. Ibuprofen, Diclofenac, Naproxen
Anticoagulants/Thrombolytics e.g. warfarin
Antiplatelet drugs e.g. clopidogrel
Systemic glucocorticoids e.g. prednisone, cortisone
SSRI antidepressants e.g. paroxetine, citalopram
Digoxin/digitalis
Antidiabetics e.g. glibenclamide, tolbutamide
Methotrexate
Valproic acid
Phenytoin or barbiturates
Thiazide diuretics
Rifampicin and isoniazid
Dovonex cream
Any cytotoxic, hormonal or immunotherapies

The following drugs may be used, but with care, as they might not work as well with the study drugs:

Calcium channel blockers e.g. verapamil, diltiazem
Statins e.g. atorvastatin, lovastatin

Alcohol should be taken in moderation only.

20 What will happen to any samples I give?

Various samples will be collected for this study. Some will be for routine testing, while others relate to this study. Samples collected in relation to this study will be regarded as a gift from you to Queen Mary University of London (QMUL). These samples will be stored securely and indefinitely by QMUL and may be used for future ethically approved research. Certain samples will be sent outside the European Union for analysis and, as for all samples, any identifiers will be removed.

The urine samples collected will be stored for analysis at a later date. Samples may also be made available to the scientific community outside of QMUL, for relevant, ethically approved research. Where this occurs, the samples will always remain pseudo-anonymised, i.e. identified by your study number only.

Most of the blood samples will be analysed immediately, except for the Vitamin D3 and research samples that will also be stored by QMUL for testing at a future date. We will also collect tissue samples from any prostate biopsies or prostate surgery you have had or will have – these samples will only be from excess tissue that has been taken as normal practice.

All samples will have your personal details removed and will be identified only by the sample number to protect your identity. They will only be used for research related purposes.

By signing the consent form you are giving your permission for your samples to be stored and/or tested.

21 Will any genetic tests be done?

We do not know exactly which tests may be carried out in the future, but it is likely that some of these will be of a genetic nature. Your sample will be identified only by a sample number, and no test results will be available individually, but will only be reported anonymously on a group basis. In order to protect you, the blood samples will be anonymised before any genetic tests are performed. Any DNA tests will only be carried out on bulk anonymised samples.

22 What will happen to the results of the research study?

It will take up to three years to complete this study, so it will be some time before any results are available. However, if the number of men joining the study is sufficient, and the Data Monitoring Committee is satisfied with the early results, then it is hoped that the larger, main study will begin. If any important information is discovered, then all men taking part in the study will be informed. Results may also be presented at relevant conferences, published in academic journals, and shared with the medical community.
If results from this research study are published, your identity will remain confidential and no personal identifiable information will be used.

23 Who is organising and funding the research?

Queen Mary University of London is organising this research and is the sponsor for the study. The research is funded by Barts and the London Charity, and
Cancer Research UK who provides funding for the project manager. The medicines for this trial

are being provided free of charge by both Bayer Healthcare and Merck Sorono pharmaceuticals. None of the staff involved in the study will receive payment specific to their involvement in this research.

24 Who has reviewed the study?

This study has been reviewed and approved by the NRES Committee London - Hampstead, a Research Ethics Committee which has given a favourable opinion to conduct this study in the UK.

25 Contact for further information

- 'local PI name'
  or
  'research nurse name'
- Tel: 'xxxx xxx xxxx' local number
- Local number for urgent advice (24 hour) Tel: 'xxx xxxx xxxxxx'

- www.provent.org.uk

Thank you for reading this information leaflet. Should you now decide to proceed with your participation in this study, you will be asked to sign a consent form. Please note that you will be given a copy of this patient information leaflet and a copy of the signed consent form to keep.

PIS Template with thanks to:
P Knapp, DK Raynor, J Silcock, B Parkinson.
Can user testing of a clinical trial patient information sheet make it fit-for-purpose? – a randomised controlled trial. *BMC Medicine* 2011, 9:89. doi:10.1186/1741-7015-9-89.