Data included in Table S5 from Audrey *et al* 2011 linked to verbatim data from omitted Donovan *et al* 2003

Audrey *et al 2011* data			**From Donovan *et al* 2003 – data relevant for recruitment and/or retention (monograph Chapter 3)**
Data from paper reported as 'findings' in Table S5	*'Changes planned before the full trial'*	*Theme label for 'Findings associated with code'*	
Patients and recruiters also had difficulty with randomization. Patients often expressed lay views that cancer should be removed or came with media information that was biased in favour of radical treatments.	It was necessary to emphasize that recruiters must be genuinely uncertain about the best treatment, believe the patient to be suitable for all three treatments, and be confident in these beliefs. Recruiters were encouraged to elicit patients' lay views and then discuss differences with ProtecT study information, explain that randomisation offered a way of resolving the dilemma of treatment choice.	Lack of clarity or understanding of randomisation	P19 -Irrespective of whether they agreed or refused randomisation, the majority could recall the major principles of the study design. Chance The men used a number of lay terms to convey their understanding, including likening the study design to 'a lottery', 'premium bonds', 'balls in a bag', 'tossing a coin', 'straws', 'rolling a die' and 'out of a hat': *I could have got anything. I mean it's a lottery really isn't it.* *They put it in a computer and all the computer is doing is like a one arm bandit.* Comparison The majority were clear that randomisation permitted comparison between treatments, with a minority indicating that they also understood bias: *To me they'll want so many to have the operation, so many to have the radiotherapy and so many to have the (monitoring) so that through the years they can find out what the best treatment has been.* *If people everyone in the survey simply chooses what treatment I can only assume that that doesn't give a fair objective sampling of the efficacy of A, B and C, something like that you know, the self selection maybe a certain type of person would choose that and that would somehow skew the objective findings of which happens or which turns out objectively to be the best for most people of this particular cancer.* *P22* - Recruiters and patients also had difficulty with randomisation and clinical equipoise. Many men had misgivings about randomisation and had

			difficulty understanding why the best treatment was not known (see above). Each of the documents contained guidance on these aspects, and they are an integral part of the training programme. P22/23 - In terms of randomisation, it was necessary to convince recruiters that randomisation could offer a reasonable way of resolving the dilemma of treatment choice, so that they could then pass on this belief and confidence to patients. They were encouraged to attempt randomisation before the end of the information appointment, as men who left without a random allocation tended to believe that they had to reach their own choice. Finally, it was made clear that patients should not necessarily have to accept or reject the allocation at the end of the appointment as some needed time to consider whether the allocated treatment was acceptable. It was also re-emphasised that patients must know that there was no compulsion whatever to accept the allocation and that they could opt for a different treatment at any time.
Patients often expressed lay views that cancer should be removed or came with media information that was biased in favour of radical treatments.	No specific changes planned to address this barrier	Strong patient treatment preferences	P22- Patients often expressed lay views that cancer needed to be surgically removed or knowledge of friends or relatives who had died of advanced disease or suffered treatment complications. Some brought information from newspapers or websites, which was often biased in favour of radical treatment.
The non-radical treatment option caused difficulties for both patients and recruiters. Although this option included regular review, recruiters often used the term 'watchful waiting' with the potential	issues identified by the qualitative research led to changes in the study information, randomisation, terminology used and presentation of the non-radical arm. The non-radical arm was renamed 'active monitoring' with additional emphasis placed on the regular scrutiny of PSA tests and the	Issues related to the control group	P21/22 - Specification and presentation of the non-radical arm It rapidly became clear that the non-radical treatment option caused difficulties for patients and recruiters. Initially, the arm was termed 'conservative monitoring' to emphasise the lack of radical intervention and regular review process. As the excerpt above shows, however, recruiters tended to portray monitoring as 'do-nothing' and often called it 'watchful waiting'. Patients made it clear that they interpreted this as 'no treatment' and 'watchful waiting' had the shocking implication that clinicians would just 'watch while I die': *Patient 1: Two [treatments] seem to be a way of getting rid of it and one seems to be 'we'll let you know when you're getting any worse' … I would*

for interpretation as 'no treatment'	availability of radical intervention if required or requested. As a result of these changes, recruiting staff were able to express confidence in this treatment option.		*imagine once you've got it, it just gets worse and worse and if you leave it too late, you-you've gone, you know, you've possibly had it."* In June 2000, the non-radical arm was re-named 'monitoring' and re-defined to involve regular PSA tests (3- or 6-monthly), with the potential for intervention if required or requested. Recruiters were asked to emphasise the generally slowgrowing nature of most prostate cancers and present monitoring first in the list of treatments (see above). To balance the detail about treatment complications potentially arising from the radical treatments, men were more clearly informed that the risk with monitoring was that future radical treatment might not be possible because the tumour itself had progressed or the patient was no longer young or fit enough for it. There was an immediate impact across the centres as patients accepted the monitoring allocation or expressed a preference for it. Continued scrutiny of information appointments showed that in two centres there was still a tendency to describe it weakly and to create distinctions between it and the radical 'active' treatments, such that patients could not accept monitoring (two separate excerpts below): *Clinic staff 2: Watching it and treating it – it's not treatment immediately, it's, it's a different form of management: you're managing the disease rather than treating immediately, you're monitoring it and treating it if [it] shows signs of progression … if you monitor it, it may not cause problems for some time … if it does start to progress and cause problems you deal with them usually with hormone treatment.* *Patient: Well I suppose it's better for me to say now you know that I feel that I would rather have something done about it at this stage.* *Clinic staff 3: Monitoring – obviously older people they often choose that because they feel, you know, if they may not be around in ten years time and it may be a good bet to take* *Patient: Hmm* *Clinic staff 3: Some people your age still choose that treatment because it sort of balances things – you want a good quality life at the moment well we'll deal with the problem if and when it comes up.* Documents 2 and 3 re-stated what monitoring should involve, with the addition that test results should be presented graphically and the inclusion

			of anonymised examples of 'good' and 'not so good' information presentation. In the training programme, the non-radical arm was re-named 'active monitoring', with a strong emphasis on the close scrutiny of regular test results to ensure that radical treatments should remain an option for those who would want them if (but only if) their prostate cancer began to show evidence of progression. Recruiting staff expressed much greater confidence in this: *Clinic staff 4: The first one would be to be monitored very closely and not to receive any active intervention and that would be by watching you every 3 months certainly for the first year, we will bring you back, we'll do the blood test we check the prostate and if the disease remains stable then there is obviously you know everybody's happy. If the blood test starts to change it is extremely sensitive and it would give us an indication that there may be more activity there, so then all the options are discussed again. So that's option number one.*
Early recordings of information appointments and patient interviews showed that the treatments were not presented or interpreted equally. Surgery and radiotherapy were described in detail as aggressive, curative treatments while monitoring was portrayed briefly as a more passive process of watching and waiting.	Recruiters were asked to change the order in which the treatments were presented (active monitoring, surgery, and radiotherapy) and to describe their respective advantages and disadvantages in equivalent detail. Issues of randomization and clinical equipoise were clarified for both patients and recruiters.	clinical equipoise	P19/20 - Clinical equipoise is generally taken to be the position that clinicians do not have evidence to decide which of two or more treatments will be the most effective and so are unsure which to recommend. Most men indicated that they understood this concept by stating that the study was being conducted because clinicians do not currently know the best treatment for localised prostate cancer: *They [study clinical staff] emphasised frequently that they don't really know which is the best (treatment) option, what's the best for me or another patient.* *They're doing the study because they don't know which is the best way to go, which is the most satisfactory. So in order to check that out they would like to have as many people um randomly going in and saying well I don't mind which one I have.* It can be seen from the above that almost all the men interviewed were able to recall and understand the main principles of the randomised design. This did not automatically mean, however, that they found these principles acceptable. Many of the men had strong feelings that clinicians should have been able to decide on the best treatment based on clinical factors:

			I understood enough about it (random allocation) yea yeah. Not saying that I agree with it. Well, I agree with them having to, trying to get an equal number of people on each one but um I still feel that somewhere along the line (doctors) must have a little bit more preference for one (treatment) or the other. In making their decision about whether or not to consent to randomisation, the men had to weigh up their understanding of the purposes of the study design with their own beliefs about how sensible it seemed: *Well I think (random treatment allocation) is quite dodgy. You'd have thought that when you come down to a particular individual their particular circumstance like their age, like the extent of the cancer, like the degree of dispersion of the cancer like the level of the PSA, I mean all those individual factors you'd have thought would have some impact on the decision over the treatment. How would you feel if you were told you've got I don't know breast cancer or something and we've got three random treatments wouldn't you try and identify want to identify with the doctor the best treatment for you as an individual? See what I mean? So that is a bit bit odd that but of course it's the state. He said if I couldn't make me mind up that they would put the three things or something into a computer and let that do it for us. Well I wasn't happy with that part of it like (N2). Well I, I didn't think it was right to decide what operation you were going to have you know. He has a mind of his own you know. Well the treatment basically what he said it was either the knife or the radiotherapy or this wait and see business which would be, if I would agree, by computer random choice and I said well yes because I've got int back of my mind that whoever's programmed that computer has got to have some kind of medical knowledge because obviously someone whose got a very large cancer, which could cause death straight away or within a few month, I can't imagine his name being down on a wait and see basis. What I'm trying to say, there's got to be a level somewhere where they can say yes we'll wait, no we can't wait, I'm hopin', I'm puttin' me faith in it.* Some found comfort in the idea that they would have time and opportunity to think about the allocation and decide freely whether or not to accept it:

			I did agree to (randomisation of treatment), on the understanding of course that I didn't have to accept the randomised choice … I was happy (with random treatment allocation) because I knew that I had an alternative to make my own decision if it wasn't what I wanted. One man very succinctly indicated that randomisation provided a way to make a treatment decision in the face of uncertainty: *Didn't know which other way to go. I found it an immensely difficult decision to make.* The men struggled with competing views but eventually had to decide whether or not to participate in the trial. The difficulties inherent in participating in a randomised trial were encapsulated by S5: *I understood that (treatments were equally effective), but I just find it difficult to deal with a random approach to anything. To feel that this very important decision, which is genuinely a decision about the possibility of life or death at some point in the future, being down to chance, I find that difficult to accept.* P22- In terms of equipoise, we found it necessary to emphasise that the recruiter must be genuinely uncertain about the best treatment and thus to believe the patient to be suitable for all three treatments. Even more important, they needed to be confident in this belief. We further emphasised that the aim of the information appointment was to describe the treatments in terms of probably having equivalent mortality outcomes but different complications and side-effects [……] It was necessary to help recruiters feel comfortable about challenging views and information that was biased. *I ought to be able to do better than that. I ought to work it out, the one that is most appropriate for me. I think well one of three is going to be better than the other two for me.*
Patients interpreted trial and clinical terminology	Issues identified by the qualitative research led to changes in the study information, randomisation,	Communicating study information and associated terminology	P20/21- …..the findings from the qualitative research were introduced into the conduct of the trial through the circulation of documents and training. The findings from the qualitative research had an impact on the conduct of the feasibility study in four major ways:

quite differently than intended by practitioners and this was evident in the early stages of ProtecT when, for example, 'trial' was sometimes interpreted as 'try and see'.	terminology used and presentation of the non-radical arm. Recruiters were asked to change the order in which the treatments were presented (active monitoring, surgery, and radiotherapy) and to describe their respective advantages and disadvantages in equivalent detail. Recruiters were asked to replace 'trial' with 'study'.		• organisation of study information • terminology used in study information • specification and presentation of the nonradical arm • presentation of randomisation and clinical equipoise. Organisation of study information The original study patient information was based on the results of the team's systematic review of the literature1 and was written with the intention that treatments should be presented in a standard way with surgery first, radiotherapy second, and monitoring third. Recordings of the information appointments and subsequent patient interviews in the early part of the study showed clearly that the treatments were not presented or interpreted equally. The following extract from one information appointment indicates how surgery and radiotherapy were portrayed in detail as aggressive, curative treatments, and monitoring briefly and weakly as 'wait and see': *Clinic staff 1: We believe that you are suitable for any of these three treatment possibilities … The first treatment is that of radical prostatectomy. Probably the simplest answer is to remove the prostate gland completely – that that gives you the opportunity of removing the whole of the cancer in its entirety. The problem is that radical prostatectomy is a major operation and there are risks … [26 lines of detail follow]* *… The second method is radiotherapy – you are trying to destroy the cancer cells by means of X-rays without removing the gland. In other words the X-ray beam destroys the cancer cells and the prostate gland remains in situ… [29 lines of detail follow]* *… The final treatment is what we call watchful waiting. The basis of this is that we don't know whether your tumour is going to progress or not, and we can simply just watch it carefully … [10 lines of detail follow]* *… We can do [randomisation] for the three treatments, that is surgery, radiotherapy or watchful waiting, or if you didn't want to consider watchful waiting, just to compare two treatments which actually try to cure the disease, either surgery or radiotherapy*

			By July 2000, fewer patients accepted an allocation of, or expressed a preference for, monitoring compared with radical treatments. Recruiters were asked to present the treatments in the following order: 1) monitoring, 2) surgery and 3) radiotherapy and to describe in similar detail each of the different modes of management and side-effect profiles. Terminology used in study information We were aware that certain terms may be interpreted by patients differently from intended.23,24 The word 'trial' was often confused with the monitoring treatment option and some recruiters assumed patients had refused randomisation when they had only rejected the monitoring arm. Included in the early patient information was a phrase intended to reflect evidence of good 10- year survival: 'the majority of men with prostate cancer will be alive 10 years later.' Patients interpreted this phrase as an (unexpected) suggestion that some might be dead in 10 years – an idea that shocked some in their 50s and 60s. Changes to terminology were introduced in document 1 and reinforced in the training programme. Recruiters replaced 'trial' with 'study' and presented positive information about survival in terms of 'most men with prostate cancer live long lives even with the disease.'

Omitted Stein *et al* 2016: extracted data (from OPTIMA HTA feasibility report) mapped to themes reported in El Feky *et al*

Barrier or facilitator	Theme label for 'Findings associated with code'	Data from Stein *et al* 2016: data relevant for recruitment and/or retention (monograph Chapter 4)
Recruitment – barrier	Lack of clarity or understanding of randomisation	-
	Lack of clinical equipoise	The issue of uncertainty was an important theme to arise from audio-recorded consultations, particularly in relation to the discussions about chemotherapy benefits and the accuracy of the test. There were differences in how recruiters framed chemotherapy provision at the start of the consultation, which in turn had implications for patient understanding. Recruiters' explanations ranged from presenting chemotherapy as a treatment with definite benefits, to framing it as an uncertainty that required careful balancing of benefits and side effects/complications. There were occasional examples in which patients still believed that they would definitely benefit from and/or receive chemotherapy even after the trial had been explained. Uncertainty surrounding use of the Oncotype DX test in treatment decision-making was another difficult concept to communicate according to recruiters' interview accounts (i.e. oncologists and research nurses). Overselling the benefits of the test could prompt patients to pay for the test privately, whereas an overly cautious approach ran the risk of obscuring any incentives for participating in OPTIMA prelim. These considerations raised the dilemma of how best to reassure patients while conveying the inherent risk of participating in a study in which treatment allocation may be determined by a test that requires further research: The trouble is if in our initial interview we sort of really down play the test as not being useful, then nobody *would want to go in the trial in the first place. And if we play it too much they think 'well it's such a great test, I don't want to risk not having it in the trial' and go and find out the information. So again, it's that fine balance (p63)*
	Strong patient treatment preferences	Screening logs and interview informants' accounts suggested that patients' preference either for or against chemotherapy was the most common reason for declining the trial (50% of reasons for decline in final screening logs: 33% for and 17% against): We have a very good functioning wider unit [. . .]. There's nothing that's blocking us from doing it other than patient preference. Onc3 There were few (if any) examples in consultations where patients expressed strong preferences, but there were some examples where patients appeared to be influenced by other clinicians that they had seen prior to the oncologist (e.g. surgeons). There were also examples of patients showing misunderstandings about trial participation while explaining their decision to refuse the trial; however, the recruiters did not always address these misconceptions, instead accepting the patients' decisions without further discussion. A common thread that ran throughout recruiters' interviews was that breast cancer patients in particular were thought likely to have set preferences given the influence of the media, peers and the well-publicised nature of the disease. As such, some recruiters completely disassociated themselves from patients' decisions about trial participation and many indicated that they would accept patients' preferences with no further exploration. Recruiters' discomfort in exploring patients' decisions and/or preferences stemmed from concern that raising these

		issues would jeopardise their relationships with patients or leave them susceptible to accusations of coercion (p64)
	Issues related to the control group	-
	Communicating study information and associated terminology	Communication and information provision were largely explored through audio-recorded consultations, although data from staff interviews sometimes provided a useful backdrop for exploring particular challenges. Recruitment consultations varied in length and structure across and between centres, with some formats more conducive to explaining the study than others. Difficulties emerged in relation to how trial-specific processes were explained to patients, and staff attitudes also played a role in influencing the direction consultations took – particularly when it came to exploring patients' views and perspectives on OPTIMA prelim participation (p63) A fundamental challenge to recruitment identified by interview informants was the perceived difficulty in explaining the OPTIMA prelim trial design. Having an arm that split into two further arms, combining random and test-directed treatment allocations, and the partially blinded design were all thought of as potentially confusing to patients. Some interview informants had directly experienced patients dismissing the trial on this basis: This particular lady just didn't go into any detail at all she said, I just didn't know what it was talking about, and I said, and I tried to explain bits of it to her, but no, she said, I just, I don't, I just want to, I don't understand it, she just said locked her mind off completely to it. RN4 In the light of the above, analysis of audio-recorded consultations focused on recruiters' explanations of trial processes and scrutinised information exchange that led up to evidence of patient misconceptions or confusion. Particular practices were identified as being potentially detrimental to patient understanding. These included absent or incomplete explanations of 'randomisation', 'blinding' and unclear descriptions of the treatment(s) provided in each trial arm. Explanations of the trial arms also revealed examples of loaded terminology, including use of the words 'standard' and 'experimental' (see Appendix 8) (p63) The TMG meetings revealed that a particular point of concern was a line in the PIS that highlighted the uncertainty surrounding the test's accuracy. Based on TMG members' experiences (not audio-recorded), patients had reportedly refused the trial once they had read the following statement: The test might not work so well for patients with larger tumours or involved lymph glands. We do not believe this to be the case. However if it was, then in the future we might realise that we should have given you chemotherapy. It was noted that this issue reportedly materialised after (rather than within) the first oncology consultation (i.e. once the patients had read the information sheets). This prompted us to consider how the Oncotype DX test was described in consultations, with a focus on how uncertainty was communicated and responded to (see Appendix 8 for details). Overall, recruiters varied in how they conveyed uncertainty, which in turn had implications for patients' understandings of the trial aims and design (p64) Recruiters varied in the extent to which they presented OPTIMA prelim as the primary focus of the discussion. This was influenced by the extent to which they covered diagnostic information and non-

		OPTIMA prelim-related treatments within the first oncology consultation. Some consultations were particularly long (up to 52 minutes), covering non-trial-related information in some detail prior to introducing the OPTIMA prelim study. In some ways, it could be considered that many appointments were not 'recruitment consultations' at all. Although there was the opportunity to present the OPTIMA prelim study, this opportunity was not always fully utilised in some consultations. In other cases, the study was presented as a 'next step' in a series of 'information blocks', rather than the heart of the consultation. Some recruiters successfully tailored information provision around explanations of the trial, whereas other struggled to do this, resulting in the aims and key details of the trial becoming somewhat lost (p64)
	Issues around the eligibility criteria	Recruiters' unease surrounding various aspects of the eligibility criteria was widespread, reported by staff members from every centre participating in interviews. OPTIMA prelim staff varied in their readiness to accept increasing risk (in terms of disease status). Increasing lymph node involvement, tumour size and grade caused discomfort surrounding the upper thresholds of the eligibility criteria stated in the protocol. (p62) Some clinical informants gave general or specific examples of refraining from offering the trial to patients on the basis of their clinical judgement. Failure to approach patients at a clinician's discretion would not breach the study protocol; the eligibility criteria clearly stated: Patient must be fit to receive chemotherapy and other trial-specified treatments with no concomitant medical, psychiatric or social problems that might interfere with informed consent, treatment compliance or follow up. However, an issue that arises is whether or not the decision not to inform patients about the opportunity to take part in the OPTIMA prelim study was always appropriate or well founded. Such judgements, if applied differently across different centres, could have had implications for the numbers of patients being approached for the OPTIMA prelim (p62)
	Practical barriers	-
	Commitment of staff and participants to the trial	-
	Beliefs and expectations about trial participation	Patients' concern about the delay attributed to waiting for the Oncotype DX test result was a dominant theme to emerge from audio-recorded consultations. Almost every consultation analysed supported this, with most patients asking about how long the testing process would take. Although some recruiters reassured patients that the delays associated with OPTIMA prelim had no implications for treatment safety, this was not consistently done across consultations. This, therefore, also represented a missed opportunity to address patients' concerns and provide reassurance (p64)
	Mismatch between the trial protocol and clinical care pathways	-
	Participation burden	-
	Lack of confidence in approaching study participants	Although research nurses were well versed in the inclusion and exclusion criteria, some felt that they did not always have the necessary expertise or voice to flag a patient as an OPTIMA prelim candidate at a MDT

		meeting. This suggested that potentially eligible patients were at risk of falling through the net at the stage of initial eligibility screening.(p62)
Recruitment – facilitator	Personal gain and making a difference	-
	Communicating study information	-
	Social networks and experience of research	-
Retention - barrier	Burden of follow-up questionnaires	-
	Practical barriers	-