



NCIC Clinical Trials Group  
NCIC Groupe des essais cliniques

# RADICALS

## Radiotherapy and Androgen Deprivation In Combination After Local Surgery A randomised controlled trial in prostate cancer

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MRC PR10  
NCIC CTG PR.13

### Protocol

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## GENERAL INFORMATION

This document describes the RADICALS trial and provides information about procedures for entering patients into it. This is an Intergroup trial which is led by the NCRI Prostate Clinical Studies Group and coordinated by the MRC Clinical Trials Unit. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact their participating group to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator.

- **Compliance**

The trial will be conducted in compliance with the protocol, principles of GCP, UK Data Protection Act (DPA number: Z5886415), NHS research governance and other regulatory requirements or their national equivalents.

- **Sponsor(s)**

MRC: Medical Research Council, 2<sup>nd</sup> Floor David Phillips Building, Polaris House, North Star Avenue, Swindon SN2 1FL.

NCIC CTG: NCIC Clinical Trials Group

- **Trial Management Group members**

Listed in Appendix A VII

- **Participating Groups**

MRC Clinical Trials Unit including Danish and Irish sites  
NCIC Clinical Trials Group (NCIC CTG)

## Information for MRC Investigators

- **Funder in UK**

Cancer Research UK and Medical Research Council

- **Scientific Approval**

The RADICALS trial has been scientifically approved by the Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research UK and is thus part of the NCRN/NCRI portfolio of prostate cancer trials.

- **Ethics Approval**

Royal Free Hospital Research Ethics Committee. Ref: 07/Q0501/48

- **Regulatory Approval**

CTA reference 00316/0223/001-0001, 17<sup>th</sup> April 2007

- **Finance**

No payments will be made to centres because approaches are standard, and no free or discounted drugs are provided. This trial is NRCN adopted and therefore UK NCRN nurse time will be available to support the study.

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- **Funder**

Canadian Cancer Society – Research Institute

- **Scientific Approval**

NCIC CTG

- **Finance**

The rate of per case funding is the standard per case funding amount for each patient enrolled at each centre. For more information please see:

[http://www.ctg.queensu.ca/trials/generic\\_forms\\_public/centre\\_funding.pdf](http://www.ctg.queensu.ca/trials/generic_forms_public/centre_funding.pdf)

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## APPENDIX A – COMMON APPENDIX

A I: Potential Pathways through RADICALS
A II: Surgical Quality Assurance
A III: Toxicity table
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A V: Patient Selection - Radiotherapy Timing Randomisation
A VI: Quality of life
A VII: Trial Committee Members

## APPENDIX B – GROUP-SPECIFIC APPENDIX

See Group-Specific Appendix B for page numbers and Appendices covering:

- Procedures for Site Accreditation
- Commitment Form
- Radiotherapy Quality Assurance
- GP Letters
- Ethics and Regulatory
- Insurance
- Finance
- Patient Information Sheet
- Consent Form

**ACRONYMS AND GLOSSARY**

<b>AD</b>	Androgen Deprivation
<b>AE</b>	Adverse event
<b>AP</b>	Anterior/Posterior
<b>AR</b>	Adverse reaction
<b>ARO</b>	Academic Radiation Oncology
<b>BAUS</b>	British Association of Urological Surgeons
<b>CF</b>	Consent form
<b>CI</b>	Chief Investigator
<b>CI</b>	Confidence Interval
<b>CRF</b>	Case Report Form
<b>CT</b>	Computerised Tomography
<b>CTA</b>	Clinical Trials Authorisation
<b>CTAAC</b>	Clinical Trials Awards and Advisory Committee
<b>CTCAE</b>	Common Terminology Criteria for Adverse Events
<b>CTG</b>	Clinical Trials Group
<b>CTU</b>	Clinical Trials Unit
<b>CTV</b>	Clinical Target Volume
<b>DCF</b>	Data Clarification Form
<b>DMC</b>	Data Monitoring Committee
<b>DSS</b>	Disease Specific Survival
<b>EORTC</b>	European Organisation for Research and Treatment of Cancer
<b>EPC</b>	Early Prostate Cancer
<b>ERC</b>	Endpoint Review Committee
<b>EU</b>	European Union
<b>EudraCT</b>	European Union Drug Regulatory Agency Clinical Trial
<b>FBC</b>	Full Blood Count
<b>FFTF</b>	Freedom Free Treatment Failure
<b>GCP</b>	Good Clinical Practice
<b>GnRHa</b>	Gonadotrophin releasing hormone analogue
<b>GRO</b>	General Registrar's Office
<b>GS</b>	Gleason Score
<b>HE</b>	Health Economics
<b>HR</b>	Hazard Ratio
<b>HT</b>	Hormone Therapy
<b>IB</b>	Investigator's Brochure
<b>ICH</b>	International Conference of Harmonisation
<b>IDMC</b>	Independent Data Monitoring Committee
<b>IMP</b>	Investigational Medicinal Products
<b>IRB</b>	Institutional Review Board
<b>ISRCTN</b>	International standard randomised controlled trial number
<b>JCOG</b>	Japanese Clinical Oncology Group
<b>LHRH</b>	Luteinising Hormone-Releasing Hormone
<b>LR</b>	Left/Right
<b>LREC</b>	Local Research Ethics Committee
<b>LTHT</b>	Long Term Hormone Therapy
<b>MHRA</b>	Medicines and Healthcare Regulatory Authority
<b>MLC</b>	Multi-leaf Collimation
<b>MRC</b>	Medical Research Council
<b>MRI</b>	Magnetic Resonance Imaging
<b>NCIC CTG</b>	NCIC Clinical Trials Group
<b>NCRI</b>	National Cancer Research Institute
<b>NCRN</b>	National Cancer Research Network
<b>NHS</b>	National Health Service

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<b>NHSCR</b>	National Health Service Central Register
<b>ONS</b>	Office for National Statistics
<b>PI</b>	Principal Investigator
<b>PIS</b>	Patient information Sheet
<b>PSA</b>	Prostate Specific Antigen
<b>PTV</b>	Planning Target Volume
<b>QA</b>	Quality Assurance
<b>QL</b>	Quality of life
<b>RADICALS</b>	Radiotherapy and Androgen Deprivation In Combination After Local Surgery
<b>RADICALS-RT</b>	RADICALS Radiotherapy Timing Randomisation
<b>RADICALS-HD</b>	RADICALS Hormone Duration Randomisation
<b>RP</b>	Radical Prostatectomy
<b>RT</b>	Radiotherapy
<b>RTOG</b>	Radiation Therapy Oncology Group
<b>SAE</b>	Serious adverse event
<b>SAR</b>	Serious adverse reaction
<b>SF12</b>	Short Form 12
<b>SI</b>	Superior/Inferior
<b>SmPC</b>	Summary of Product Characteristics
<b>SOP</b>	Standard operating procedures
<b>SPC</b>	Summary of product characteristics
<b>SSA</b>	Site specific assessment
<b>STHT</b>	Short Term Hormone Therapy
<b>SUSAR</b>	Suspected unexpected serious adverse reaction
<b>SV</b>	Seminal Vesicle
<b>SWOG</b>	South West Oncology Group
<b>tds</b>	Three times daily
<b>TMG</b>	Trial Management Group
<b>TSC</b>	Trial Steering Committee
<b>TROG</b>	Trans-Tasman Radiation Oncology Group
<b>UAR</b>	Unexpected adverse reaction

# 1. SUMMARY

## 1.1 Abstract and summary of trial design

### 1.1.1 Type of design

RADICALS is an international, multi-centre, open-labelled, randomised controlled trial in prostate cancer. It is a trial with two separate randomisations for overlapping patient groups.

One randomisation is performed within 22 weeks after radical prostatectomy (**RADICALS-RT** or the **Radiotherapy Timing Randomisation**; see section 4 for eligibility criteria). In this, patients are randomised between early post-operative radiotherapy and deferred post-operative radiotherapy (for PSA failure).

The other randomisation is performed shortly before the administration of post-operative radiotherapy and concerns the addition of hormone therapy (**RADICALS-HD** or the **Hormone Duration Randomisation**). In this, patients are randomised between radiotherapy with no hormone therapy, radiotherapy with short-term hormone therapy or radiotherapy with long-term hormone therapy. Randomisation between all three arms is encouraged but patients can be randomised (i) just between short-term and long-term hormone therapy or (ii) just between short-term hormone therapy and no hormone therapy.

Patients joining the RADICALS-RT are encouraged to join the RADICALS-HD (if and when they have RT) but are not required to do so. Patients would need to consent separately to each randomisation. Patients who have not taken part in RADICALS-RT may still enter RADICALS-HD alone if post-operative radiotherapy is clinically indicated, either early post-surgery or in the deferred setting for PSA failure.

### 1.1.2 Disease/patients studied

Patients with non-metastatic adenocarcinoma of the prostate who have had a radical prostatectomy will be eligible for RADICALS. Patients at increased risk of post-operative recurrence (see section 4) will be eligible for RADICALS-RT. Patients who are due to receive post-operative RT will be eligible for the Hormone Duration Randomisation.

### 1.1.3 Trial interventions – research and control

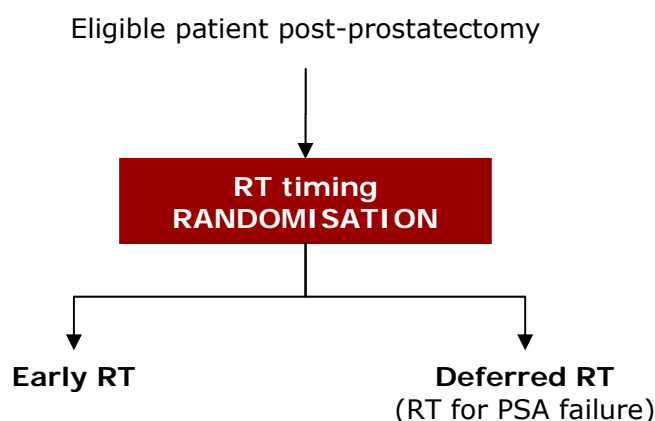
There are two interventions in the trial – radiotherapy and hormone therapy.

### 1.1.3.1 RADICALS-RT: Radiotherapy Timing Randomisation – see Figure 1

- Early post-operative RT to prostate bed
- Deferred RT: RT to prostate bed given in the event of PSA failure.

The radiotherapy to be used is defined in the protocol by the RADICALS Radiotherapy Subgroup. It will use standard techniques and the dose-fractionation schedules will be 66 Gy in 33 fractions over 6.5 weeks or 52.5Gy in 20 fractions over 4 weeks. For more details refer to Section 6.1.

**Figure 1: RADICALS-RT**



### 1.1.3.2 RADICALS-HD: Hormone Duration Randomisation – see Figure 2

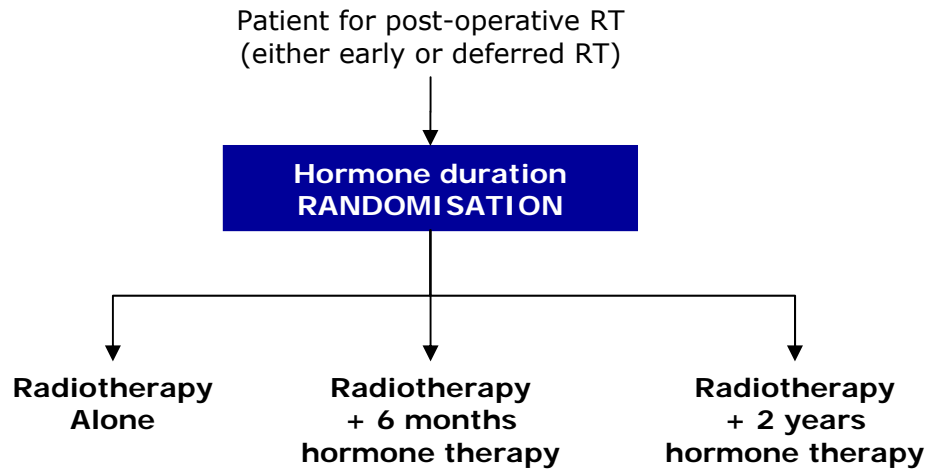
- No hormone therapy with RT
- Short-term hormone therapy (6 months) commencing shortly before RT
- Long-term hormone therapy (24 months) commencing shortly before RT

Hormone therapy may be either LHRH agonist or bicalutamide 150mg daily. For more details refer to Section 6.2. For Canadian patients, hormonal therapy will consist of LHRH analogue therapy (in addition to antiandrogen for tumour flare, if desired) as bicalutamide monotherapy is not approved for use in Canada.

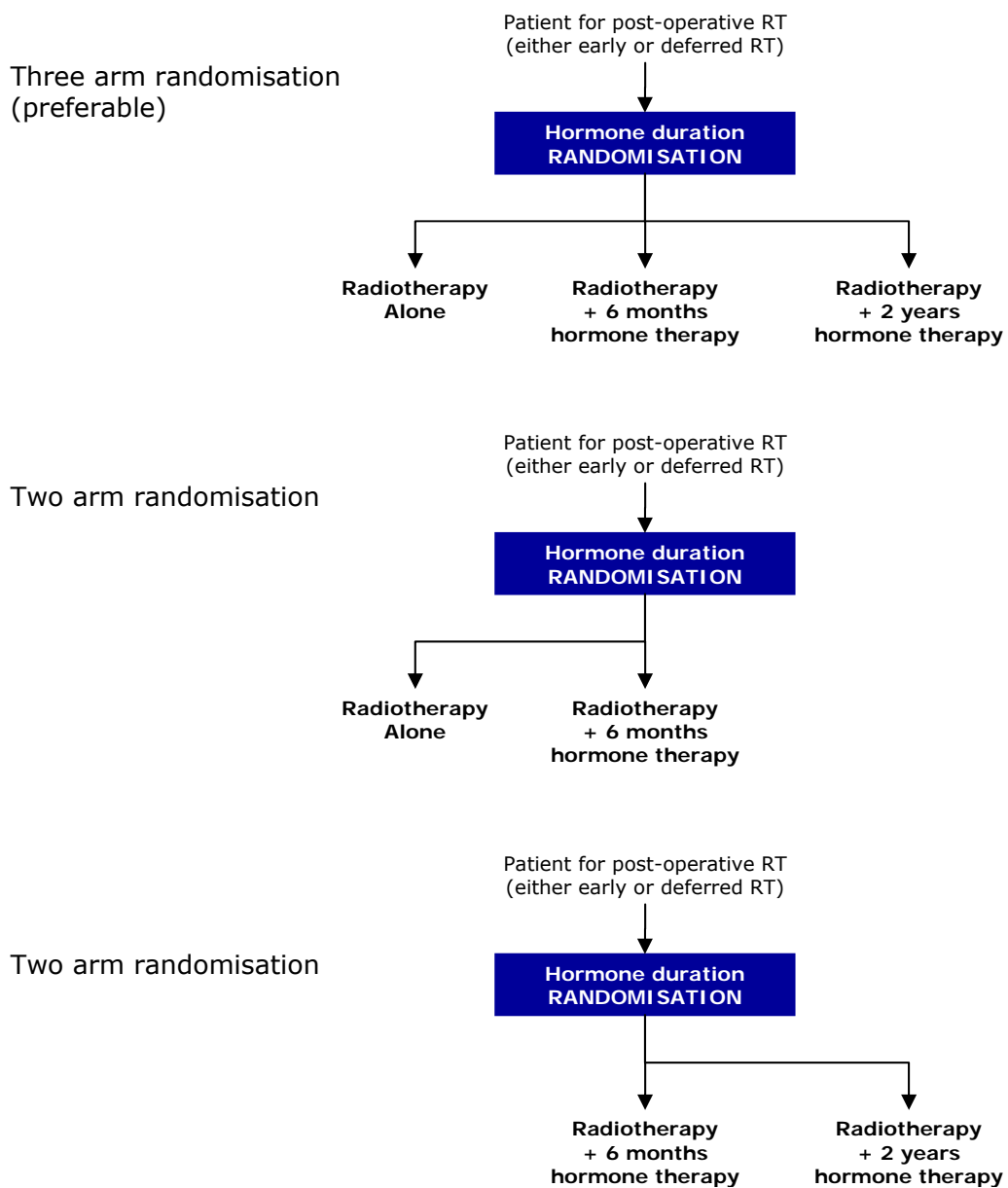
It is preferable to randomise patients between all three arms in RADICALS-HD but it is permissible to randomise patients between two of the three arms – see Figure 3. Patients can be randomised between:

- RT + no hormone therapy vs RT + 6m hormone therapy vs RT + 24m hormone therapy
- RT + no hormone therapy vs RT + 6m hormone therapy
- RT + 6m hormone therapy vs RT + 24m hormone therapy

**Figure 2: Hormone Duration Randomisation**



**Figure 3: Two- and three-arm Hormone Duration Randomisations**



#### 1.1.4 Outcome measures

##### 1.1.4.1 RADICALS-RT

**Primary:** Freedom from distant metastases (any distant metastases or prostate cancer death)

**Secondary:** Disease-specific survival (i.e. death due to prostate cancer)

Freedom from treatment failure  
Clinical progression-free survival  
Overall survival  
Non-protocol hormone therapy  
Treatment toxicity  
Patient reported outcomes

##### 1.1.4.2 RADICALS-HD

**Primary:** Disease-specific survival (i.e. death due to prostate cancer)

**Secondary:** Freedom from distant metastases (any distant metastases or prostate cancer death)

Freedom from treatment failure  
Clinical progression-free survival  
Overall survival  
Non-protocol hormone therapy  
Treatment toxicity  
Patient reported outcomes

It is estimated that approximately 1150 patients will need to be recruited into RADICALS-RT and approximately 2000 patients into the RADICALS-HD. Many patients can be in both randomisations. Patients are permitted to be randomised between two of the three arms in RADICALS-HD. For more details refer to Section 9.

#### 1.1.5 Trial Duration

The trial is planned to address these questions over 12-13 years with 5½ to 6½ years of accrual and 6 to 7 years of further Follow-up. The patient group is men with non-metastatic adenocarcinoma of the prostate who have had a radical prostatectomy. Treatment duration within the trial will range from zero months (i.e. a proportion of patients, maybe 60%, allocated to deferred radiotherapy will never need it) to 24 months (for patients allocated long-term hormone therapy). Follow-up is required every 4 months for 2 years, every 6 months from 2 to 5 years and then annually. This broad patient group has a good long-term prognosis and full, long-term Follow-up data are essential to understand the impact of these treatments. For more details refer to Section 7.1.

### **1.1.6 Data recorded directly on CRFs**

Data will be recorded on case report forms (CRF). The original should be sent to the appropriate participating group and a copy kept at the local centre. The type of data to be recorded is detailed in Section 7, the Assessments and Procedures section.

### **1.1.7 Ancillary studies/substudies**

Patient reported outcomes will be collected to assess sexual function, urinary function, bowel function and general quality of life throughout the course of the trial. For more details refer to Section 13.1.

Health economics will be assessed by patient reported questionnaire. For more details refer to Section 13.2.

It is planned to collect baseline blood samples and prostatectomy specimens for future translational studies in order to identify and validate novel biomarkers of disease recurrence. For more details refer to Section 13.3. The protocol will be amended appropriately to reflect any changes regarding translational studies.

## **2. BACKGROUND**

### **2.1 Introduction**

Prostate cancer is the commonest cancer in UK men, with an incidence in 2008 of 37,000 cases (1). Radical prostatectomy is a standard of care for men presenting with localised disease. Conventional practice following surgery has been observation, with additional treatment, such as radiotherapy (RT) or hormone therapy (HT), used in the salvage setting for those who develop recurrent disease. The routine use of post-operative adjuvant therapy has shown benefits for other cancer types, such as breast and colorectal cancer, and is sometimes used in prostate cancer, but has not been well studied. Large randomised trials are needed to evaluate the role of adjuvant therapy following radical prostatectomy.

### **2.2 Rationale and objectives**

Radical prostatectomy is a common operation. Hospital Episodes Statistics report 4,904 such operations were performed in England in 2010 (2). This is a significant under-estimate because it excludes operations performed outside the NHS. If rates of PSA testing in the UK continue to increase (3), then both the incidence of diagnosed prostate cancer, and the proportion of patients presenting with localised disease, will also rise. Thus, the number of radical prostatectomies performed each year in the UK is set to increase. According to the Institute for Clinical Evaluative Sciences, the number of radical prostatectomies per year in Canada is estimated to be between 5000 and 7000 (4).

Although the number of radical prostatectomies being performed is increasing there is considerable uncertainty over the optimal management strategy for patients that have had a prostatectomy. The two main management questions relate to the timing of radiotherapy and the use of hormone therapy in conjunction with post-operative radiotherapy (5-7). RADICALS will address both of these questions.

### **2.3 The case for a trial of immediate versus early salvage treatment after radical prostatectomy**

There are three randomised controlled trials of adjuvant radiotherapy to the prostate bed published to date. EORTC 22911 recruited 1005 patients with pT3 disease post-radical prostatectomy, who were randomised between observation

and adjuvant RT (8-9). A statistically significant advantage was seen for adjuvant radiotherapy in terms of biochemical progression-free survival (hazard ratio (HR) 0.49, 95.3% CI 0.41 – 0.59;  $p < 0.0001$ ) with 61% and 41% event-free at 10 years. An advantage was also reported for adjuvant radiotherapy in terms of clinical progression-free survival (HR 0.81, 95% CI 0.65 – 1.01;  $p = 0.054$ ) with 70.3% and 64.8% PFS event-free at 10 years. However, there was no evidence of a difference in overall survival ( $p > 0.1$ ) with 10-year survival rates of 76.9% with adjuvant RT and 80.7% with observation.

The second randomised controlled trial, SWOG 8794 (NCIC CTG PR-2) had a similar design: 425 men with pT3 disease were randomised to either observation or adjuvant radiotherapy to the prostate bed, with median follow-up at the time of analysis of 10.6 years (10). Once again, adjuvant radiotherapy was associated with a statistically significant improvement in biochemical control (HR 0.43 95% CI 0.31, 0.58,  $p < 0.001$ ). At 15 years, there was a statistically significant advantage for adjuvant radiotherapy for metastases-free survival (HR 0.74 95% CI 0.57, 1.00,  $p = 0.053$ ), and overall survival.

The third trial, the German Radiotherapy Group trial ARO 96-02, randomised 307 men with pT3 disease to either observation or adjuvant RT to the prostate bed (11). We note that 20% of patients never received their allocated RT. At a median follow-up of 3.3 years, analysis by treatment received, rather than by intention to treat, found that adjuvant radiotherapy was associated with improved biochemical control (81% vs 60% event-free at 4 years, HR 0.4,  $p < 0.0001$ ). These early results are consistent with those of EORTC 22911 and SWOG 8794, but ARO 96-02 was not sufficiently powered to address the effect of adjuvant treatment on clinical outcomes such as survival.

Standard practice following radical prostatectomy has evolved since the SWOG 8794 and EORTC 22911 trials were designed in the mid-1980s. In particular, the routine use of sensitive PSA assays means that contemporary patients with an undetectable post-operative PSA level have a lower risk of relapse than in the past and so less scope to benefit from adjuvant treatment. In addition, post-operative biochemical relapse can be detected earlier than clinical relapse was previously, and early detection may lead to an improvement in the efficacy of salvage RT. For both of these reasons, the benefits seen for adjuvant RT in SWOG 8794 and EORTC 22911 should not lead to the general acceptance of treatment in the adjuvant setting. Instead, the results provide a strong rationale for a comparison between adjuvant treatment and the current standard of care, which is observation with early salvage treatment for biochemical failure.

There is no consensus among UK oncologists on whether to use adjuvant or early selective salvage radiotherapy. A survey of 49 UK urological oncologists found that 25 (51%) did, and 24 (49%) did not recommend adjuvant RT for pT3 margin-positive cases (12). In a second survey of 188 UK Oncologists and Urologists there was widespread uncertainty regarding the use both of adjuvant radiotherapy and the mode, timing and duration of hormone therapy (13). This finding highlights the need for randomised studies addressing this issue. In designing the RADICALS trial, another survey was completed by 102 UK and Canadian urologists and oncologists. The responses reported clinicians offering adjuvant radiotherapy to between 0% and 30% of their post-operative patients with a median offering adjuvant radiotherapy to 3% of post-operative patients.

## **2.4 The case for a trial of hormone therapy duration in men receiving radiotherapy post-prostatectomy**

Several randomised trials have demonstrated that the addition of hormone therapy improves overall survival in men receiving primary radiotherapy for prostate cancer e.g. EORTC 22863 (14), RTOG 86-10 (15), RTOG 85-31 (16), and a trial from Boston (17). However, until recently there were no reported randomised controlled trials addressing the role of hormone therapy in men receiving post-operative radiotherapy.

Three retrospective non-randomised studies have compared the outcome of salvage RT alone versus salvage RT plus short-term (4-6 months) hormone therapy, and have observed improved biochemical control rates with the addition of hormone therapy (18-20).

In 2010, the first results from a randomised trial in this setting, RTOG 96-01, were presented at the ASTRO annual conference (21). The trial recruited 771 patients with PSA failure after radical prostatectomy and randomised them between early salvage RT alone versus early salvage RT plus 2 years of hormone therapy with bicalutamide 150mg daily, with overall survival as the main outcome measure. The overall survival data are immature, but an advantage for adjuvant bicalutamide was reported in terms of freedom from distant metastases at 7 years (93% vs 87%,  $p < 0.04$ ). The RTOG 96-01 trial (21) does not provide information on the use of short-term hormone therapy.

A further trial, RTOG 85-31 randomised patients with locally advanced prostate cancer between RT alone versus RT plus long-term hormone therapy. Just 139 of the 977 patients in this trial had previously had a radical prostatectomy, and there are no published data concerning the outcome of this subgroup (16;22).

The Early Prostate Cancer (EPC) Program accrued 4400 men who had radical prostatectomy and were randomised between observation versus 2 years adjuvant bicalutamide 150 mg. At a median follow-up of 7.4 years, there was no evidence of a difference in overall survival, but the data remain immature in this predominantly low-risk population. This very large trial serves to underline that at present there is no proven role for adjuvant hormone therapy alone after radical prostatectomy (23-24). It is important to note that this trial will not answer the questions RADICALS is posing, since the indications for post-operative radiotherapy were not specified, and because salvage treatment was delayed until clinical (rather than biochemical) progression was observed.

A small trial of adjuvant hormone therapy in men with pathologically involved pelvic lymph nodes, EST-3886, was stopped after 98 patients had been accrued because an overall survival advantage for adjuvant treatment was observed (25-26).

One question that has received little or no attention to date is that of the optimum duration of hormone therapy in patients receiving post-operative radiotherapy to the prostate bed. The surveys of UK urological and oncological opinion (12-13), mentioned above, found that the use of hormone therapy was variable, with most urologists recommending radiotherapy alone. Only 35% of urologists and 34% of oncologists were using hormone therapy in combination with radiotherapy. Among those oncologists who used hormone therapy in combination with post-operative RT, short-term hormone therapy (defined as 3 to 12 months) was recommended by 31% of respondents, long-term hormone therapy (defined as >12 months) by 25%, while the remaining 44% used both short-term and long-term hormone therapy depending on the characteristics of the patient. Similarly, in the survey conducted in planning the RADICALS trial, respondents were using none, short-term and long-term hormone therapy for a median (quartiles) of 50% (0%, 90%), 0% (0%, 50%) and 10% (0%, 33%) of their patients receiving adjuvant post-operative radiotherapy and 50% (0%, 90%), 13% (0%, 50%) and 5% (0%, 30%) of their patients receiving salvage post-operative radiotherapy i.e. there is significant variation in clinical practice.

In the context of primary (i.e. not post-operative) RT for prostate cancer, the appropriate duration of hormone therapy was addressed by RTOG 92-02 (27), which randomised 1554 men receiving RT for locally advanced disease between short-term hormone therapy (4 months) and long-term hormone therapy (28 months). Long-term hormone therapy was associated with improved 5-year cause-specific survival (95% vs 91%,  $p=0.006$ ), with no evidence to date of a significant difference in overall survival at 5 years (80% vs 79%,  $p=0.73$ ). Similarly, results were reported from TROG 96-01, the largest randomised trial to date addressing the role of neoadjuvant androgen deprivation prior to RT in predominantly high risk non-metastatic disease (28). The use of 6 months neoadjuvant androgen deprivation reduced the risk of distant progression (HR 0.49, 95% CI 0.31-0.76,  $p=0.001$ ) and death from any cause (HR 0.63, 95% CI 0.48-0.83,  $p=0.0008$ ). The use of 3 months neoadjuvant androgen deprivation did not provide good evidence of a benefit.

The current pattern of UK practice, with no consensus regarding the need for, or duration of, hormone therapy in men receiving post-operative RT, combined with the increasing popularity of radical prostatectomy, provides a strong rationale for a phase III study. RADICALS-HD will investigate the question of RT alone versus RT plus short-term hormone therapy versus RT plus long-term hormone therapy in this setting. The duration of short-term hormone therapy will be 6 months, based on TROG 96-01 (28), and long-term hormone therapy will be for 2 years, based on RTOG 92-02 (27) and RTOG 96-01 (21). Long-term results from RTOG 96-01 were presented at conferences in 2010 and showed favourable outcomes for 2 years ADT over no ADT.

## **2.5 Other ongoing relevant studies and trials**

### **2.5.1 RADICALS-RT**

There are two other trials asking complementary questions to RADICALS-RT which were active in Apr-2011. These are the TROG 08.03 RAVES and FNCLCC-GETUG-17/0702 trial, both of which randomise patients between immediate post-op RT and salvage RT for PSA failure. ADT is not given with RT in RAVES whereas 6m ADT is given with RT in GETUG-17. There are differences between these trials and RADICALS-RT, notably the earlier primary outcome measures, but the primary design is sufficiently complementary that combined analyses are planned for long-term outcome measures in due course.

### **2.5.2 RADICALS-HD**

There are also complementary trials to RADICALS-HD. The EORTC 22043-30041 trial of adjuvant treatment after radical prostatectomy randomises patients between adjuvant radiotherapy alone versus adjuvant radiotherapy plus 12 months of hormone therapy. Combined analyses are planned in the future.

In the early salvage setting, the FNCLCC-GETUG-16/0504 trial compares RT alone versus RT plus 6 months ADT, and the RTOG 05-34 SPPORT trial compares early salvage RT to the prostate bed alone against supplementing this with 4 to 6 months ADT or 4 to 6 months ADT and pelvic RT.

In addition to the trials listed above, it is also pertinent to consider RTOG P-0011, which was originally designed as a 3-arm trial in men at high risk of recurrence following radical prostatectomy, with the randomisation between adjuvant RT, long-term adjuvant hormone therapy (24 months) or RT plus long-term hormone therapy. The trial was modified to a 2-arm trial comparing adjuvant RT +/- hormone therapy to improve recruitment although the trial closed early. The current UK standard of care, namely observation with salvage treatment in the event of PSA failure, was not included in the trial. Similarly, a German study known as AP 26/99 and ARO 00/01 planned to randomise around 900 patients with isolated PSA relapse to early salvage radiotherapy with or without short-term HT (6 months) (29). The trial closed in 2003 because of poor accrual.

Completion of recruitment to RADICALS will be facilitated in the UK by favourable attitudes of UK urologists towards radiotherapy, the centralisation of radical prostate cancer surgery in Cancer Centres, the established multidisciplinary team pattern of working, and the NCRN infrastructure.

### **2.5.3 Other trials**

In addition to the above trials which have completed recruitment of patients, we note that the Japanese Clinical Oncology Group are running a trial (JCOG 0401) for patients with isolated PSA failure after prostatectomy where patients are randomised to radiotherapy with hormone therapy or hormone therapy alone (30). The target is 200 patients. This trial does not address the key question of the timing of post-operative radiotherapy.

## **2.6 Risks and benefits**

The treatments described in this protocol reflect additional treatment given after surgery. Each of the management strategies tested in RADICALS are familiar in clinical practice, therefore the potential adverse effects, risks, hazards and benefits are similar to those which would be experienced in standard practice. It is intended that RADICALS can define the most appropriate strategy for this group of patients, addressing the balance of benefits against risks.

## **2.7 Conclusions**

In summary, the three existing phase III trials of adjuvant RT against observation listed above (8-11) will be of very limited value in practice, either because they have been superseded by clinical developments or because they are too small. The paucity of randomised trials addressing the optimum duration of hormone therapy in the post-operative setting is an important omission. The popularity of radical prostatectomy, together with current oncological and urological opinion in the UK, Canada and elsewhere, presents an opportunity for a large, randomised trial addressing both the timing of post-operative treatment (early versus deferred) and the duration of hormone therapy (none versus short-term versus long-term) used in addition to prostate bed RT.

### **3. SELECTION OF CENTRES/CLINICIANS**

In order to participate in RADICALS, investigators and centres must be registered with one of the participating groups and must fulfil a set of basic criteria.

**Each investigator must:**

- Regularly undertake treatment of prostate cancer
- Have appropriate experience of conducting trials according to the principles of Good Clinical Practice (GCP)
- Comply with protocol treatment and follow-up schedule
- Maintain a local Trial Master File which will contain essential documents for the conduct of the trial
- Submit all trial data in a timely manner and as described in the protocol. Individual centres may be suspended on the recommendation of the Trial Management Group (TMG) if data returns are poor or if trial conduct is violated in other ways
- Notify the trials unit immediately of all Serious Adverse Events (SAEs). The initial SAE report must be promptly followed by detailed written reports
- Comply with Radiotherapy Quality Assurance
- Not disclose any trial data without the approval of the Trial Steering Committee (TSC)
- Retain all trial related documents for 15 years after completion of the trial

**Each centre must:**

- Conduct the trial in compliance with the principles of GCP and applicable regulatory requirements
- Have an adequate number of qualified staff and adequate facilities, for the foreseen duration of the trial, to conduct the trial properly and safely
- Must ensure that all staff assisting with the trial are adequately informed about the protocol and their trial related duties
- Obtain necessary local approvals
- Allow on-site monitoring
- Have PSA test with an assay sensitivity of 0.1ng/ml or lower

For information about additional site registration criteria, trial documentation and local procedures, see local Appendix B.

## 4. SELECTION OF PATIENTS

Patients with non-metastatic adenocarcinoma of the prostate who have had a radical prostatectomy will be eligible for RADICALS. **All patients must fulfil the main entry criteria and the criteria relevant to the randomisation they are taking part in.** Patients who are taking part in RADICALS-RT can also take part in RADICALS-HD when they have radiotherapy. Complete inclusion and exclusion criteria are listed in Table 1.

**Table 1: Patient inclusion and exclusion criteria**

	Inclusion	Exclusion
<b>All Patients</b>	<ul style="list-style-type: none"> <li>• Patient has undergone radical prostatectomy</li> <li>• Prostatic adenocarcinoma</li> <li>• Written informed consent</li> </ul>	<ul style="list-style-type: none"> <li>• Bilateral orchidectomy</li> <li>• Prior pelvic RT</li> <li>• Other active malignancy likely to interfere with protocol treatment or follow-up</li> <li>• Known distant metastases from prostate cancer</li> <li>• Pre-operative hormone therapy within previous 6 months</li> <li>• Previous pre-operative hormone therapy for longer than 8 months</li> <li>• Any post-operative hormone therapy*</li> </ul>
<b>RADICALS-RT</b>	<ul style="list-style-type: none"> <li>• Post-operative PSA <math>\leq 0.2</math>ng/ml</li> <li>• Ideally more than 4 weeks and less than 22 weeks after radical prostatectomy<sup>#</sup></li> <li>• One or more of: <ul style="list-style-type: none"> <li>▪ pT3/4</li> <li>▪ Gleason 7-10 (biopsy or surgical sample)</li> <li>▪ Pre-operative PSA <math>\geq 10</math>ng/ml</li> <li>▪ Positive margins</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Post-operative biochemical failure, defined as EITHER two consecutive rises in PSA and final PSA <math>&gt; 0.1</math>ng/ml OR three consecutive rises in PSA</li> <li>• Ideally more than 22 weeks since radical prostatectomy<sup>#</sup></li> </ul>
<b>RADICALS-HD</b>	<ul style="list-style-type: none"> <li>• Patient due to receive post-operative RT (early or deferred)</li> </ul>	<ul style="list-style-type: none"> <li>• PSA <math>&gt; 5</math>ng/ml at the time of randomisation</li> </ul>

<sup>#</sup>Patients randomised to early RT ideally should start trial treatment within 26 weeks after radical prostatectomy

\* Patients joining only the 6 months vs 2 years comparison in RADICALS-HD may begin post-operative hormone therapy prior to randomisation. However, this MUST be discussed with trials office before randomisation in this circumstance.

## 4.1 Investigations prior to each randomisation

All patients must have the following tests prior to randomisation according to the timings in the table below.

**Table 2a: Timing of Investigations – Radiotherapy Timing Randomisation**

Test	Timing
Bone scan*	16 weeks prior to randomisation
PSA**	<ul style="list-style-type: none"><li>• Within 30 days prior to randomisation</li><li>AND</li><li>• At least 30 days after surgery</li></ul>

\* Bone scan only required if Gleason score  $\geq 8$  and post-operative PSA is detectable. Additional investigations are at the clinician's discretion.

\*\* PSA assay must have a sensitivity of 0.1ng/ml or lower

**Table 2b: Timing of Investigations – Hormone Duration Randomisation**

Test	Timing
Bone scan <sup>#</sup>	Within 16 weeks prior to randomisation
PSA	Within 4 weeks prior to randomisation

<sup>#</sup> Bone scan only required if PSA > 2. Additional investigations are at the clinician's discretion.

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## 5. RANDOMISATION & ENROLMENT

### 5.1 Trial randomisation options

RADICALS is an international, multi-centre, open-labelled, randomised controlled trial. Blinding of treatment allocation in the trial is impracticable and will not be used. RADICALS is a trial with two separate randomisations.

#### 5.1.1 RADICALS-RT: Radiotherapy Timing Randomisation

This randomisation, ideally performed within 22 weeks after radical prostatectomy (RP), is defined as '**Radiotherapy Timing Randomisation**'. If the patient meets the eligibility criteria (see Table 1 in Section 4 and Appendix A V), he may be randomised between early radiotherapy and deferred radiotherapy for PSA failure.

#### 5.1.2 RADICALS-HD: Hormone Duration Randomisation

This randomisation, normally performed before the administration of post-operative radiotherapy, is defined as '**Hormone Duration Randomisation**'. This means that for patients receiving deferred RT, enrolment to RADICALS-HD may take place months or years after radical prostatectomy (see Figures 1-4). Patients entering into this randomisation may have already been in RADICALS-RT or not. Prior to their radiotherapy, patients may be randomised between the following 3 arms: no hormone therapy, short-term hormone therapy and long term hormone therapy. All patients taking part in RADICALS-HD may elect to be randomised between two, rather than all three, arms to facilitate comparisons and trial recruitment.

### 5.2 Randomisation contacts

To enter a patient, the randomisation CRFs (CRFs 1a, 1b, 2 and 3 or 4 & PSA History Log) should be completed and the relevant Trials Group contacted (see below for relevant contact details).

**Randomisation contact details:**

<b>MRC Randomisations</b>	<b>Tel: +44 (0)20 7670 4777</b>
<b>Monday-Friday</b>	<b>09.00 – 17.00 (GMT)</b>
<b>NCIC CTG Randomisations</b>	<b>Tel: +1 613-533-6430</b>
	<b>Fax: +1 613-533-2941</b>
<b>Monday – Friday</b>	<b>08.00 – 18.00 (EST)</b>

A patient ID number and treatment will be allocated and given over the phone. In addition, a letter confirming these details will be sent. The patient ID number will be the primary way in which the patient will be identified and should be used in all correspondence.

### **5.3 Co-enrolment guidelines**

Co-enrolment to other trials is permitted, providing this does not interfere with assessment of RADICALS outcome measures. See Section 6.7 for further detail.

## 6. TREATMENT OF PATIENTS

### 6.1 Guidance for RADICALS-RT

Patients in RADICALS-RT will be allocated to either early post-operative RT or deferred RT. RT will be given as 66Gy in 33 fractions over 6.5 weeks or 52.5Gy in 20 fractions over 4 weeks. Treatment with radiotherapy (or hormone treatment – see section 6.2) will commence within 2 months after the randomisation for early RT patients or within 2 months after biochemical failure for deferred RT patients. For information on radiotherapy quality assurance see Section 10.2.

#### 6.1.1 Early post-op radiotherapy

Patients allocated to early radiotherapy to the prostate bed will start treatment within approximately 2 months of RADICALS-RT and ideally within 26 weeks after surgery. Radiotherapy will be according to guidelines given in Section 6.1.3. Patients allocated early post-operative radiotherapy can also enter RADICALS-HD if they wish: this is encouraged. Alternatively, the use of hormones can be decided by the responsible investigator. Radiotherapy will be delayed by 2 months, up to 8 months after surgery, if the patient is due to receive hormone therapy.

#### 6.1.2 Deferred radiotherapy

This is a monitoring policy, with deferred RT to prostate bed given in the event of biochemical failure. PSA will be tested at each follow-up visit (see Section 7) and more often if rising PSA is detected. Biochemical failure is defined as EITHER two consecutive rising PSA levels and a PSA of greater than 0.1 ng/ml OR three consecutive rising PSA levels. If post-operative biochemical failure is confirmed, patients will receive radiotherapy as described in Section 6.1.3 and should be offered entry to the RADICALS-HD; this is encouraged. Radiotherapy will be delayed by 2 months if the patient is due to receive hormone therapy.

#### 6.1.3 Radiotherapy technique

##### 6.1.3.1 Radiation therapy

Radiotherapy to start within approximately 2 months of randomisation. Treatment should be CT planned with the patient supine, with empty rectum and comfortably full bladder. Recommended doses are in Section 6.1.3.4.

##### 6.1.3.2 Physical factors

Megavoltage equipment is required with effective photon energies  $\geq 6\text{MV}$ . Minimum source-to-axis distance is 100cm. The treatment technique will typically be by a 3-field or 4-field coplanar technique with blocks or multi-leaf

collimation (MLC) leaf positions designed for all fields to protect uninvolved structures. Intensity-Modulated Radiation Therapy (IMRT) techniques may be used, subject to the RADICALS Radiotherapy Quality Assurance (RTQA) reviewers' approval.

#### 6.1.3.3 Treatment volumes guidance

Please note that the following treatment volumes are for guidance only.

**Prostate bed: Clinical Target Volume (CTV).** The CTV will include the prostate bed in all patients. The pelvic lymph node regions may also be included at the investigator's discretion. Information which may be used to define the prostate bed CTV include:

- i. Histopathologic information of prostate size and tumour extent to specific boundaries of the surgical resection
- ii. Pre-operative imaging e.g. pelvic CT/MRI studies
- iii. Post-operative anatomy on planning CT scan

The definition of the prostate bed CTV is based on the estimated location of the pre-operative prostate volume plus sites of possible microscopic tumour extension, plus the extent of the surgical bed, and should normally include any surgical clips provided that the normal-tissue dose-constraints are satisfied. The original volume of seminal vesicles (including any residual seminal vesicle tissue post-op) will not be considered target if they were not pathologically involved with tumour, and if the predicted pre-operative risk of seminal vesicle involvement was less than 15% using the Roach formula ( $\% \text{ seminal vesicle (SV) involvement risk} = \text{PSA} + 10 \times [\text{GS} - 6]$  where GS=Gleason Score. If there was pathologic involvement of the seminal vesicles, or if the predicted risk of involvement was greater than 15%, then the seminal vesicles will be considered target.

**Low-risk** = <15% according to the Roach formula

**High-risk** =  $\geq$ 15% according to the Roach formula

**Inferior border:** 5mm cranial to the superior border of the penile bulb

**Anterior border:** As follows:

- i. Caudal (less than 2cm above anastomosis) – posterior aspect of symphysis pubis
- ii. Cranial (more than 2cm above anastomosis) – posterior 1/3 of bladder wall

**Posterior border:** Anterior rectal wall

**Lateral border:** Medial border of obturator internus and levator ani muscles

**Superior border:** As follows:

- i. If SV low-risk and pathologically uninvolved: base of SV
- ii. If SV high risk or pathologically involved: tips of SV
- iii. If SV absent, the superior border should be determined with reference to the estimated position of the pre-operative SV using the longitudinal dimension superiorly from urogenital diaphragm to reflect preoperative size of prostate, together with the position of any surgical clips.

**Prostate bed – Planning Target Volume:** The planning target volume (PTV) will add 1.0 cm in all directions, for day-to-day variation in set up and for CTV motion.

**Prostate bed – Field size:** The maximum unshaped field size in each axis (anterior/posterior (AP), left/right (LR) and superior/inferior (SI)) will typically be between 8.0 and 12.0cm.

**Pelvic lymph nodes – Clinical Target Volume:** The CTV will include the prostate bed in all patients. The pelvic lymph node regions may also be included at the investigator's discretion. The pelvic nodal CTV will include the internal iliac/obturator, external iliac, pre-sacral and pre-sciatic nodal regions.

**Pelvic lymph nodes – Planning Target Volume:**

- Inferior border: inferior border of prostate bed PTV
- Lateral borders: pelvic sidewalls
- Anterior border: posterior symphysis
- Posterior border: anterior S2-3 junction
- Superior border: lower 1/3 sacro-iliac (S-I) joints

**Pelvic lymph nodes – field borders:**

Determined by PTV above. Conformal blocks/MLC leaves may be used to shield inferior part of rectum and anus, the base of the penis, and the antero-superior part of the bladder.

#### 6.1.3.4 Radiation Doses

##### (a) Prostate bed

Radiotherapy will be given once a day, five sessions a week. The dose shall be prescribed at the intersection of the central rays of the beams. The prescribed dose to the intersection of the central rays of the beams will be one of the following:

- **66Gy given in 33 fractions over 6.5 weeks**
- **52.5Gy given in 20 fractions over 4 weeks**

The minimal dose to the PTV shall not be less than 95% of the prescribed dose; the maximum, not more than 105% of the prescribed dose.

##### (b) Pelvic lymph nodes

Radiotherapy will be given once a day, five sessions a week. The dose shall be prescribed at the intersection of the central rays of the beams. The prescribed doses to the intersection of the central rays of the beams will be:

- **46Gy given in 23 fractions over 4.5 weeks**

#### 6.1.3.5 Critical Normal Structures

The dose-volume objectives are provided in Tables 3 and 4. These are for guidance only.

**Table 3: Dose & Volume Objective: Daily fractions of 2 Gy**

<b>Structure</b>	<b>Dose</b>	<b>Volume objective</b>
<b>Bladder</b>	50 Gy	< 80%
	60 Gy	< 50%
<b>Rectum</b>	30 Gy	< 80%
	40 Gy	< 70%
	50 Gy	< 60%
	60 Gy	< 50%
	66 Gy	< 30%

**Table 4: Dose & Volume Objective: 52.5Gy in 20 fractions over 4wks**

<b>Structure</b>	<b>Isodose</b>	<b>Volume objective</b>
<b>Bladder</b>	40 Gy	< 80%
	48 Gy	< 50%
<b>Rectum</b>	24 Gy	< 80%
	32 Gy	< 70%
	40 Gy	< 60%
	48 Gy	< 50%
	52.5 Gy	< 30%

## 6.2 Guidance for RADICALS-HD

### 6.2.1 RT alone

Patient would be treated with post-operative radiotherapy alone as described in Section 6.1. Radiotherapy should ideally start as soon as possible but within 2 months after randomisation.

### 6.2.2 Short-term hormone therapy plus RT

Trial treatment should ideally start as soon as possible but within 2 months after randomisation. Radiotherapy should commence approximately 2 months after starting hormone treatment. Treatment using a gonadotrophin releasing hormone analogue (GnRHa) should be given for 6 months. Because of the possibility of tumour 'flare', an anti-androgen (such as cyproterone acetate 100mg tds) should be used for one week prior to the first GnRHa administration, and continued for a total of 3 weeks. The choice of GnRHa may vary according to local practice (e.g. goserelin, leuprorelin), but in this arm the use of 3-month depot preparations should be avoided. Where possible, one month preparations (e.g. goserelin 3.6mg, leuprorelin 3.75mg) should be used in order to hasten testosterone recovery after the treatment period. Bicalutamide monotherapy 150mg daily or degarelix each for 6 months are acceptable alternatives. For Canadian patients, hormonal therapy will consist of LHRH analogue therapy (in addition to antiandrogen for tumour flare, if desired) or degarelix because bicalutamide monotherapy is not approved for use.

#### 6.2.2.1 Dispensing Hormone therapy

Centres will use routinely available products (either LHRH agonists or bicalutamide monotherapy) that will be stored and dispensed in the usual way. For Canadian

patients, hormonal therapy will consist of LHRH analogue therapy (in addition to antiandrogen for tumour flare, if desired) or degarelix because bicalutamide monotherapy is not approved for use.

### **6.2.3 Long-term hormone therapy plus RT**

Trial treatment should ideally start as soon as possible but within 2 months after randomisation. Radiotherapy should commence approximately 2 months after starting hormone treatment. Treatment using a gonadotrophin releasing hormone analogue (GnRHa) should be given for 24 months. Because of the possibility of tumour 'flare', an anti-androgen (such as cyproterone acetate 100mg tds) should be used for one week prior to the first GnRHa administration, and continued for a total of 3 weeks. The choice of GnRHa may vary according to local practice (e.g. goserelin, leuprorelin). In this arm, the use of 3-month depot preparations (e.g. goserelin 10.8mg, leuprorelin 11.25mg) is encouraged in the interests of patient convenience, but 1 month or 2 month depots are acceptable. Bicalutamide monotherapy 150mg daily, or degarelix, for 24 months are acceptable alternatives. In the case of bicalutamide, patients should be considered for prophylactic radiotherapy to bilateral breast buds (8Gy single fraction using orthovoltage radiation) to prevent painful gynaecomastia. For Canadian patients, hormonal therapy will consist of LHRH analogue therapy (in addition to antiandrogen for tumour flare, if desired) or degarelix because bicalutamide monotherapy is not approved for use.

#### **6.2.3.1 Dispensing Hormone therapy:**

Centres will use routinely available products (either LHRH agonists or bicalutamide monotherapy) that will be stored and dispensed in the usual way. For Canadian patients, hormonal therapy will consist of LHRH analogue therapy (in addition to antiandrogen for tumour flare, if desired) or degarelix because bicalutamide monotherapy is not approved for use.

## **6.3 Stopping trial treatments**

A patient may stop allocated trial treatment for the following reasons:

1. Unacceptable toxicity
2. Intercurrent illness which prevents further treatment
3. Withdrawal of consent for treatment
4. Any alteration in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion

The reason should be recorded on the follow-up forms. Unless a patient states otherwise, it should be assumed that consent is given to continue to record trial data.

## **6.4 Accountability and unused drugs**

As all drugs are licensed in the countries in which the trial will be performed, drug accountability measures will not be necessary. Drugs should be obtained as per local practice.

## **6.5 Measures of compliance and adherence**

Date of treatment, dose, delays and reasons for delays or dose modifications of all study treatment will be recorded on case report forms.

## **6.6 Non-trial treatment**

### **6.6.1 Medications permitted/not permitted**

No other therapies for other prostate cancer (e.g. bilateral orchidectomy, oestrogens, cytotoxic chemotherapy) are acceptable prior to disease progression. 5-alpha reductase inhibitors, soya, selenium and vitamin E are acceptable non-trial therapies.

### **6.6.2 Data on concomitant medication**

Concomitant medication relevant to serious adverse events will be recorded on Serious Adverse Event forms.

## **6.7 Co-enrolment guidelines**

Ideally, patients should not be participating in any other clinical trial of prostate cancer treatment when they enter RADICALS. However, there are some planned trials that overlap and fit with RADICALS which patients may join if participation does not interfere with RADICALS or other trials. Similarly, once enrolled, patients should not enter any other trials that will interfere with the RADICALS assessments until the patient has had a treatment failure event reported (see Section 9.2.2). After this point, the patient may be entered into further studies.

The primary outcome measures of RADICALS are freedom from distant metastases and disease-specific survival. Therefore, Follow-up to RADICALS must continue and must not be affected by co-enrolment to other studies. It is preferable that the participating group's trials unit should be notified in writing, with details of the trial: trial name, sponsor, randomisation arms, study endpoints and a declaration that RADICALS Follow-up will not be impeded, before a patient is co-enrolled or after randomisation if the patient is already co-enrolled.

## 7. ASSESSMENTS AND FOLLOW-UP

### 7.1 Case report form timings

Table 5 presents a summary of the timing of the required trial case report forms to be completed by the centre for participating patients.

**Table 5: Summary of timing of case report forms (CRFs)**

Trial case report forms	Timing from randomisation
Baseline Information form (CRF 1a)	Pre-randomisation
Patient History Form (CRF1b)	Pre- <b>or</b> Post-randomisation
Co-morbidity form (CRF 2)	Two weeks prior to randomisation
PSA History Log	Pre-randomisation
Randomisation forms (CRF 3 = both randomisations) (CRF 4 = HD randomisation alone)	At randomisation
Radiotherapy forms (CRF 5)	After administration of radiotherapy
Follow-up forms* (CRF 6)	Month 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, then annually until year 15
Patient Reported Outcome forms**	Pre-randomisation, 1, 5 and 10 years
Disease Event form (CRF 7)	<i>As needed</i>
Serious adverse event form (CRF 8)	<i>As needed</i>
Death Report form (CRF 9)	<i>As needed</i>

\*Timed from most recent randomisation

\*\*Patient reported outcomes only reported by patients in RADICALS-RT

### 7.2 Procedures for assessing efficacy

#### 7.2.1 PSA measurements

PSA will be tested regularly at each follow-up visit and more often if clinically indicated. The assay used must have a sensitivity of 0.1ng/ml or lower.

#### 7.2.2 Efficacy parameters

The primary outcome measure is for RADICALS-RT is freedom from distant metastases. This will be defined as any distant metastases or death from prostate cancer. Bone scans are not mandated at set times but should be performed as clinically indicated. The primary outcome measure for RADICALS-HD is disease-

specific survival. The event will be death from prostate cancer, timed from randomisation.

All men should be followed-up until death. With regards to ascertaining causes of death, particular attention will be paid to men who are reported as having died from prostate cancer without previously reporting progression or recurrence, and men who are reported as having died from non-prostate cancer causes after developing hormone refractory disease. There will be a review of causes of death performed independent from allocated trial arm.

### **7.3 Procedures for assessing safety**

There are no tests in addition to standard practice to assess patient safety. Patients will be seen every 4 months for 2 years, every 6 months from 2 to 5 years, then annually thereafter. Secondary malignancies, toxicities and SAEs will be recorded on CRFs and/or SAE forms which will be monitored by the Independent Data Monitoring Committee (IDMC).

### **7.4 Other assessments**

#### **7.4.1 Patient reported outcomes**

Quality of life will be assessed using self-administered questionnaires in the subgroup of patients entered in RADICALS-RT. These questionnaires have approximately 50 questions and are collected pre-randomisation and at 1, 5 and 10 years after randomisation. Further details are given in Section 13.1.

#### **7.4.2 Health economics**

Data for the health economics substudy will be collected on both CRFs and patient administered questionnaires (EQ-5D). The EQ-5D questionnaire will be completed by the patients together with the patient reported outcome forms at baseline and at 1, 5 and 10 years after randomisation. Further details are given in Section 13.2.

### **7.5 Loss to follow-up**

Every effort should be made to follow-up all patients who have been randomised. Patients should, if possible, remain under the care of an oncologist or urologist for the duration of the trial. If care of a patient is returned to the primary lead physician, it is the responsibility of the trial investigator who obtained the patient's consent to

participate in the trial to ensure that the data collection forms are completed. Patients may transfer to another centre (see Section 8.2). Where it applies, the consent of patients should be obtained for their names to be flagged for survival information through national registries (e.g. NHSCR in England/Wales and GRO in Scotland). If the clinician moves, appropriate arrangements should be made to arrange for trial follow-up to continue at the centre.

## **7.6 Trial closure**

For the purposes of current regulations, the trial will be considered closed 10 years after recruitment has been completed and survival data have been published. However, further observational Follow-up of all patients enrolled in the trial will continue until all randomised patients have died. This will initially be via the hospital, but in the longer term may employ national registers.

## 8. STOPPING TRIAL TREATMENT

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection. If a patient wishes to stop trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up.

### 8.1 Withdrawal from the trial completely

In very rare cases, if a patient explicitly withdraws consent to have **any** data recorded their decision must be respected and the trials unit must be notified in writing of this decision. All communication surrounding the withdrawal should be noted in the patient's records and no further RADICALS CRFs should be completed for that patient. Patients can change their minds about withdrawal at any time and re-consent to participate in the trial. Follow-up data should be collected **only** from the point of when consent was re-instated.

### 8.2 Patient transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient. If the patient moves from the local area, arrangements should be made for trial follow-up to be undertaken by their new local centre. Details of other participating centres can be obtained from the trials unit. A copy of the patient RADICALS CRFs will need to be provided to the new site.

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## 9. STATISTICAL CONSIDERATIONS

### 9.1 Method of Randomisation

Randomisation will be performed centrally at the MRC Clinical Trials Unit using a computer-implemented algorithm. The method of randomisation will be minimisation over a number of clinically important stratification factors with an allocation probability of 80%. Each comparison will have an independent randomisation programme.

### 9.2 Outcome Measures

RADICALS considers a number of primary and secondary outcome measures; all outcome measures are relevant to both trial randomisations unless otherwise stated. All outcome measures will be timed from the relevant randomisation.

#### 9.2.1 Primary outcome measure - RADICALS-RT

RADICALS-RT was originally designed to detect an absolute improvement of 5% in disease-specific survival at 10-years from 90% to 95% with 80% power. Since the trial was designed in 2006, further information on disease-specific survival in similar patient cohorts has become available from prospective RCTs, including EORTC 22911 (8) and SWOG 8794 (10). These provide useful estimates as they are both clinical trials and recruited partly during the PSA era; such information was not previously available. The results of these trials show that death from causes other than prostate cancer is a major competing risk, with around only one in four deaths being attributed to prostate cancer and a 10-year disease-specific-survival (DSS) of around 94%; this patient cohort is performing much better than had been anticipated originally. With further treatments (e.g. docetaxel) being available and standard of care at the time of relapse and the development of castrate-refractory disease, the time from the development of distant metastases until death from prostate cancer has lengthened. An absolute improvement of 5% is not a reasonable assumption if these estimates hold true.

However, the role of adjuvant RT remains controversial and a clinical trial is required to resolve this issue. RADICALS-RT will do this. Therefore, focus has turned towards distant metastases, which is an earlier but clinically important and objective outcome measure. The primary outcome measure for RADICALS-RT is now **freedom-from-distant-metastases**.

Disease-specific survival, therefore, becomes an important secondary outcome measure. At the main analysis of distant metastases, the trial would expect around 41 deaths from prostate cancer and would have 59% power to detect a halving of the risk of prostate cancer death from 6% at 10-years to 3%, ie DSS improves from 94% to 97%. With further follow-up, RADICALS-RT could attain 80% power for DSS after additional 6 years of follow-up (total duration of the trial would be 18.5 years). However, the question of DSS would be addressed sooner through combined analysis with two parallel trials: RAVES and GETUG-17 (see Section 9.6).

### **9.2.2 Primary outcome measure – RADICALS-HD**

The primary outcome measure in RADICALS-HD remains as **disease-specific survival (DSS)** i.e. the event is death from prostate cancer or death from treatment for prostate cancer. Causes of death in patients diagnosed with prostate cancer can be difficult to confirm. A reported death from prostate cancer would be expected to be preceded by a report of hormone refractory metastatic prostate cancer. The clinician's discretion should be used to decide if death during treatment is related to prostate cancer. All UK patients will be flagged with the NHS Central Register (NHSCR) or equivalent for mortality data to support the data collected on the case report forms (CRFs).

### **9.2.3 Secondary outcome measures**

- **Disease-specific-survival** – (RADICALS-RT only)
- **Freedom from treatment failure:** PSA progression when on androgen deprivation
- **Clinical progression-free survival:** Clinical progression of prostate cancer or initiation of non-protocol hormone therapy or death from prostate cancer.
- **Overall survival:** Death from any cause
- **Non-protocol hormone therapy:** Initiation of hormone therapy other than that randomised
- **Treatment toxicity:** Incidence of severe toxicity or serious adverse events
- **Patient reported outcomes:** See Section 13.1 for details

## 9.3 Sample Size

### 9.3.1 Basic assumptions

The original sample size calculations were performed using the `-art-` package in Stata 9(31). The sample size re-calculation was performed in Stata 11.1. using version 1.0.8 (date 24mar2010) of `-art-`, including `-artsurv-` for the main calculation and `-artpep-` for variations. In terms of accrual and follow-up, we assume 5½ to 6½ years of recruitment, attaining a constant rate of accrual by 3 years after initiation of the trial in RADICALS-RT; a steady rate of accrual may be reached slightly later in time in RADICALS-HD as the rate may not peak until patients allocated deferred radiotherapy in RADICALS-RT start to experience biochemical failure. After recruitment, we assume a further 7 years of Follow-up. Clinically, we assume that, in RADICALS-RT, we should only be interested in treatment options with an absolute increase in 10-year freedom-from-distant-metastases of 5%. In RADICALS-HD, we should only be interested in treatment options with an absolute increase in 10-year disease-specific survival of 6%, at least.

The sample sizes have been calculated separately for the two randomisations because of potential variation in the underlying assumptions, an uncertain proportion of patients joining RADICALS-RT and RADICALS-HD and some uncertainty about accrual rates. A number of scenarios relating to trial recruitment and assumptions have been calculated and are reported elsewhere but are available upon request. Selected scenarios are reported here.

### 9.3.2 RADICALS-RT sample size

In the patients suitable for this randomisation, the control arm is assumed to be deferred radiotherapy i.e. radiotherapy at PSA relapse.

When the trial was originally designed, there was uncertainty about the likely event rate but it was anticipated that a modest absolute effect in the order of 5% would be required to convince clinicians to adopt adjuvant radiotherapy for all patients. The original sample size calculations anticipated that around 2,600 patients would need to be recruited over 5½ years and followed-up for a further 7 years in order to obtain 80% power to detect an improvement from 70% to 75% or 90% power to detect an improvement from 80% to 85%.

From SWOG 8794 and EORTC 22911, the proportion of patients free of distant metastases at 10 years is estimated to be 90%. We would look to test whether adjuvant RT can improve this to 95% (hazard ratio 0.487), which is seen as the minimum clinically significant improvement required to routinely introduce adjuvant

RT to this patient population; this mirrors the size effect observed in SWOG 8794. This is tested using the superiority design. With 80% power, a two-sided 5% significance level, accrual lasting 5½ years (reaching peak accrual rates after 3 years) and a further 7 years of follow-up, we would need to recruit 1,063 patients in order to observe 66 distant metastases events. This sample size assumes that 30% of patients are lost to follow-up and around 30 patients randomised from 30 months onward. Therefore, the target sample size will be reduced from 2,600 to around 1,063 patients. This assumes that 30% of patients are lost to follow-up between 5 and 10 years.

If the peak accrual is lower, at around 25 patients per month, accrual would be extended by 1 year, to around 6½ years and around 1,160 patients would be randomised; this should address the question with the same power and in the same overall timescale.

### **9.3.3 RADICALS-HD sample size**

Patients would be suitable for this randomisation if they are planned for post-operative radiotherapy regardless of whether this is the early or deferred setting.

There is some uncertainty in the baseline disease-specific survival (DSS) rate for patients receiving early RT *and* for patients receiving deferred RT. It is assumed that patients receiving early radiotherapy do at least as well as patients receiving deferred radiotherapy, timed from randomisation to RADICALS-HD. There is also uncertainty over the proportion of early and deferred patients that would join the trial; it is assumed that at least as many patients in the deferred setting will be randomised, if not two to three times more.

Since the trial was designed in 2006, further information on the baseline estimates of disease specific survival have become available from similar patient cohorts, including data from the RTOG 9601, SWOG 8794 and EORTC 22911 trials. These provide useful estimates as they are clinical trials and recruited partly during the PSA era; such information was not previously available when RADICALS-HD was designed.

Sites and patients are encouraged to join the three-way randomisation of no-HT vs STHT vs LTHT in RADICALS-HD as this is the most efficient for the trial. However, it has become apparent that the three-way randomisation is less well supported than either of the two separate potential two-way randomisations: no-HT vs STHT and STHT vs LTHT. These are each clinically important questions and the trial will address

both. It will not be possible to address one of the originally envisaged comparisons: no-HT vs LTHT with any reasonable degree of power, although the comparison will be performed. Therefore, there are two main comparisons in RADICALS-HD:

1. RT-only (no-HT) vs RT + short-term hormone therapy (STHT)
2. RT+ short-term HT (STHT) vs RT + long-term HT (LTHT)

It is assumed that patients who enter RT+STHT vs RT+LTHT comparison have a slightly higher risk of a disease event than patients who enter RT-only vs RT+STHT comparison because the clinician assumes that some HT is required; therefore, their 10 year DSS rate is estimated as being lower.

#### **9.3.3.1 Comparison: no-HT vs RT+STHT**

It is estimated that DSS will be 85% at 10 years in patients on the no-HT arm. This superiority trial is testing whether addition of STHT to RT can improve this to 91% (hazard ratio HR=0.58). A total of 1263 patients (128 events) in a comparison of no-HT vs STHT would allow for 80% power to detect an increase of 6% in 10-year DSS with a 3% significance level (accounting for the multiple use patients who join the three-way randomisation). This assumes that 30% of patients are lost to follow-up. Peak accrual would be around 31 patients per month in the comparison of no-HT vs RT+STHT.

If peak accrual is lower, at around 25 patients per month, accrual would be extended by 1 year to around 6.5 years and around 1368 patients would be randomised; this should address the question in the same timescale with the same power.

#### **9.3.3.2 Comparison: RT+STHT vs RT+LTHT**

It is estimated that DSS will be 87% at 10 years in patients on the STHT arm. This is lower than the estimated 91% 10-yr DSS in the research arm (STHT) in the previous comparison if STHT is more effective than no-HT, as we anticipate that higher risk patients will enter the STHT vs LTHT comparison. This superiority trial is testing whether the LTHT can improve disease-specific survival to 93% at 10 years (hazard ratio HR=0.52). A total of 1077 patients (91 events) in a comparison of STHT vs LTHT would allow for 80% power to detect an increase in 10-year DSS of 6% with a 3% significance level (accounting for the multiple use patients who join the three-way randomisation). This assumes that 30% of patients are lost to follow-up.

This could be achieved in 5<sup>1</sup>/<sub>2</sub> years with 26 patients randomised each month from 30 months onwards. Patients would be followed-up for 7 years after the end of

recruitment. The numbers above allow for a certain percentage of patients to be lost to follow-up.

If the peak accrual is lower, at around 20 patients per month, accrual would be extended by 1 year to around 6.5 years and around 1129 patients would be randomised; this should address the question in the same timescale with the same power.

#### **9.3.4 Overall sample size**

The overall sample size will depend on how many patients are recruited to both RADICALS-RT and RADICALS-HD, and how many patients join the three-arm Hormone Duration Randomisation. It is anticipated that, of patients who have undergone radical prostatectomy, 10% will have a definite indication for non-randomised early radiotherapy and 50% will have a definite indication for following a non-randomised policy of deferred radiotherapy. The value of early radiotherapy will be uncertain in the remaining 40% who, if they meet the eligibility criteria, should be randomised in RADICALS-RT. No formal overall sample size is estimated, but around 2500 patients will be recruited.

Given the number of radical prostatectomies performed each year in the participating countries, these are feasible target sample sizes.

#### **9.3.5 Pilot phase**

RADICALS incorporates an 18-month feasibility stage during which randomisation rates, and the trial as a whole, will be carefully assessed. Continuation of the trial beyond the feasibility stage was conditional on satisfactory patient accrual. The trial's progress has been repeatedly reviewed by the TMG, TSC and IDMC as well as the funding body. The decision to review and update the sample size calculations has been taken with full discussion and support, particularly by given the efforts to encourage the accrual. Accrual rates will be monitored throughout the trial.

### **9.4 Interim Monitoring and Analyses**

Formal interim analyses of the accumulating data will be performed at regular intervals (at least, annually) for review by an Independent Data Monitoring Committee (IDMC, see Section 15.3). These analyses will be performed by statisticians at the MRC CTU. The IDMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further Follow-up. A decision to

discontinue recruitment, in all patients or in selected subgroups, would be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make recommendations to the Trial Steering Committee (TSC, see Section 15.2) as to the continuation of the trial.

The trial oversight committees will be asked to continue to monitor and comment on any deviation of the accruing data from the underlying assumptions e.g. higher or lower rates of death from prostate cancer than expected or type of patient randomised.

## **9.5 Statistical Analysis Plan**

The analyses to be performed for RADICALS will be presented in detail in a separate Statistical Analysis Plan. In short, the main analyses will be performed for patients in RADICALS-RT and separately for patients in RADICALS-HD. The main outcome measures will be compared using the standard time-to-event methods of Kaplan-Meier with formal comparisons using log-rank tests and graphically represented with survival plots. Analyses in the hormone duration comparisons will be stratified by the timing of post-operative radiotherapy (early RT vs deferred RT).

## **9.6. Individual Patient Data Meta-Analysis**

### **9.6.1 RADICALS-RT**

Disease-specific survival is an important secondary outcome measure for RADICALS-RT. The question of DSS would be addressed sooner through combined analysis with two parallel trials: RAVES and GETUG-17. These would contribute 470 and 718 patients respectively. Together with RADICALS-RT, this would bring the total number of patients available for a meta-analysis of individual patient data (IPD) to 2174, allowing a more timely assessment of the question of disease-specific survival. Furthermore, a full systematic review would also be conducted to ensure that all other relevant clinical trials that were identified and appraised. Combined analyses of all outcome measures would be planned. Formal agreements will be developed with all trial groups.

### **9.6.2 RADICALS-HD**

Other international groups are conducting overlapping clinical trials therefore, we plan to also undertake a meta-analysis using IPD including RADICALS-HD, GETUG-16, EORTC 22043/30041, RTOG 05-34 (SPPORT) and RTOG 96-01 and any other relevant trial identified in a full systematic review. Together these trials will provide increased power for analysis of both disease-specific survival and overall survival. Formal agreements will be developed with all trial groups.

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## **10. QUALITY ASSURANCE AND CONTROL**

### **10.1 Compliance**

RADICALS will be conducted according to the protocol, relevant Standard Operating Procedures (SOPs), GCP and relevant national regulatory requirements.

### **10.2 Radiotherapy quality assurance**

The RADICALS Radiotherapy Quality Assurance (RTQA) Group, consisting of radiation oncologists and radiotherapy physicists, will give information and guidance regarding implementation of the protocol, monitor compliance with the protocol, and provide feedback on the RTQA accreditation (where necessary).

RTQA accreditation is required by all centres (see Appendix B). However, centres that have been RTQA accredited for another multi-centre prostate radiotherapy trial in the UK (e.g. MRC RT01 or CHHIP) will be automatically granted RADICALS RTQA accreditation.

The RADICALS website will include sample cases to illustrate the Clinical Target Volumes described in the protocol section 6.1.3.3.

### **10.3 Monitoring and audit**

A risk assessment has been carried out and an appropriate monitoring plan has been developed. Monitoring will be a combination of central monitoring (e.g. database checks) and the IDMC review as described in Section 15.3. There will be limited on-site monitoring: all participating investigators and groups must agree to direct access to all trial related sites, source data documents and reports for the purpose of monitoring by the sponsor and audit and inspection by domestic and foreign regulatory authorities.

### **10.4 Data handling**

The site will retain a copy of each CRF. All data recorded in each CRF, will be entered onto the RADICALS trial clinical database. A comprehensive validation check program will identify missing, illogical and/or inconsistent data. Trained data management personnel will review the resulting discrepancy report, correcting any data entry errors. If investigator input is required to clarify or correct any missing, ambiguous

or inconsistent data, the data manager will generate a Data Clarification Form (DCF). The Data Manager will send this form to the investigator for completion. When the completed DCF is returned to data management, the data on the clinical database will be corrected accordingly.

# 11. SAFETY REPORTING

ICH GCP requires that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol. Section 11.1 lists definitions, Section 11.3 gives details of the institution/investigator responsibilities and Section 11.4 provides information on MRC CTU responsibilities.

## 11.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply in this trial protocol. These definitions are given in Table 6. These definitions apply to RADICALS investigators in UK and Canada.

**Table 6: Terms and definitions for adverse events**

Term	Definition
<b>Adverse Event (AE)</b>	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
<b>Adverse Reaction (AR)</b>	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
<b>Unexpected Adverse Reaction (UAR)</b>	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.
<b>Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)</b>	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: <ul style="list-style-type: none"> <li>• results in death</li> <li>• is life-threatening*</li> <li>• requires hospitalisation or prolongation of existing hospitalisation**</li> <li>• results in persistent or significant disability or incapacity</li> <li>• consists of a congenital anomaly or birth defect</li> </ul>

## **11.2 Clarifications and General Exceptions**

Life-threatening (\*), in the definition of 'serious', refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalisation (\*\*) is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious

Please note that SAEs should also be reported as routine toxicities where that toxicity is also collected on one of the routine assessment forms.

## **11.3 Trial-Specific Exceptions to Expedited SAE Notification and Reporting**

Disease progression, or death as a result of disease progression, are not considered to be SAEs and should be reported on the Follow-up form (CRF 6) or Death Report form (CRF 9) respectively.

Due to the seriousness of the disease in this study, the following situations that fulfil the definition of an SAE are excluded from expedited notification on an SAE form and should be reported on the Follow-up Form.

- Elective hospitalisation to simplify treatment or procedures
- Elective hospitalisation for pre-existing conditions that, in the investigator's opinion, have not been exacerbated by trial treatment

There are no other treatment-related toxicities that result in hospitalisation for symptom control which are excluded from expedited reporting. Life-threatening or fatal events should still be reported on the SAE form.

### **11.3.1 Institution Responsibilities**

All non-serious AEs/ARs, whether expected or not, should be recorded in the toxicity (symptoms) section of the Follow-up form (CRF 6) and sent to the MRC CTU within one month of the form being due. SAEs/SARs should be notified to the MRC CTU as described below.

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be should be graded using the NCI CTCAE v3.0. The full list is available at <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.

A flowchart is given at the end of this section to help explain the notification procedures. Any questions concerning this process should be directed to the MRC CTU in the first instance.

### **11.3.2 Investigator Assessment**

#### **(a) Seriousness**

When an AE/AR occurs, the investigator responsible for the care of the patient must first assess whether the event is serious using the definition given in Table 5. If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and the trials unit notified.

#### **(b) Causality**

The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions in Table 7. There are 5 categories: unrelated, unlikely, possible, probable and definitely related. If the causality assessment is unrelated or unlikely to be related the event is classified as a SAE. If the causality is assessed as either possible, probable or definitely related then the event is classified as a SAR.

#### **(c) Expectedness**

If the event is a SAR the Investigator must assess the expectedness of the event. The definition of an unexpected adverse reaction (UAR) is given in Table 6. If a SAR is assessed as being unexpected it becomes a SUSAR.

**Table 7. Definitions of causality for adverse events**

<b>Relationship</b>	<b>Description</b>	<b>Event Type</b>
<b>Unrelated</b>	There is no evidence of any causal relationship	SAE
<b>Unlikely</b>	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	SAE
<b>Possible</b>	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	SAR
<b>Probable</b>	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
<b>Definitely</b>	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

**(d) Notification**

The MRC CTU should be notified within one working day of the investigator becoming aware of an event that requires expedited reporting. Investigators should notify the MRC CTU of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to the MRC CTU indefinitely (i.e. no matter when they occur after randomisation).

**Notification Procedure:**

- a. The SAE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then re-fax to the MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.
- b. Send the SAE form by fax to the MRC CTU within one working day of the investigator's knowledge of the event.  
Fax Number: see box, below

- c. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE form by ticking the box marked 'Follow-up' and faxing to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.
- d. Staff at the institution must notify their local research ethics committee of the event (as per the institutions standard local procedure).

### 11.4 MRC CTU Responsibilities

Medically qualified staff at the MRC CTU and/or the Chief Investigator (or a medically qualified delegate) will review all SAE reports received. The causality assessment given by the local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU is undertaking the duties of trial sponsor and is responsible for the reporting of all SUSARs and other SARs to the regulatory authorities and the research ethics committees as appropriate.

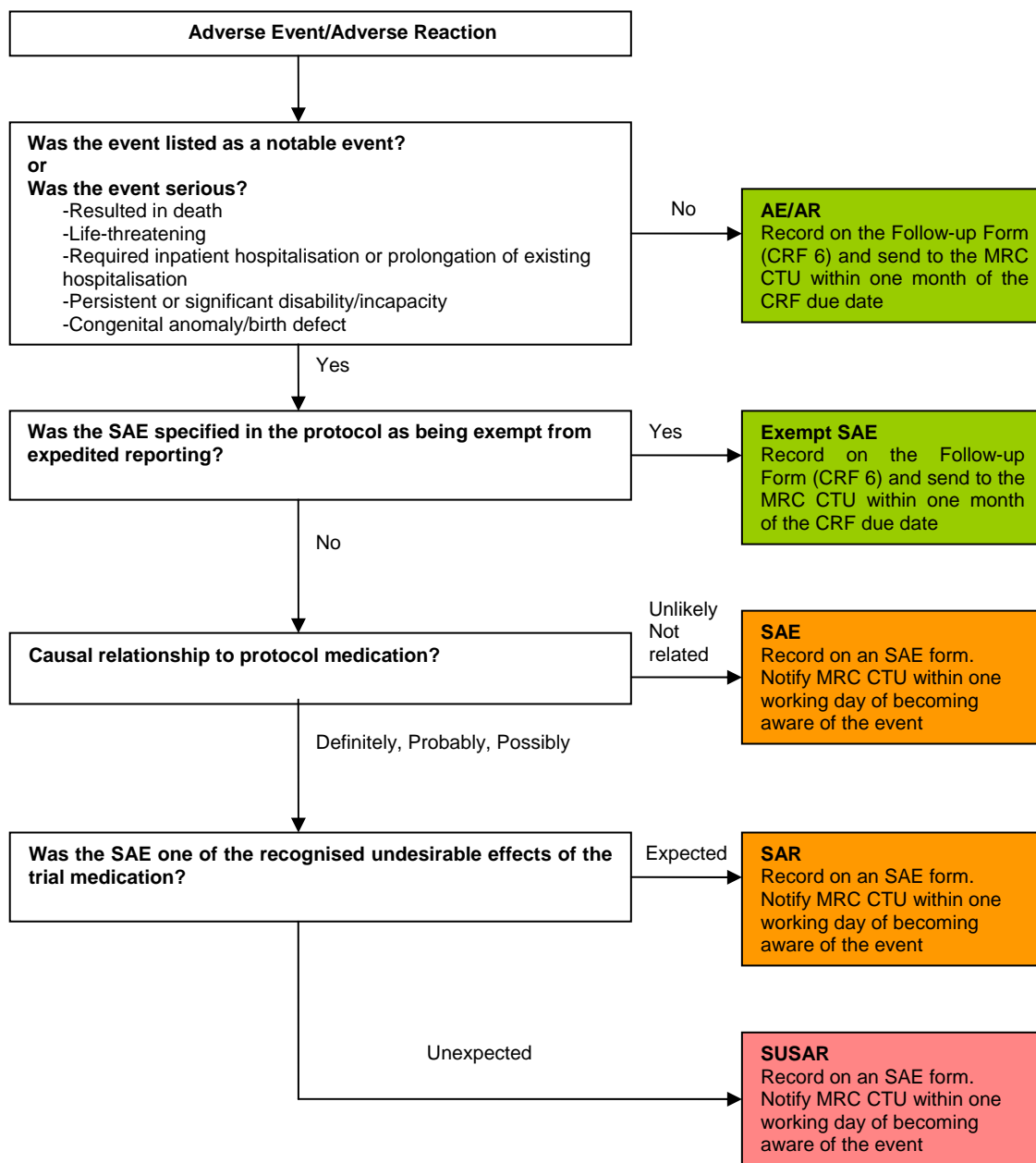
The MRC CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

## **SAE NOTIFICATION**

Within one working day of becoming aware of an SAE, please fax a completed SAE form to the MRC Clinical Trials Unit on:

**Fax: +44 (0)20 7670 4818**

**Figure 4: Safety Reporting Flowchart**



<b>CRF:</b> Case report form	<b>IB:</b> Investigator's brochure
<b>SAE:</b> Serious adverse event	<b>SAR:</b> Serious adverse reaction
<b>SPC:</b> Summary of product characteristics	<b>SUSAR:</b> Suspected unexpected serious adverse reaction

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## 12. ETHICAL CONSIDERATIONS

Participation in a randomised controlled trial means that the patient and clinician are not able to choose all aspects of patient treatment but do choose to be randomised. Patients will receive different treatments and toxicities are different by arm; this will all be explained to patients. All trial treatments and Follow-up schedules are routine practice across the UK. This trial is designed to fit with clinical practice; there are:

- No additional visits or assessments required by the trial
- No additional risks caused by participating in the trial and trial treatment.

The study will abide by the principles of the Declaration of Helsinki. Each patient's consent to participate in the trial should be obtained after a full explanation of the treatment options, including the conventional and generally accepted methods of treatment.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of Follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient must remain free to withdraw at any time from the protocol treatment and trial Follow-up without giving reasons and without prejudicing his/her further treatment.

The investigator must ensure that patient's anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs patients will not be identified by their names, but by an identification code. The investigator should keep a patient enrolment log showing codes, names and addresses.

A statement of MRC policy on ethical considerations in clinical trials of cancer therapy, including the question of informed consent, is available from the MRC Head Office web site (<http://www.mrc.ac.uk>).

## **13. ANCILLARY STUDIES**

### **13.1 Patient-Reported Outcomes**

There are limited patient-reported data (Quality of Life (QL) scores) on symptoms and morbidities associated with treatments after radical prostatectomy. No single questionnaire can adequately collect data in all of these areas. Therefore, patients will be asked to complete a number of short questionnaires.

Patient-reported outcome data will be collected from patients in the Radiotherapy Timing Randomisation in the UK and Canada, at least, via self-administered questionnaires. The questionnaires will assess general quality of life and health economics (SF-12, EQ-5D), urinary function (ICSmaleSF), bowel function (Vaizey) and sexual function (SHIM: IIEF-5).

The main objectives of this study are to determine the impact of:

- RT on general QL, sexual function, urinary function and bowel function
- Duration of hormone therapy on general quality of life, and sexual function

QL will be assessed prior to randomisation and at 1, 5 and 10 years. A separate quality of life protocol describes the study in more detail (see Appendix A VI).

### **13.2 Health economics**

It is expected that clinical and quality of life issues will primarily drive the interpretation of trial results. However, data will be collected to allow potential health economic analyses. The trial will collect core data on resource use (treatments, in-patient and out-patient hospitalisations), and patients will regularly complete EQ-5D questionnaires which will generate preference-based measures of quality of life for possible calculation of quality-adjusted life-years. The trial will take around a decade to mature given the usually good prognosis of this patient group. A separate sub-protocol will be developed prior to any planned analyses.

### **13.3 Translational research**

Optional translational studies will be planned and introduced early during the trial, subject to funding applications. The protocol will be amended appropriately to reflect any changes regarding translational studies.

## **14. APPROVALS AND INDEMNITY**

### **14.1 Ethics approvals**

The trial protocol has received the favourable opinion of a main Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries. Local ethics approvals and other related documentation required are detailed in local Appendix B.

### **14.2 Regulatory Approval**

This is a trial of Investigational Medicinal Products (IMPs) and therefore must be approved by the national competent authority. Details of national approvals are given in local Appendix B.

### **14.3 Indemnity**

Each collaborating group has ensured that appropriate arrangements for indemnity to cover the liability of the investigator, including insurance where necessary, have been made according to their national guidelines. See guidelines in local Appendix B.

## **15. TRIAL COMMITTEES**

### **15.1 Trial Management Group (TMG)**

A Trial Management Group (TMG) has been formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the Data Centres. The TMG will be responsible for the day-to-day running and management of the trial and will meet at least 3 times a year by teleconference. Further details of TMG functioning are presented in the TMG charter.

### **15.2 Trial Steering Committee (TSC)**

The Trial Steering Committee (TSC) has membership from TMG plus independent members, including the chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC charter.

### **15.3 Independent Data Monitoring Committee (IDMC)**

The Independent Data Monitoring Committee (IDMC) is the only group who sees the confidential, accumulating data to the trial. Reports to the IDMC will be produced by the MRC CTU statisticians. The IDMC will meet within 6 months of the trial opening with the frequency of meetings dictated by the IDMC. The IDMC will consider data in accordance with the analysis plan (see Section 9.5) and will be advisory to the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm be discontinued.

Further details of IDMC functioning, and the procedures for interim analysis and monitoring are provided in the IDMC charter.

### **15.4 Endpoint Review Committee (ERC)**

The Endpoint Review Committee will be a small group, comprising at least one person blind to allocated treatment, will review the primary outcome measure (prostate cancer deaths). Details of the criteria and principles are part of the analysis plan which is in Section 9.5.

### **15.5 Quality of life Subgroup**

The Quality of Life Subgroup issues guidance surrounding quality of life, including selection of the quality of life tools, and guidance on administration of the questionnaire.

### **15.6 Radiotherapy Quality Assurance Subgroup**

The Radiotherapy Quality Assurance Subgroup developed the RT quality assurance (QA) plan and issued guidance on delivering RT in this trial.

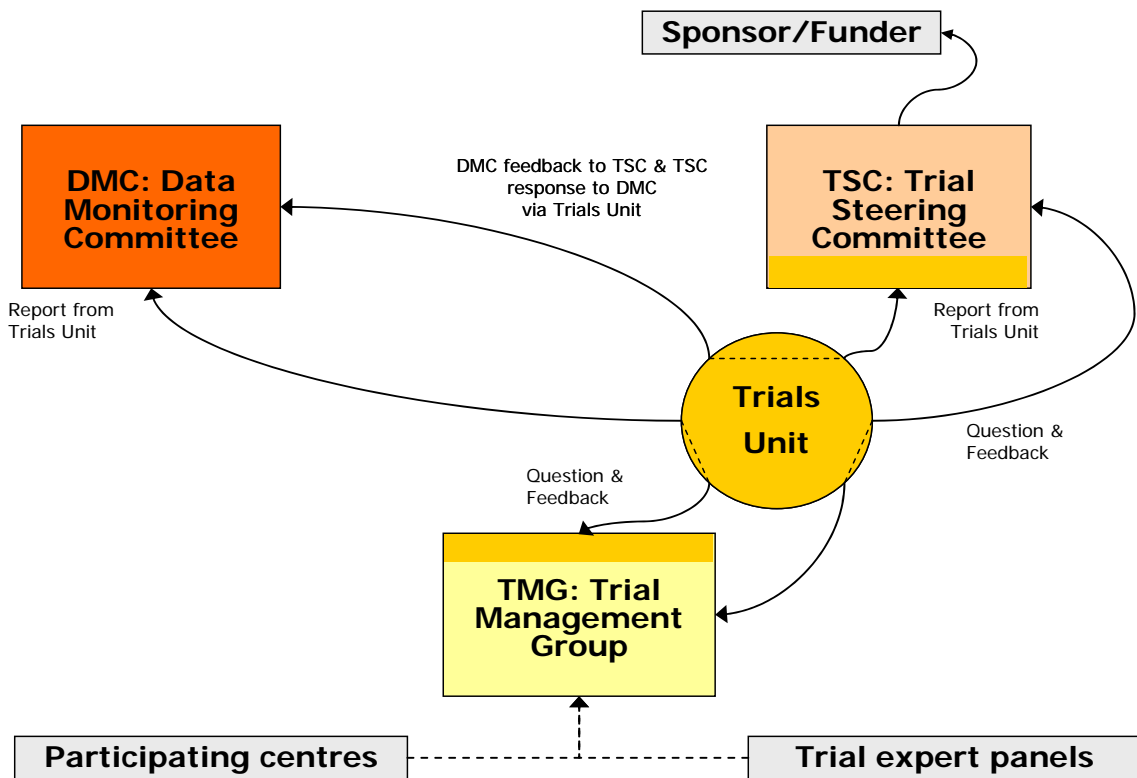
### **15.7 Pathology Quality Assurance Subgroup**

The Pathology Quality Assurance Subgroup developed the pathology QA plan and issued guidance on reporting pathology for trial.

### **15.8 Translational Studies Group**

The Translational Studies Group aim to develop and implement appropriate and high quality bolt-on studies.

Figure 5. Diagram of relationships between trial committees



## **16. PUBLICATION POLICY**

The results from different centres and participating groups will be analysed together and published as soon as possible. Individual groups/clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study until the Trial Management Group has published its report. The Trial Management Group will form the basis of the Writing Committee and will advise on the nature of all publications.

## 17. PROTOCOL AMENDMENTS

This is version 4.0 of the protocol.

### 17.1 Protocol

#### 17.1.1 Amendments made to Protocol version 1.0 March 2007

1. Page ii – CTA reference added
2. Page iii – Ethics information removed
3. Page iii – Colleen Savage replaced as Intergroup Affairs Study Coordinator by Andrea Hiltz
4. Page 3 – Radiotherapy Quality Assurance added to list of Appendix B contents
5. Section 6.1.3.5 – Dose and volume objectives in Tables 3 and 4 changed
6. Section 10.3 – Reference to section 10.3 removed
7. Section 11.2 – Sentence added to remind that routine toxicities should be reported as SAEs
8. Section 11.4 - <CRF name> updated to Follow-up Form (CRF6) in Figure 4

#### 17.1.2 Amendments made to Protocol version 1.1 June 2007

1. Page ii – Lillian Tsang replaced as Data Manager by Lindsey Masters
2. Page iii – Fred Saad added as a NCIC CTG Medical Expert
3. Section 1.1.1 – Explanation of three-way and two-way randomisation added
4. Section 1.1.3.2 – Information on free Eligard supply for patients in Canada removed
5. Section 4 – Prior hormone therapy removed from main entry exclusion criteria
6. Section 4 – Neoadjuvant treatment removed from main entry exclusion criteria
7. Section 4 – Hypogonadism removed from main entry exclusion criteria
8. Section 4 – Hormone therapy within previous 6 months added to main entry exclusion criteria
9. Section 4 – Radiotherapy Timing Randomisation exclusion criterion changed to more than 5 months since radical prostatectomy and a clarification that trial treatment should ideally start within 5 months after surgery added
10. Section 4 – Within 3 months after radical prostatectomy removed from Radiotherapy Timing Randomisation inclusion criteria
11. Section 4 – Hormone Duration Randomisation exclusion criteria changed from PSA > 10ng/ml to 5ng/ml
12. Section 5.2 – Randomisation CRF numbers updated to 1a, 1b, 2 and 3 or 4
13. Section 5.3 – Overall Summary of trial updated to include patients allocated to deferred RT with no PSA rise
14. Section 6.1.3.3 – Guidance added to title of treatment volumes section
15. Section 6.1.3.4 – Text changed to 'minimal dose to the PTV not less than...'
16. Section 6.2.2 – Eligard information for patients in Canada removed
17. Section 6.2.2.1 – Information on free Eligard supply for patients in Canada removed
18. Section 6.2.3 – Eligard information for patients in Canada removed
19. Section 6.2.3.1 – Information on free Eligard supply for patients in Canada removed
20. Section 7.1 – Numbering of Baseline Information Form changed to 1b
21. Section 7.1 – Patient History Form (CRF1b) added

### 17.1.3 Amendments made to Protocol version 2.0 January 2008

1. Section 6.1.3.2 – Statement added to confirm that Intensity-Modulated Radiation Therapy (IMRT) may be used.
2. Section 6.1.3.3 – Statement added to clarify that treatment volumes are for guidance only.
3. Section 6.1.3.5 – Tables 3 & 4 – Dose volume objectives for the bladder have been updated as follows:
 

<i>Dose</i>	<i>Volume Objective</i>
50Gy	80%
60Gy	50%
4. Section 10.2 – Updated explanation of the role of the radiotherapy quality assurance (RTQA) group and requirements for the RTQA process.

### 17.1.4 Amendments made to Protocol version 2.2 December 2008

1. Page ii – Lindsey Masters replaced by Ben Spittle as Data Manager
2. Page ii – Gordana Jovic included as Statistician
3. Page iii – NCIC CTG funder renamed Canadian Cancer Society – Research Institute
4. Section 1.1 and throughout document – immediate radiotherapy now referred to as early radiotherapy and early salvage radiotherapy policy now referred to as deferred radiotherapy.
5. Section 1.1 and throughout document – 5 months changed to 22 weeks for clarity.
6. Section 1.1 – Clarification that patients joining the Radiotherapy Timing Randomisation and allocated to early radiotherapy are encouraged to but not required to also join the Hormone Duration Randomisation.
7. Section 1.1.3.2 – Clarification of the possibility to randomise between all three arms or two of the three arms of the Hormone Duration Randomisation including diagrams (Figure 3).
8. Section 4 – Patient inclusion and exclusion criteria
  - i. Clarification that *pre-operative* hormone therapy within previous 6 months is an exclusion criterion
  - ii. Addition of clarification that previous pre-operative hormone therapy for longer than 8 months is an exclusion criterion as is any post-operative hormone therapy
  - iii. Addition of more specific inclusion criteria for Radiotherapy Timing Randomisation
  - iv. Change of inclusion criterion from PSA  $\leq 0.4\text{ng/ml}$  to  $\leq 0.2\text{ng/ml}$
9. Section 4.1 – Addition of Timing of Investigations table for Hormone Duration Randomisation and change of requirements for bone scans.
10. Section 5.1.1 – correction of typographical error – randomisation should be performed with five months after radical prostatectomy.
11. Section 5 – Removal of overall trial design Figure – now in Appendix A
12. Section 6.1 – Clarification that treatment with radiotherapy or hormone therapy will commence within two months of the randomisation.
13. Section 6.1.1 – Clarification that patients allocated to early radiotherapy in the Radiotherapy Timing Randomisation can also join the Hormone Duration Randomisation if they wish or the use of hormones can be decided by the investigator.
14. Section 6.1.3 – Additional clarification that radiotherapy should start within approximately two months of randomisation.
15. Section 6.1.3.3 – Clarification of formula to calculate % SV involvement risk.

16. Section 6.2 – Clarification that radiotherapy should ideally start within 2 months after randomisation and that radiotherapy should begin 2 months after hormone therapy.
17. Section 6.2 – Clarification that bicalutamide monotherapy is not approved for use in Canada.
18. Section 6.2.2 – Inclusion of degarelix as acceptable treatment for 6 months
19. Section 6.5 – Removal of sentence regarding study specific drug logs for study medication in Canada.
20. Section 13.1 – Inclusion of Canada in patient-reported outcomes study.

### **17.1.5 Amendments made to Protocol version 3.0 October 2009**

1. Page i – Amendment made to show compliance with principles of GCP.
2. Page i – Sponsor address updated.
3. Page i – Danish and Irish sites included as MRC CTU sites.
4. Page ii – Clarification that Cancer Research UK and Medical Research Council are funding the trial in the UK.
5. Page ii - Ben Spittle replaced by Paul Patterson as Data Manager
6. Page ii – MRC CTU address updated.
7. Section 1.1 and throughout document – Radiotherapy Timing Randomisation and Hormone Duration Randomisation also referred to as RADICALS-RT and RADICALS-HD.
8. Section 1.1.4 – Outcome measures listed separately for RADICALS-RT and RADICALS-HD
9. Section 1.1.4.1 – RADICALS-RT primary outcome measure changed to freedom from distant metastases and disease-specific survival added to list of secondary outcome measures.
10. Section 1.1.4.2 – Number of patients required for each randomisation amended.
11. Section 1.1.5 – Addition of up to 6<sup>1</sup>/<sub>2</sub> years of accrual and 6 to 7 years of follow-up.
12. Section 2.1 – Updated data from other sources added.
13. Section 2.2 – Updated data from other sources added.
14. Section 2.3 – Updated data from other sources added.
15. Section 2.4 – Updated data from other sources added.
16. Section 2.5 – Addition of information on other ongoing relevant studies and trials.
17. Section 4 – Clarification that RADICALS-RT randomisation should ideally be more than 4 weeks and less than 22 weeks after radical prostatectomy.
18. Section 4 - Clarification that patients joining short-term vs. long-term hormones comparison may have post-operative hormone therapy prior to randomisation but this must be discussed with the trial team.
19. Section 4.1 – 4 weeks changed to 30 days for clarity.
20. Section 4.1 – Clarification that bone scan is only required if Gleason score is ≥8 and post-operative PSA is detectable.
21. Section 5.1.1 – Clarification that RADICALS-RT randomisation should ideally be performed within 22 weeks of surgery.
22. Section 6.1 – Clarification that treatment section is guidance.
23. Section 6.2 – Clarification that treatment section is guidance.
24. Section 6.2.2 – Inclusion of degarelix as acceptable treatment in Canada.
25. Section 6.2.2.1 - Inclusion of degarelix as acceptable treatment in Canada.
26. Section 6.2.3 - Inclusion of degarelix as acceptable treatment in Canada.
27. Section 6.2.3.1 - Inclusion of degarelix as acceptable treatment in Canada.
28. Section 6.3 – Removal of progression whilst on therapy as a reason to stop trial treatments.
29. Section 6.7 – Addition of freedom from distant metastases as a primary outcome measure.
30. Section 7.1 – Clarification that Comorbidity form (CRF2) should be completed two weeks prior to randomisation.

31. Section 7.2.2 – Addition of information about change of primary outcome measure for RADICALS-RT and clarification that bone scans are not mandated.
32. Section 9.1 – Addition of clarification that each comparison will have an independent randomisation programme.
33. Section 9.2.1 – Addition of information on new primary outcome measure for RADICALS-RT and reasons for change.
34. Section 9.2.3 – Addition of disease-specific survival as secondary outcome measure for RADICALS-RT only.
35. Section 9.3 – Updated information on sample size calculations for RADICALS-RT and RADICALS-HD and the comparisons in RADICALS-HD.
36. Section 9.5 – Statistical Analysis Plan information updated by moving information on planned comparisons in RADICALS-HD to new sections 9.3.3.1 and 9.3.3.2.
37. Section 9.6 – Addition of information on planned individual patient data meta-analyses.
38. Section 11.3 – CRF numbering corrected.
39. Section 15.3 – Updated information as IDMC has now been formed.

## **17.2 Appendices**

### **17.2.1 Amendments made to Appendix A version 1.0 March 2007**

1. Section Av – Heading spelling corrected from GUIDENCE to GUIDANCE
2. Section Avii – Colleen Savage replaced as Trial Manager by Andrea Hiltz and Chris Morash replaced as Urologist by Fred Saad.

### **17.2.2 Amendments made to Appendix B version 1.0 March 2007**

1. Section Bi – Model agreement for non-commercial research, GP letters and Accreditation Form I added to required documentation and requirements for radiotherapy quality assurance added.
2. Section Bii – Model agreement for non-commercial research added to contents of commitment form, telephone number updated and Investigators Statement, Contact Details Sheet and Delegation Log removed.
3. Section Biii – Radiotherapy quality assurance appendix added and numbering of subsequent sections changed.
4. Section Biv.2 – CTA reference added

### **17.2.3 Amendments made to Appendix A version 1.0 June 2007**

1. Section Av – Updated guidance flow diagram added
2. Section Avii – New trial committee members added

### **17.2.4 Amendments made to Appendix B version 1.1 June 2007**

1. Section Bii – Accreditation pack name changed to Site Specific Approval pack
2. Section Biii – Radiotherapy quality assurance guidance added
3. Section Bviii – Patient Information Sheet split into two sheets, one for patients entering both randomisations and one for the hormone duration randomisation only. Some minor wording changed and version changed to 3.0, January 2008
4. Section Bix – Consent Form split into two sheets, one for patients entering both randomisations and one for the hormone duration randomisation only. Consent statements added to clarify MRC CTU employees will have access to records, that name and NHS number will be taken and for participation in the quality of life study. Version changed to 2.0, January 2008.

#### **17.2.5 Amendments made to Appendix A version 2.0 January 2008**

1. Section Avi – Statement regarding non-participation of Canadian centres in the quality of life study removed.

#### **17.2.6 Amendments made to Appendix A version 2.2 December 2008**

1. Section Ai – Addition of overall trial design figure.
2. Section Aiii – Removal of WHO performance status table as grading is not required for data collection.
3. Section Av – Updated flow diagram depicting criteria for suitable patients for each radiotherapy groups. This is reflected in the updated eligibility criteria in section 4 of the protocol.
4. Section Avii – Addition of Angela Lee to trial committee and Lindsey Masters replaced by Ben Spittle as Data Manager.

#### **17.2.7 Amendments made to Appendix B version 2.1 December 2008**

1. Section Biv – Updated GP letters with amended wording and specification of which patient group each are applicable to. Version updated to v3.0.
2. Section Bv – SSA replaced with R&D approval.
3. Section Bviii – Patient Information Sheets amended to relate to each separate randomisation and introduction to section added.
4. Section Bix – Updated consent forms for each separate randomisation and introduction added.
5. Section Bix.2 – Removal of question 8 regarding quality of life study as this is not applicable to these patients.

#### **17.2.8 Amendments made to Appendix A version 3.0 October 2009**

1. Section Av – Clarification of patient selection for RADICALS-RT
2. Section Av – Updated PSA value from >0.1 to >0.2.
3. Section Avi – Blank version number and date removed.
4. Section Avii – Trial Committee Members list updated

#### **17.2.9 Amendments made to Appendix B version 3.0 October 2009**

1. Section Bii – MRC CTU address updated
2. Section Biii – MRC CTU address updated
3. Section Biv – Date and version of document added and date of letter space clarified.
4. Section Bviii – Date and version of patient information sheets updated.
5. Section Bviii – Information about sample size and recruiting countries updated.
6. Section Bix – Date and version of consent forms updated
7. Section Bix – Date and version of patient information sheets referred to updated.

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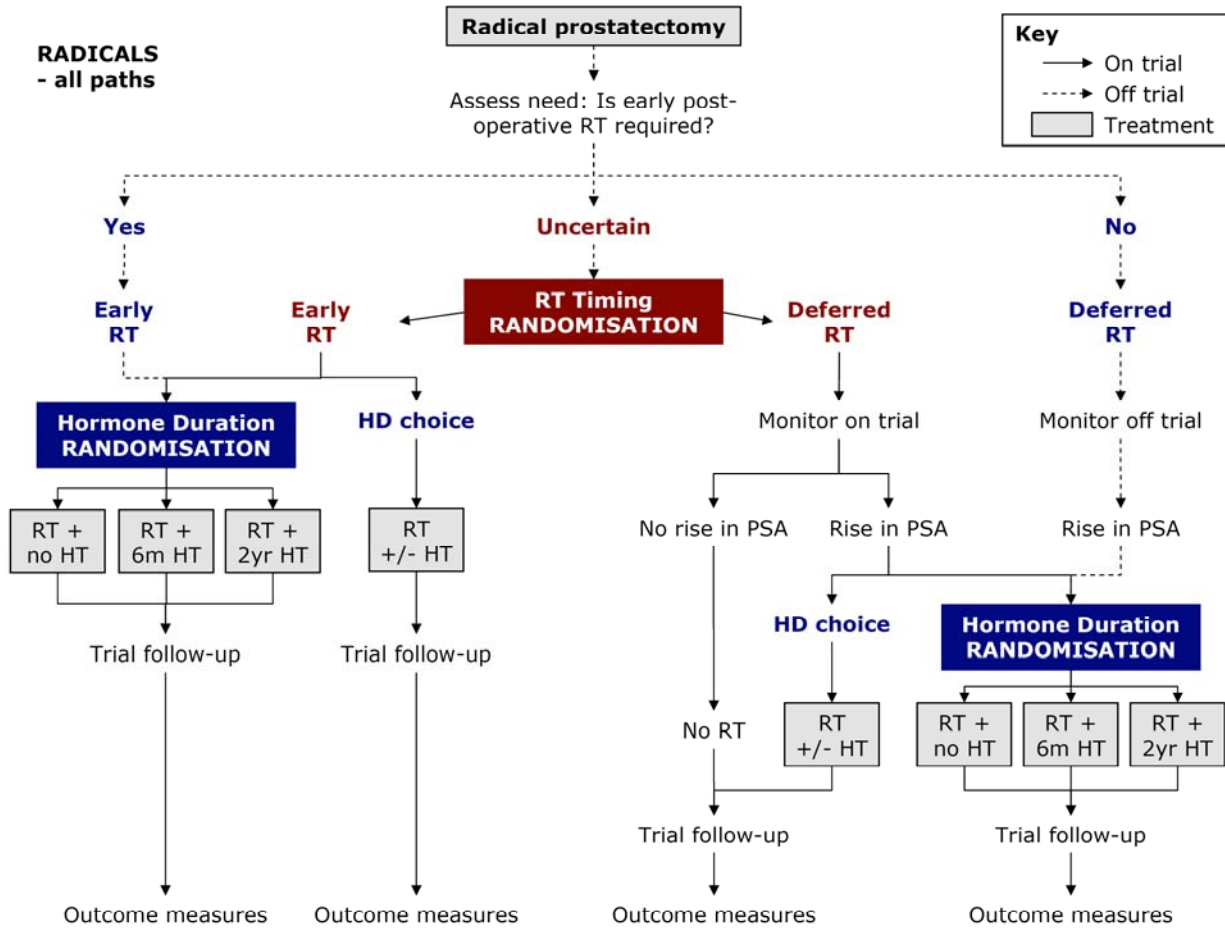
# APPENDIX A

## Common Appendix

### CONTENTS

<b>A I: Potential Pathways through RADICALS .....</b>	<b>2</b>
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# A 1: POTENTIAL PATHWAYS THROUGH RADICALS



Depictions of all possible paths are available from MRC CTU.

## **A II: SURGICAL QUALITY ASSURANCE**

In general, quality assurance (QA) of surgery in radical prostatectomy is poorly defined with no significant studies that report on the standard of surgical quality in the treatment of clinically localised prostate cancer. The only study published with regard to EORTC genitor-urinary (GU) centres carrying out radical prostatectomy was reported in the European Journal of Cancer 2001 (H Van Poppel et al). In this study the quality parameters were as follows: blood loss; duration of surgery; pathological margin status; serum PSA at three months; incontinence status at catheter withdrawal and after three months.

There are several entry points into the RADICALS trial, and collecting quality assurance data months or years after surgery would be difficult. However, some of the quality assurance data will be collected post-operatively, for example from the pathology report.

## A III: TOXICITY TABLE

### RTOG Toxicity

#### Instructions:

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused death of the patient.
4. Refer to detailed toxicity guidelines in the protocol, or to RTOG Headquarters for toxicity not covered on this table.
5. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
6. An accurate baseline prior to start of therapy is necessary.

Toxicity	Grade				
	0	1	2	3	4
Diarrhoea	None	Increase of 2-3 stools per day over pre-Rx	Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools/day or incontinence or severe cramping	Increase of $\geq 10$ stools/day or grossly bloody diarrhoea, or need for parenteral support
Proctitis	None	Increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	Increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	Increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	Perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Cystitis	None	Mild	Moderate	Severe	Life-threatening
Haematuria	None	Micro only	Gross/no clots	Gross + clots	Requires transfusion
Urethral stricture	None	-	-	Urethral stricture	-

The Common Toxicity Criteria for Adverse Events (CTCAE) can be downloaded from <http://ctep.cancer.gov/forms/CTCAEv3.pdf>

## A IV: TNM STAGING

pT: Pathological Tumour stage

pN: Pathological Regional lymph nodes

M: Systemic spread

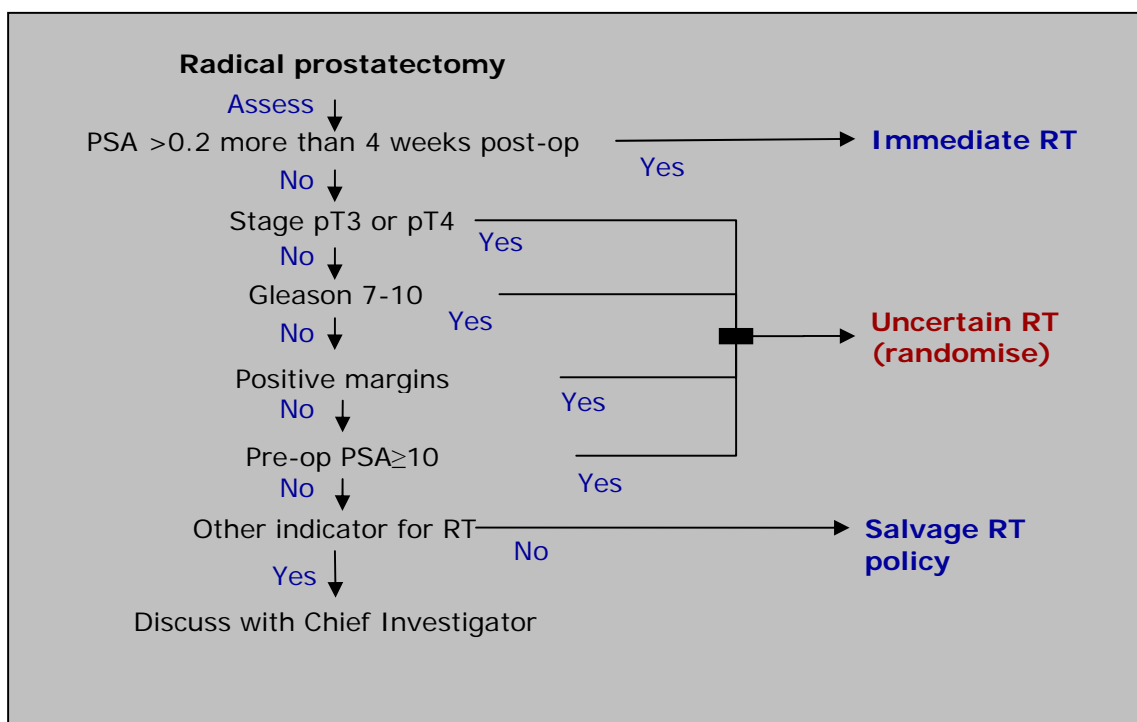
Tumour Stage	Sub-stage	Definition
<b>pT2</b>	pT2a	<b>Confined within the prostate (detectable by DRE)</b> Tumor involves half of the lobe or less
	pT2b	Tumor involves more than one half of one lobe but not both lobes
	pT2c	Tumor involves both lobes
<b>pT3</b>	pT3a	<b>Tumor extends through the prostate capsule but has not spread to other organs</b> Unilateral extracapsular extension
	pT3b	Bilateral extracapsular extension
	pT3c	Tumor invades seminal vesicle(s)
<b>pT4</b>	pT4a	<b>Tumor is fixed or invades adjacent structures other than seminal vesicles</b> Tumor invades bladder neck and/or external sphincter and/or rectum
	pT4b	Tumor invades levator muscles and/or is fixed to pelvic wall

Nodal Stage	Sub-stage	Definition
<b>pN0</b>	-	No lymph nodes metastasis
<b>pN1</b>	-	Metastasis in single lymph node <2 cm in greatest dimension
<b>pN2</b>	-	Metastasis in single lymph node >2cm but <5 cm in greatest dimension, or multiple lymph nodes, none >5 cm
<b>pN3</b>	-	Metastasis in lymph node >5 cm in greatest dimension

Metastasis Stage	Sub-stage	Definition
<b>M0</b>	-	No distant metastasis
<b>M1</b>	M1a	Non-regional lymph node metastasis
	M1b	Bone metastasis a) Axial skeleton only b) Extending to peripheral
	M1c	Metastasis at other sites

## A V: PATIENT SELECTION – RADICALS-RT

Allocation of patients to the immediate, uncertain or deferred radiotherapy groups will be dependent on which criteria the patients meet. The diagram, below, shows how patients should be selected for the radiotherapy groups. If there is uncertainty as to which group patients should be in, please discuss with the Chief Investigator.



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## A VI: QUALITY OF LIFE

(To be presented on local headed paper)

### Quality Of Life Questionnaires - An Explanation

Trial Number	
--------------	--

Version 3.0, November 2008

**Acronym and title of study: RADICALS: Radiotherapy and Androgen Deprivation In Combination After Local Surgery**  
**ISRCTN: 40814031**

#### About your questionnaire

We think it is important to find out how patients feel, both physically and emotionally, during and after treatment. In order to collect this information, we have designed a brief questionnaire. We would like you to complete this questionnaire before, during and after your treatment.

The questionnaire asks how you have been feeling during the past week, and is designed to assess your day-to-day wellbeing, as well as asking about any side-effects you may be experiencing. Your completed questionnaires will be sent to the Medical Research Council Clinical Trials Unit where they will be treated in confidence and analysed together with those from patients in other hospitals to help plan future treatments.

We ask about a range of symptoms as the questionnaire is designed for use in many areas of cancer research. Please feel free to discuss any symptoms or concerns with your doctor.

#### Completing the questionnaire

If possible, complete the questionnaire on your own. Please make sure the correct date is written at the top before you start. Try to answer all the questions but do not spend too much time thinking about each answer, as your first response is likely to be the most accurate. If a question does not apply to you, please write alongside "not applicable" or "NA" for short, but do not leave any question blank.

When you attend hospital for the first time, you will be asked to complete a questionnaire. We would like you to complete further questionnaires a year later, 5 years and then 10 years later. If you are not given a questionnaire, please remind your doctor. You can, of course, decline to complete the questionnaire at any time without affecting your relationship with your doctor.

Thank you for your help.

## A VII: TRIAL COMMITTEE MEMBERS

Name	Role	Site	TMG	QL	HE	RTQA	Path	Trans
Chris Parker	Chief Inv; Oncologist	Royal Marsden Hosp & Inst Cancer Res	✓	✓	✓	✓	✓	✓
Charles Catton	Oncologist	Princess Margaret Hospital, Toronto	✓			✓		
Noel Clarke	Urologist	Salford Hospitals, Manchester	✓					
William Cross	Urologist	St. James's Institute of Oncology	✓					
Andrea Hiltz	Trial Manager	NCIC Clinical Trials Group	✓					
Howard Kynaston	Urologist	University Hospital Wales, Cardiff	✓					
Angela Lee	Clinical Nurse Specialist	Queen's Hospital, Romford	✓					
John Logue	Oncologist	Christie Hospital	✓			✓		
Ralph Meyer	Director, NCIC CTG	NCIC Clinical Trials Group	✓					
Ian Jamieson	Research Partner	Bath, UK	✓					
Gordana Jovic	Statistician	MRC Clinical Trials Unit	✓					
Peter Meidahl	Oncologist; Danish PI	Rigshospitalet, Copenhagen	✓					
Claire Murphy	Trial Manager	MRC Clinical Trials Unit	✓	✓	✓	✓	✓	✓
Wendy Parulekar	Physician Coordinator	NCIC Clinical Trials Group	✓					
Paul Patterson	Data Manager	MRC Clinical Trials Unit	✓					
Heather Payne	Oncologist	University College Hospital, London	✓			✓		
Raj Persad	Urologist, Surgical Champion	Bristol Royal Infirmary	✓					
George Rodrigues	Oncologist	London Regional Cancer Prog., Ontario	✓					
Fred Saad	Urologist	University of Montreal	✓					
Mike Sawkins	Research Partner	Surrey, UK	✓					
Matthew Sydes	Project Lead; Trial Stat	MRC Clinical Trials Unit	✓	✓	✓	✓	✓	✓
Colin Cooper	Trans Researcher	Institute of Cancer Research, Sutton						✓
Alistair Henderson	Urologist; QL expert	St Luke's Cancer Centre, Guildford		✓				
Rollo Moore	Physicist	Royal Marsden Hospitals				✓		
Mark Sculpher	Health Economist	University of York			✓			
Richard Stephens	Senior Statistician	MRC Clinical Trials Unit		✓				
Murali Varma	Pathologist	University Hospital Wales, Cardiff					✓	

### Key

TMG = Trial Management Group

QL = Quality of Life Group

HE = Health Economics Group

RTQA = Radiotherapy Quality Assurance Group

Path = Pathology Group

Trans = Translational Research Group

# APPENDIX B

## Local Appendix

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## **B I: SITE ACCREDITATION PROCEDURES**

### **Institution Approval Process**

To participate in the RADICALS trial, Investigators and trial centres must be registered with the RADICALS Trial Manager at MRC CTU and must fulfil the set of basic criteria which can be found in Section 3 of the main protocol.

Those centres that meet the criteria for RADICALS will be issued with the RADICALS site file documentation to apply for their Site Specific Approval (SSA) and MRC CTU accreditation documents. A radiotherapy quality assurance exercise must also be completed.

Each selected centre must provide the following documentation to the MRC CTU:

- Completed RADICALS Commitment Form consisting of:
  - Completed investigator statement (signed by the institution PI)
  - Full contact details for all trial associated site personnel
  - Completed delegation log (signature list and delegation of responsibilities)
  - Model agreement for non-commercial research
- CV for each participating investigator
- Confirmation of favourable site-specific assessment (SSA)
- Confirmation of local Research and Development (R&D) approval
- A copy of the most recent version of the patient information sheets, consent form and GP letters on local headed paper
- Completed site file self-assessment form
- RADICALS Accreditation Form I

Up-to-date copies of these must be stored in the local site file and also at MRC CTU. Once all of this documentation has been received, confirmation of institution approval will be sent to the Principal Investigator at each institution by the trial team at the MRC CTU.

The Clinical Trial Authorisation (CTA) for the RADICALS trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating investigators/centres. Trial staff at the MRC

CTU will perform the task; hence it is vital to receive full contact details for all investigators prior to their entering patients.

A radiotherapy quality assurance exercise makes up part of the RADICALS accreditation process (see appendix BIII). To complete this, the following documentation must be provided:

- RADICALS Accreditation Form II
- RT Credentialling Form (x2 + outline examples for 2 past patients)

Centres wishing to be accredited should ensure that the centre giving radiotherapy to patients has completed the radiotherapy quality assurance exercise.

On receipt of the above documents at the MRC CTU, written confirmation will be sent to the Principal Investigator and to the first point of contact to confirm that their centre has been approved to randomise patients.

## **B II: COMMITMENT FORM**

The RADICALS commitment form must be completed by all centres wishing to participate. This consists of 4 parts:

- Investigator Statement
- Signature list and delegation of responsibilities
- Full contact details for all site personnel
- Model agreement for non-commercial research

### **Investigator Statement**

Completed by the principal investigator at each participating institution and sent to MRC CTU before entering any patients into this study.

### **Signature list and delegation of responsibilities**

Completed by all trial staff and sent to MRC CTU before entering any patients to this study. This must be updated whenever there are changes to trial staff.

### **Full contact details list for site personnel**

Contact details are required for

- Clinicians responsible for medical care of patients
- Staff responsible for CRF completion

### **Model Agreement for non-commercial research**

Signed by a representative of the trust as a contract between the trust and the Medical Research Council.

The commitment form can be found in the RADICALS site specific approval pack which can be requested from the trial office. For more information, contact:

RADICALS Trial  
MRC Clinical Trials Unit  
Aviation House  
125 Kingsway  
London WC2B 6NH  
Tel: 020 7670 4747  
Email: radicals@ctu.mrc.ac.uk

## **B III: RADIOTHERAPY QUALITY ASSURANCE**

The RADICALS radiotherapy quality assurance exercise is part of the accreditation process (see appendix BI). It involves centres providing information about radiotherapy at their centre, or the centre where radiotherapy would be administered, and sending outline examples of two previous patients who would have been eligible for RADICALS to be reviewed. Figure 1 shows the flowchart to be used to guide centres through the radiotherapy quality assurance process.

Centres wishing to randomise patients who will receive radiotherapy treatment at another centre should ensure that this centre completes the radiotherapy quality assurance exercise.

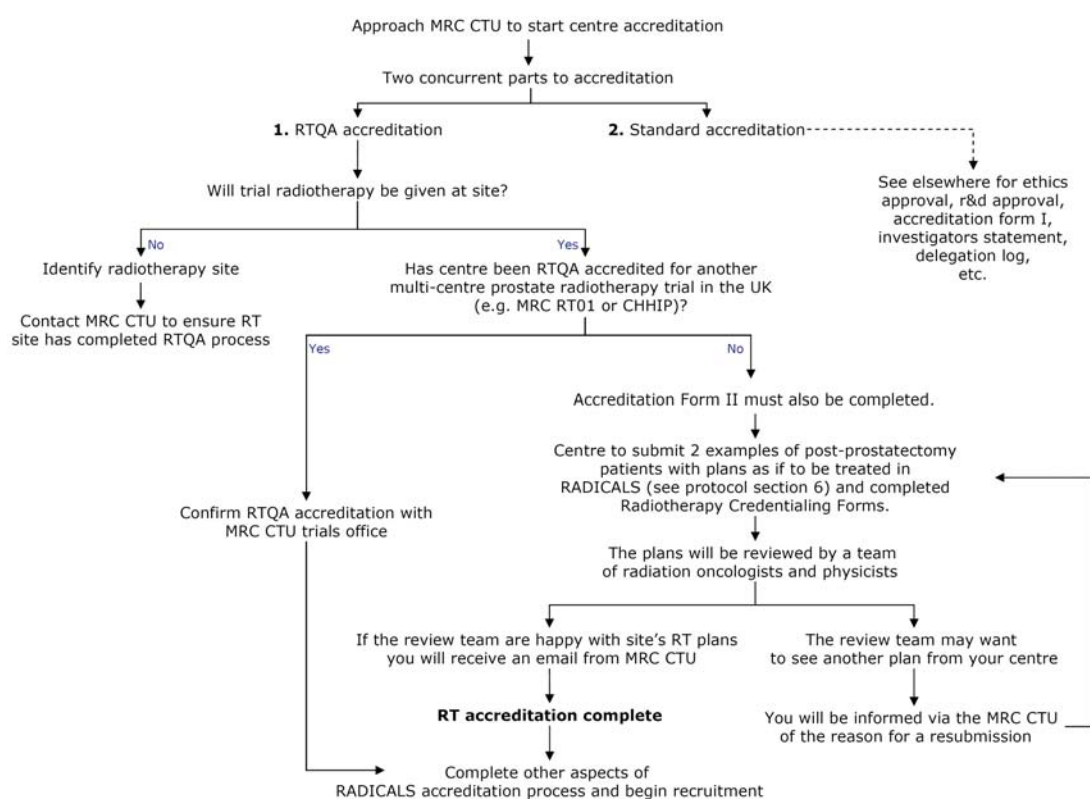
### **Accreditation Form II**

This form should be completed by the radiotherapy centre to provide us with details of equipment and treatment.

### **RT Credentialling Form**

Centres should choose two patients previously treated at their centre that would have been eligible for RADICALS. This is an exercise for us to check that radiotherapy planning is being carried out correctly. The submitted plan should conform to the guidelines set out in Table 3 or 4.

Figure 1: Radiotherapy Quality Assurance Flowchart



Centres must submit 2 anonymous examples of post-prostatectomy patients with plans as if to be treated in RADICALS (see protocol section 6) and completed Radiotherapy Credentialling Forms.

The plans should be either:

- existing plans for patients who have already been treated to the protocol specifications or
- new plans for patients suitable for RADICALS who were previously treated to a different specification

We ask for centres to send 3 printed copies for review, to consist of:

- All CT slices from 1 slice superior to 1 slice inferior of the PTV (or at least images every 5mm). Also sagittal and coronal reconstructions through the isocentre.

- Include CTV, PTV and normal tissue contours on each image (Note: please provide contour outlines rather than solid colourwash to enable review of outlines against CT data)
- Include appropriate isodose contours on at least the 3 planes through the isocentre (50%, 70%, 90%, 95%, 100%, 105%)
- DVH graph for PTV and normal tissues

### **RADICALS Post-accreditation RTQA guidelines**

Radiotherapy centres that have completed and passed a radiotherapy quality assurance exercise for a trial of radiotherapy for men with prostate cancer e.g. RT01 or CHHIP, are not required to complete the RADICALS RTQA exercise.

These centres should complete the standard accreditation documents and provide the trial office with the name of the trial for which RTQA was completed and passed.

The trial office will then confirm that the centre has been accredited by email and all the relevant documents will be sent by post.

Once the centre has been accredited, the RADICALS team will ask them to participate in a post-accreditation RTQA review. The centre is asked to submit RT plans for the first two patients randomised to RADICALS plus Radiotherapy Credentialling Forms. The plans should be identified only by the RADICALS trial numbers. Centres may find it a helpful exercise to receive feedback from the RADICALS team on their first RADICALS patients without impeding further recruitment to the trial.

When submitting post-accreditation RT plans, for each patient we ask for 3 printed copies for review, to consist of:

- All CT slices from 1 slice superior to 1 slice inferior of the PTV (or at least images every 5mm). Also sagittal and coronal reconstructions through the isocentre.

- Include CTV, PTV and normal tissue contours on each image (Note: please provide contour outlines rather than solid colourwash to enable review of outlines against CT data)
- Include appropriate isodose contours on at least the 3 planes through the isocentre (50%, 70%, 90%, 95%, 100%, 105%)
- DVH graph for PTV and normal tissues

The plans should be sent to: RADICALS Trial, MRC Clinical Trials Unit, Aviation House, 125 Kingsway, London WC2B 6NH.

They will be sent to an oncologist and a physicist for review and the trial team will feed back the reviewer's comments to the centre. If the reviewers have any issues about the plans that they may wish to discuss with the centre, they will be contacted and possibly be asked for plans of the second randomised patient to be submitted.

## B IV: GP LETTERS

### B IV.1 Radiotherapy Timing Randomisation

This letter is only for patients joining the Radiotherapy Timing Randomisation only at this time point.

**(To be presented on local headed paper)**

Centre Number: xxx

Trial Number: xxxxx

Date and version: June 2011, V4.0

Date of letter: dd/mm/yyyy

Dear Dr \_\_\_\_\_

**RADICALS: Radiotherapy and Androgen Deprivation In Combination After Local Surgery (ISRCTN40814031)**

Your patient, \_\_\_\_\_ (date of birth dd/mmm/yyyy), has consented to be entered to the above trial.

Your patient has been allocated to receive:

Early Radiotherapy

Deferred Radiotherapy

Please find enclosed a copy of the patient information sheet for this trial.

You will be kept up to date with your patient's progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr \_\_\_\_\_ at \_\_\_\_\_ (Hospital)

Tel: \_\_\_\_\_

Kind regards,

Name  
Position

**B IV.2: GP Letter – Hormone Duration Randomisation**

This letter is only for patients joining the Hormone Duration Randomisation only.

**(To be presented on local headed paper)**

Centre Number (if applicable): xxx

Trial Number: xxxxx

Date and version: June 2011, V4.0

Date of letter: dd/mm/yyyy

Dear Dr \_\_\_\_\_

**RADICALS: Radiotherapy and Androgen Deprivation In Combination After Local Surgery (ISRCTN40814031)**

Your patient, \_\_\_\_\_ (date of birth dd/mmm/yyyy), has consented to be entered to the above trial.

Your patient has been allocated to receive:

Radiotherapy Alone

Radiotherapy + 6 months Hormone Therapy

Radiotherapy + 2 years Hormone Therapy


Please find enclosed a copy of the patient information sheet for this trial.

You will be kept up to date with your patient’s progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr \_\_\_\_\_ at \_\_\_\_\_(Hospital)

Tel: \_\_\_\_\_

Kind regards,

Name  
Position

**B IV.3: GP Letter – Both Randomisations**

This letter is only for patients joining both the Radiotherapy Timing and the Hormone Duration Randomisation simultaneously

**(To be presented on local headed paper)**

Centre Number (if applicable): xxx

Trial Number: xxxxx

Date and version: June 2011, V4.0

Date of letter: dd/mm/yyyy

Dear Dr \_\_\_\_\_

**RADICALS: Radiotherapy and Androgen Deprivation In Combination After Local Surgery (ISRCTN40814031)**

Your patient, \_\_\_\_\_ (date of birth dd/mmm/yyyy), has consented to be entered to the above trial.

Your patient has been allocated to receive:

Early Radiotherapy

and

Radiotherapy Alone

Radiotherapy + 6 months Hormone Therapy

Radiotherapy + 2 years Hormone Therapy

Please find enclosed a copy of the patient information sheet for this trial.

You will be kept up to date with your patient's progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr \_\_\_\_\_ at \_\_\_\_\_ (Hospital)

Tel: \_\_\_\_\_

Kind regards,

Name

Position

## **B V: ETHICS AND REGULATORY ISSUES**

The main ethical concerns are presented in the main protocol Section 12.

### **B V.1 Ethics**

In the UK, the trial has received favourable opinion from the main REC which is Royal Free Hospital and Medical School. Local R&D approval is required from each participating centre.

### **B V.2 Regulatory**

In this trial, hormone therapy is being used as an investigational medicinal product. A Clinical Trial Authorisation (CTA) has been obtained from the medicines Healthcare Products Regulatory Agency (MHRA). The CTA number is 00316/0223/001-0001.

## **B VI: INSURANCE**

The MRC and NHS are both publicly funded bodies and are not allowed to purchase advance insurance to cover indemnity because they are backed by the resources of the Treasury.

The MRC will give sympathetic consideration to claims for non-negligent harm suffered by a person as a result of trial or other work supported by MRC. This does not extend to liability for non-negligent harm arising from conventional treatment where this is one arm of a trial. The MRC acts as its own insurer and does not provide cover for non-negligent harm in advance for participants in MRC-funded studies.

Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in an MRC-supported study. MRC does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is a NHS Trust or not.

## **B VII: FINANCE**

There are no payments to sites, clinicians or patients for participating in RADICALS.

Both radiotherapy and hormone therapy are standard treatment and costs will therefore be picked up by the participating centre. The follow-up schedule fits in with routine practice so there will be no additional trial visits for patients, therefore no travel expenses will be paid for the trial.

The trial has been adopted by the National Cancer Research Network (NCRN) and so NCRN resources will be available.

## **B VIII: PATIENT INFORMATION SHEETS**

### **B VIII.1 Introduction**

There are two RADICALS patient information sheets (PIS).

- Patients eligible for the Radiotherapy Timing Randomisation according to section 4 of the protocol should receive the Radiotherapy Timing Randomisation **PIS** in section B VIII.2.
  - Patients that join the Radiotherapy Timing Randomisation and are allocated early radiotherapy can then join the Hormone Duration Randomisation if they wish but are not required to do so. If the patient does wish to participate in the Hormone Duration Randomisation as well, they should receive the Hormone Duration Randomisation PIS in section B VIII.3 soon after the first randomisation.
  - Patients that join the Radiotherapy Timing Randomisation and are allocated to deferred radiotherapy should be monitored. In the event of a biochemical failure they should be offered entry to the Hormone Duration Randomisation and receive the Hormone Duration Randomisation PIS in section B VIII.3.
- Patients due to receive post-operative radiotherapy either early or deferred and are eligible according to section 4 of the protocol should receive the Hormone Duration Randomisation PIS in section B VIII.3.

Please note that the version number of the Radiotherapy Timing Randomisation patient information sheet and the Hormone Duration Randomisation patient information sheet differs from that of Appendix B of the protocol.

## B VIII.2 Radiotherapy Timing Randomisation

Please note the version number of the information sheet differs from that of the appendix.

(To be presented on local headed paper)

### The RADICALS trial – Radiotherapy Timing Randomisation

#### Clinical trial of treatment after surgery for prostate cancer

MRC PR10  
ISRCTN40814031, NCT00541047

Date and version: June 2011, Version 5.0

Dear (Patient's Name),

This patient information sheet is in two parts. **Part A** is a summary of the RADICALS study. **Part B** gives more detailed information on the study and administration issues. Please read both sections before making your final decision.

You have had surgery to remove your prostate as treatment for your prostate cancer. We would like you to take part in a research study to help us answer the important question:

- When should radiotherapy be used after surgery?

Before you decide, it is important for you to understand why the research is being carried out and what it will involve. Please read the following information carefully and discuss it with anyone else if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

---

#### Where to find more information

If you have any further questions about your disease or clinical trials, please discuss them with your study doctor. You may also find it helpful to contact **Prostate Cancer Support Federation**, a patient led cancer charity covering the UK, (helpline: 0845 601 0766; [www.prostatecancerfederation.org.uk](http://www.prostatecancerfederation.org.uk)), **CancerBACKUP**, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3DR; web site [www.cancerbackup.org.uk](http://www.cancerbackup.org.uk)) and **The Prostate Cancer Charity** (telephone: 0845 300 8383; address: The Prostate Cancer Charity, 3 Angel Walk, London W6 9HX; web site <http://www.prostate-cancer.org.uk/>)

#### Contact for Further Information

For further information about the trial please contact:  
(Centre to add name and telephone number for a local contact: This can be a doctor and/or nurse involved in the study locally. Out of hours contact information should also be given).

## **PART A**

### **A1. What is the purpose of the study?**

The study will answer important questions for men like you who have had surgery for prostate cancer. We would like you to help us find out when radiotherapy should be used after surgery for prostate cancer.

Radiotherapy is often used in combination with surgery in other types of cancer. This is because it is often better for patients than using surgery alone. In prostate cancer, surgery alone is a standard approach, and we want to know if adding radiotherapy would be better.

### **A2. Why am I being invited?**

You are being invited because you have recently had surgery for prostate cancer.

### **A3. Do I have to take part?**

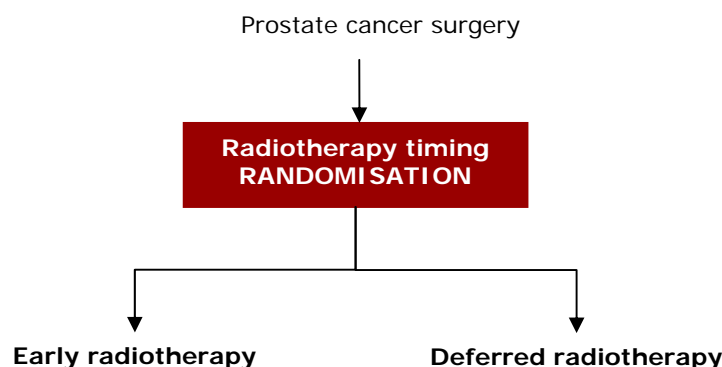
No. The RADICALS study will involve about 3000 men like you from UK, Canada, Denmark and Ireland who are being treated for prostate cancer. It is up to you to decide whether or not to take part. We will describe the study and go through this information sheet, which we will then give to you. If you do decide to take part you will be asked to sign a consent form to show you have agreed to take part. It is important that you know you are still free to withdraw at any time and without giving a reason. If you decide to withdraw at any time, or decide not to take part now, this will not affect the standard of care that you receive from the doctors and nurses here.

### **A4. What happens in the study?**

Radiotherapy may be used after surgery for prostate cancer at one of two different times: It may either be used within a few months after surgery to reduce the risk of cancer recurrence in the future or, alternatively, it may be used later to treat recurrent disease if it occurs. RADICALS will compare these two approaches. If you agree to take part, you would be allocated to one of these two approaches:

- Early radiotherapy (3 to 6 months after surgery)
- Deferred radiotherapy (only if your PSA (Prostate Specific Antigen) level starts to rise)

We are not sure which way of treating patients is best so we need to make a comparison. An important part of making a fair comparison is "random allocation". Men who choose to join the study are put into groups by a computer and each group is given one of these two study treatments. The results are compared to see if one treatment is better. You have an equal chance of receiving either treatment. Allocating treatments this way means that the groups of men receiving each of the two treatments should be similar and the comparison fair. Figure 1 shows a diagram of this comparison.

**Figure 1. Radiotherapy Timing Comparison****A5. What does radiotherapy involve?**

Radiotherapy involves treatment with x-rays. It does not make you radioactive. A week or two before radiotherapy, you will have a CT scan of the pelvis to assist with planning the treatment. Radiotherapy is given daily, 5 days a week for between 4 and 6 ½ weeks. Each day, the treatment lasts 5 to 10 minutes, is painless, and does not affect your ability to drive. There is published evidence that shows that radiotherapy to the prostate area after surgery is well tolerated with minimal side effects. You might find travelling for radiotherapy tiring in addition to any effects of the treatment itself.

**A6. What does deferred radiotherapy involve?**

If you are allocated to deferred radiotherapy, you will have regular blood tests to monitor your PSA levels. If these regular tests show that your PSA levels are rising, you will then be treated with radiotherapy.

**A7. What are the side-effects of any treatment received when taking part?**

All treatments can have unwanted effects (side-effects). Leaflets are available which describe radiotherapy in more detail. Please ask your study doctor if you would like more information. The main side-effects which may occur during or after the radiotherapy treatment include:

- loose or frequent bowel movements
- discomfort in the back passage
- loss of pubic hair
- tiredness
- reddening of the skin in the treated area

These side effects are common, but are typically mild and settle down within a few weeks after the end of radiotherapy.

There is also a risk of long-term side-effects from radiotherapy, which include:

- loss of the ability to have an erection (impotence)
- change in bowel habit, such as an increase in frequency or urgency of bowel movements
- bleeding from the bowel

Impotence is a common late side-effect of treatment, but significant, long-term side-effects on the bowel are unusual (about 1 in 20).

#### **A8. What are the other possible disadvantages and risks of taking part?**

No other disadvantages or risks are expected.

#### **A9. What are the possible benefits of taking part?**

Using radiotherapy routinely after surgery might reduce the risk of the cancer coming back. We cannot promise the study will help you personally. The information we get should help improve the treatment of other patients like you with prostate cancer in the future.

#### **A10. What would happen to me if I took part?**

If you join the study, you would follow one of the treatment approaches described above. Your care and follow-up at the hospital (including blood tests for PSA measurements) in the study may continue for 10 years or more but this is just like standard care.

If you have radiotherapy during the trial, you may be asked to join up with an additional, optional part of the trial which is looking at using hormone therapy. Your study doctor would tell you more about this at the time.

#### **A11. What do I have to do?**

All men who take part in the RADICALS study will have a follow-up appointment every 4 months for 2 years, then every 6 months up to 5 years then annually after 5 years. This is just the same as if you did not join the study. At each follow-up appointment with your study doctor, you will have standard medical tests which include a PSA test.

We would also like you to complete a questionnaire with about 50 questions. We will use these answers to learn how treatment affects your quality of life. You will be asked to complete the questionnaire four times: before you join the study, one year after joining the study, then at 5 years and 10 years.

---

This is the end of **Part A**. If you have any questions about anything you have read, ask your study doctor or nurse.

**Part B** has more specific information about the study. Please make sure you read **Part B** too, before deciding if you want to take part in the study.

## **PART B**

### **B1. Who is organising and funding the research?**

The RADICALS study is organised by the Medical Research Council and funded in the UK by Cancer Research UK on behalf of the National Cancer Research Institute. The doctors conducting the research are not being paid for including you or any other patients in the study.

### **B2. What are the alternatives for treatment?**

If you choose not to join the trial, your doctor will discuss standard care with you. Some doctors use early radiotherapy and others use deferred radiotherapy.

When radiotherapy is used after surgery for prostate cancer, it can be given with or without hormone therapy. Another part of the RADICALS trial (the Hormone Duration Comparison) will compare these two approaches. If and when you have radiotherapy, and if your doctor thinks it is appropriate, you might be asked to consider taking part in the optional Hormone Duration Comparison as well which looks at whether hormone therapy should also be used with the radiotherapy.

### **B3. What happens when the research study stops?**

Once the study treatment has finished, you will be assessed and treated according to standard practice at your hospital for men with prostate cancer.

If for any reason the research study stops or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for you to continue treatment according to the best available information at the time.

### **B4. What if relevant new information becomes available?**

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to leave the study, your study doctor will make arrangements for your treatment to continue according to the best available information at the time.

It is also possible that on receiving new information about treatment your study doctor might consider it to be in your best interest to withdraw from the study. He/she will explain the reasons and arrange for your care to continue.

### **B5. What will happen if I don't want to carry on with the study?**

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used; this is important for the integrity of the study.

**B6. What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to your study doctor who will do their best to answer your questions (see contact number on this sheet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from the hospital. If you are harmed as a result of your participation in this study due to someone's negligence, then you may have grounds for legal action but you may have to pay your legal costs. Your hospital continues to have a duty of care to you as a patient being treated within the hospital whether in a study or not. If you are harmed as result of your participation in this study, and this is not due to negligence, the Medical Research Council, who are managing this study, would sympathetically consider any claim for compensation.

**B7. Will there be expenses and payments?**

You will not be paid for taking part in this study. The follow-up visits are just the same as for routine care so travel expenses are not available. Your doctor and your hospital will not be paid anything extra if you join.

If you will be having radiotherapy, you may have to travel to another hospital to receive the radiotherapy as your hospital may not have the facilities to give radiotherapy. If you do not join the trial but do still have radiotherapy, you may still have to travel to another hospital to receive radiotherapy.

If you are allocated to receive radiotherapy now, you will need to travel for treatment more or less straight away whereas if you are allocated to receive radiotherapy if your PSA level starts to rise, it may be some time before you have to start to travel.

Transport arrangements to travel to receive radiotherapy will not be affected by the study whether private or hospital transport is used. There will be no reimbursement of costs incurred.

**B8. Will my taking part in this study be kept confidential?**

If you decide to participate in the RADICALS study, information about you will be passed to the Medical Research Council Clinical Trials Unit (MRC CTU) who are co-ordinating the study. Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Your GP, and the other doctors involved in your care, will be kept fully informed, but otherwise all information about you and your treatment will remain completely confidential. We will link with your details at the National Health Service Central Register (NHSCR), so we can check your health status in the event that you lose touch with your hospital study doctor or in the longer term. We need to keep your name and address and NHS number on file but will keep it separately from other data about you. The MRC CTU is registered under the Data Protection Act to hold such information on a confidential basis. All of the people who may see your information have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

**B9. What will happen to any samples I give?**

When you have had surgery, specimens from your cancer will be stored in the hospital pathology laboratory. If you take part in the RADICALS study, we would like to ask

your permission to retrieve some of that stored material in the future, for prostate cancer research. This research will be based in UK and would only be carried out after review by an independent research ethics committee. It involves extracting DNA or other chemicals from the tumour to see whether it is possible to predict which patients will benefit most from each treatment. These samples would be considered as a gift and no personal results from genetic tests or studies could be provided to you.

**B10. What will happen to the results of the research study?**

It is likely that the results of the RADICALS study will take over 12 years from the start of the study to be reported. This is because we need long-term follow-up information. The results will be published in a medical journal and presented at clinical conferences. You will not be identified in any report or publication. The results are important as they will answer several questions for doctors looking after men like you. This will improve the treatment for men in the future. Men in the past have taken part in research into the best treatments you are receiving now.

**B11. Who has reviewed the study?**

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being and dignity. This study has been reviewed and given favourable opinion for the UK by the Royal Free Hospital and Medical School Research Ethics Committee.

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This is the end of **Part B**. Thank you for taking the time to consider taking part in the RADICALS study. You will be given a copy of the information sheet and a signed consent form to keep.

If you have any further questions please ask your study doctor or nurse. They will be able to answer your questions and let you know where to find further information.

### B VIII.3 Hormone Duration Randomisation

Please note the version number of the information sheet differs from that of the appendix.

(To be presented on local headed paper)

#### The RADICALS trial – Hormone Duration Randomisation

#### Clinical trial of treatment after surgery for prostate cancer

MRC PR10  
ISRCTN40814031, NCT00541047

Date and version: **June 2011, Version 5.0**

Dear (Patient's Name),

This patient information sheet is in two parts. **Part A** is a summary of the RADICALS study. **Part B** gives more detailed information on the study and administration issues. Please read both sections before making your final decision.

You have previously had surgery to remove your prostate as treatment for your prostate cancer, and are now due to have radiotherapy to the prostate bed. We would like you to take part in a research study to help us answer the important question:

- How should hormone treatment be used for men having radiotherapy after surgery?

Before you decide, it is important for you to understand why the research is being carried out and what it will involve. Please read the following information carefully and discuss it with anyone else if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

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#### Where to find more information

If you have any further questions about your disease or clinical trials, please discuss them with your study doctor. You may also find it helpful to contact **Prostate Cancer Support Federation**, a patient led cancer charity covering the UK, (helpline 0845 601 0766; [www.prostatecancerfederation.org.uk](http://www.prostatecancerfederation.org.uk)), **CancerBACKUP**, an independent patient advisory group (freephone: 0808 800 1234; address: 3 Bath Place, Rivington Street, London, EC2A 3DR; web site [www.cancerbackup.org.uk](http://www.cancerbackup.org.uk)) and **The Prostate Cancer Charity** (telephone: 0845 300 8383; address: The Prostate Cancer Charity, 3 Angel Walk, London W6 9HX; web site <http://www.prostate-cancer.org.uk/>)

#### Contact for Further Information

For further information about the trial please contact:  
(Centre to add name and telephone number for a local contact: This can be a doctor and/or nurse involved in the study locally. Out of hours contact information should also be given).

## **PART A**

### **A1. What is the purpose of the study?**

The study will answer important questions for men like you who have had surgery for prostate cancer, and are now due to have radiotherapy. We would like you to help us find out which is the best way to use hormone treatment in men having radiotherapy after surgery for prostate cancer.

Some doctors use hormone treatment with the radiotherapy but other doctors do not. We want to find out which is the better approach.

### **A2. Why am I being invited?**

You are being invited because you have previously had surgery for prostate cancer and are now due to have radiotherapy.

### **A3. Do I have to take part?**

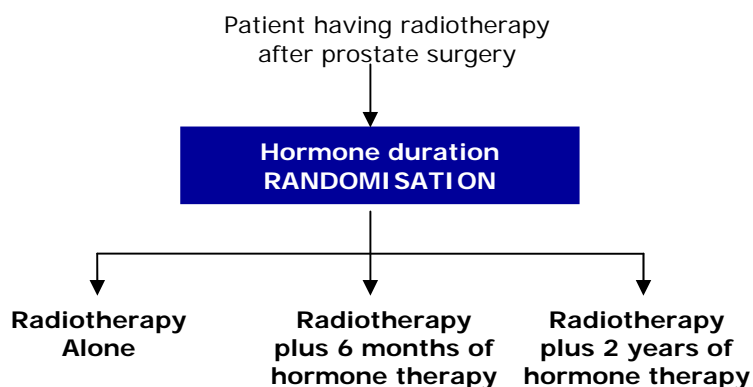
No. The RADICALS study will involve about 3000 men like you from UK, Canada, Denmark and Ireland who are being treated for prostate cancer. It is up to you to decide whether or not to take part. We will describe the study and go through this information sheet, which we will then give to you. If you do decide to take part you will be asked to sign a consent form to show you have agreed to take part. It is important that you know you are still free to withdraw at any time and without giving a reason. If you decide to withdraw at any time, or decide not to take part now, this will not affect the standard of care that you receive from the doctors and nurses here.

### **A4. What happens in the study?**

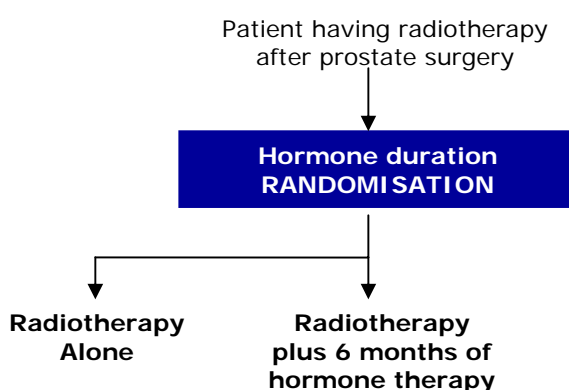
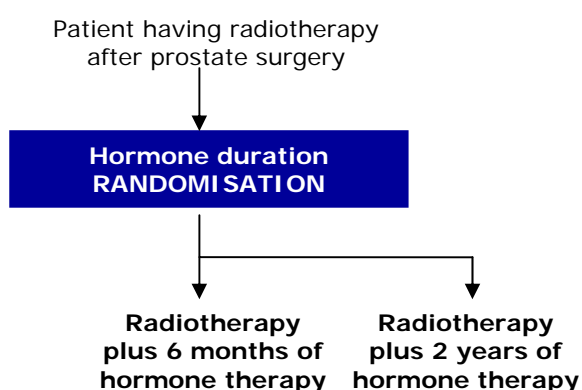
When radiotherapy is used after surgery for prostate cancer, it can be given with or without hormone treatment. RADICALS will compare these approaches. As you are about to have radiotherapy, we would like you to join this study. If you agree to take part, you would be allocated to one of these three treatments:

- either radiotherapy alone
- or radiotherapy plus 6 months hormone treatment
- or radiotherapy plus 2 years hormone treatment

We are not sure which way of treating patients is best so we need to make a comparison. An important part of making a fair comparison is "random allocation". Men who choose to join the study are put into groups by a computer and each group is given one of these three study treatments. The results are compared to see if one treatment is better. You have an equal chance of receiving each of the treatments. Allocating treatments this way means that the groups of men receiving the three treatments should be similar and the comparison fair. Figure 1 shows a diagram of this comparison.

**Figure 1. Hormone Duration Comparison**

After discussion with your doctor, you may decide to be allocated between only two of the three treatments. For example, you may choose to join the comparison of no hormone treatment and shorter hormone treatment (Figure 2) or you may choose to join the comparison of shorter hormone treatment and longer hormone treatment (Figure 3).

**Figure 2. Hormone Duration Comparison – Two-way allocation only****Figure 3. Hormone Duration Comparison – Two-way allocation only**

**A5. What does the radiotherapy involve?**

Radiotherapy involves treatment with x-rays. It does not make you radioactive. A week or two before radiotherapy, you will have a CT scan of the pelvis to assist with planning the treatment. Radiotherapy is given daily, 5 days a week for between 4 and 6 ½ weeks. Each day, the treatment lasts 5 to 10 minutes, is painless, and does not affect your ability to drive. There is published evidence that shows that radiotherapy to the prostate area after prostatectomy is well tolerated with minimal side effects. You might find travelling for radiotherapy tiring in addition to any effects of the treatment itself.

**A6. What does hormone treatment involve?**

Hormone treatment may be given either by tablets or by injections under the skin. Typically, men receive a 3 week course of tablets (known as anti-androgens) initially, and then injections (such as Zoladex or Prostag), given either monthly or 3-monthly. The first injection is given during the initial 3 week course of tablets. The injections are usually given under the skin of the abdomen, and can be uncomfortable and lead to some bruising. Hormone treatment is sometimes given using an anti-androgen tablets alone (called bicalutamide or Casodex).

**A7. What are the side-effects of any treatment received when taking part?**

All treatments can have unwanted effects (side-effects). The main side-effects of these treatments are listed below. Leaflets are available which describe radiotherapy and hormone treatment in more detail. Please ask your study doctor if you would like more information.

**A7a. Side-effects of radiotherapy**

Side-effects which may occur during or after the treatment with radiotherapy include:

- loose or frequent bowel movements
- discomfort in the back passage
- loss of pubic hair
- tiredness
- reddening of the skin in the treated area

These side effects are common, but are typically mild and settle down within a few weeks after the end of radiotherapy.

There is also a risk of long-term side-effects from radiotherapy, which include:

- loss of the ability to have an erection (impotence)
- change in bowel habit, such as an increase in frequency or urgency of bowel movements
- bleeding from the bowel

Impotence is a common late side-effect of treatment, but significant, long-term side-effects on the bowel are unusual (about 1 in 20).

**A7b. Side effects of hormone treatment**

The effect of the injections is to lower the levels of the male hormone (testosterone), which can lead to side-effects including:

- loss of sexual interest
- tiredness
- hot flushes
- weight gain
- low mood

Testosterone levels return to normal after stopping the injections, and these side-effects are reversible. Hormone treatment is sometimes given using just anti-androgen tablets (bicalutamide or Casodex). One advantage of this approach is that sexual function may be retained, but painful swelling of the breasts is a common side-effect. A dose of radiotherapy is often given to the breasts to prevent this.

**A8. What are the other possible disadvantages and risks of taking part?**

No other disadvantages or risks are expected.

**A9. What are the possible benefits of taking part?**

The use of hormone therapy might improve the outcome of radiotherapy. We cannot promise the study will help you personally. The information we get should help improve the treatment of other patients like you with prostate cancer in the future.

**A10. What would happen to me if I took part?**

If you join the study, you would follow one of the treatment approaches described above. You would be asked to visit the hospital and have blood tests (PSA measurements) just as if you were not in the study.

**A11. What do I have to do?**

All men who take part in the RADICALS study will have a follow up appointment every 4 months for 2 years, then every 6 months up to 5 years then annually after 5 years. This is just the same as if you did not join the study. At each follow-up appointment with your study doctor, you will have standard medical tests which include a PSA test.

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This is the end of **Part A**. If you have any questions about anything you have read, ask your study doctor or nurse.

**Part B** has more specific information about the study. Please make sure you read **Part B**, too, before deciding if you want to take part in the study.

## **PART B**

### **B1. Who is organising and funding the research?**

The RADICALS study is organised by the Medical Research Council and funded in the UK by Cancer Research UK on behalf of the National Cancer Research Institute. The doctors conducting the research are not being paid for including you or any other patients in the study.

### **B2. What are the alternatives for treatment?**

If you choose not to join the trial, your doctor will discuss standard care with you. Your doctor is already planning radiotherapy with you. Some doctors use hormone treatment with post-operative radiotherapy, others do not.

### **B3. What happens when the research study stops?**

Once the study treatment has finished, you will be assessed and treated according to standard practice at your hospital for men with prostate cancer.

If for any reason the research study stops or the treatment programme needs to be changed, the reasons will be explained. Arrangements will be made for you to continue treatment according to the best available information at the time.

### **B4. What if relevant new information becomes available?**

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to leave the study, your study doctor will make arrangements for your treatment to continue according to the best available information at the time.

It is also possible that on receiving new information about treatment your study doctor might consider it to be in your best interest to withdraw from the study. He/she will explain the reasons and arrange for your care to continue.

### **B5. What will happen if I don't want to carry on with the study?**

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used; this is important for the integrity of the study.

### **B6. What if there is a problem?**

If you have a concern about any aspect of this study, you should ask to speak to your study doctor who will do their best to answer your questions (see contact number on this sheet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). Details can be obtained from the hospital. If you are harmed as a result of your participation in this study due to someone's negligence, then you may have grounds for legal action but you may

have to pay your legal costs. Your hospital continues to have a duty of care to you as a patient being treated within the hospital whether in a study or not. If you are harmed as result of your participation in this study, and this is not due to negligence, the Medical Research Council, who are managing this study, would sympathetically consider any claim for compensation.

**B7. Will there be expenses and payments?**

You will not be paid for taking part in this study. The follow-up visits are just the same as for routine care so travel expenses are not available. Your doctor and your hospital will not be paid anything extra if you join.

If you will be having radiotherapy, you may have to travel to another hospital to receive the radiotherapy as your hospital may not have the facilities to give radiotherapy. If you do not join the trial but do still have radiotherapy, you may still have to travel to another hospital to receive radiotherapy.

If you are allocated to receive radiotherapy now, you will need to travel for treatment more or less straight away whereas if you are allocated to receive radiotherapy if your PSA level starts to rise, it may be some time before you have to start to travel.

Transport arrangements to travel to receive radiotherapy will not be affected by the study whether private or hospital transport is used. There will be no reimbursement of costs incurred.

**B8. Will my taking part in this study be kept confidential?**

If you decide to participate in the RADICALS study, information about you will be passed to the Medical Research Council Clinical Trials Unit (MRC CTU) who are co-ordinating the study. Occasionally staff from the MRC CTU or regulatory authorities will need to visit the hospital to review your notes to check that the information being provided is correct. Your GP, and the other doctors involved in your care, will be kept fully informed, but otherwise all information about you and your treatment will remain completely confidential. We will link with your details at the National Health Service Central Register (NHSCR), so we can check your health status in the event that you lose touch with your hospital study doctor or in the longer term. We need to keep your name and address and NHS number on file but will keep it separately from other data about you. The MRC CTU is registered under the Data Protection Act to hold such information on a confidential basis. All of the people who may see your information have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

**B9. What will happen to any samples I give?**

When you have had surgery, specimens from your cancer will be stored in the hospital pathology laboratory. If you take part in the RADICALS study, we would like to ask your permission to retrieve some of that stored material in the future, for prostate cancer research. This research will be based in UK and would only be carried out after review by an independent research ethics committee. It involves extracting DNA or other chemicals from the tumour to see whether it is possible to predict which patients will benefit most from each treatment. These samples would be considered as a gift and no personal results from genetic tests or studies could be provided to you.

**B10. What will happen to the results of the research study?**

It is likely that the results of the RADICALS study will take over 12 years from the start of the study to be reported. This is because we need long-term follow-up information. The results will be published in a medical journal and presented at clinical conferences. You will not be identified in any report or publication. The results are important as they will answer several questions for doctors looking after men like you. This will improve the treatment for men in the future. Men in the past have taken part in research into the best treatments you are receiving now.

**B11. Who has reviewed the study?**

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being and dignity. This study has been reviewed and given favourable opinion for the UK by the Royal Free Hospital and Medical School Research Ethics Committee.

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This is the end of **Part B**. Thank you for taking the time to consider taking part in the RADICALS study. You will be given a copy of the information sheet and a signed consent form to keep.

If you have any further questions please ask your study doctor or nurse. They will be able to answer your questions and let you know where to find further information.

## **B IX: CONSENT FORMS**

### **B IX.1 Introduction**

There are two RADICALS consent forms.

- Patients joining the Radiotherapy Timing Randomisation should read and sign questions 1 to 9 of the Radiotherapy Timing Randomisation consent form in section B IX.2.
  - Patients that join the Radiotherapy Timing Randomisation and are going to have radiotherapy either early or deferred can join the Hormone Duration Randomisation if they wish but are not required to do so. If the patient does wish to participate in the Hormone Duration Randomisation as well, they should read and sign questions 10 and 11 of the Radiotherapy Timing Randomisation consent form in section B IX.2.
- Patients due to receive post-operative radiotherapy either early or deferred and have not already joined the Radiotherapy Timing Randomisation should read and sign the Hormone Duration Randomisation consent form in section B IX.3.

## B IX.2 Radiotherapy Timing Randomisation

(To be presented on local headed paper)

<p><b>The RADICALS trial – Radiotherapy Timing Randomisation</b></p> <p><b>Clinical trial of treatment after surgery for prostate cancer</b></p> <p><b>Consent Form</b></p> <p>MRC PR10 ISRCTN40814031, NCT00541047</p> <p>Date and version: <b>June 2011, Version 4.0</b></p>
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Trial Number	
Responsible Investigator	

Initial boxes to agree

1. I confirm that I have read and understood the information sheet dated **June 2011 (Version 5.0)** for the above study and have been given a copy to keep. I have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Medical Research Council (MRC) Clinical Trials Unit (CTU) or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records, but understand that my confidentiality will be maintained.
4. I agree to take part in the above study.
5. I agree to my GP being informed that I am joining this study.
6. I give permission for my name and NHS number to be registered by the MRC CTU with the usual national register mechanisms (e.g. National Health Service Central Register – NHSCR) should I lose contact with my hospital doctor. I give permission for information about my health status to be obtained this way by the Medical Research Council if necessary. I understand that my confidentiality will be maintained. *(If you do not wish to give this permission, do not initial – you can still participate in the trial).*
7. I give permission for a copy of my consent form to be sent to the MRC CTU (where it will be kept in a secure location), to allow confirmation that my consent was given. *(If you do not wish to give this permission, do not initial – you can still participate in the trial).*
8. I agree to participate in the Quality of Life study and to complete the questionnaires. *(If you do not wish to give this permission, do not initial – you can still participate in the trial).*

// continued



## B IX.3 Hormone Duration Randomisation

(To be presented on local headed paper)

<p><b>The RADICALS trial – Hormone Duration Randomisation</b></p> <p><b>Clinical trial of treatment after surgery for prostate cancer</b></p> <p><b>Consent Form</b></p> <p>MRC PR10 ISRCTN40814031, NCT00541047</p> <p>Date and version: <b>June 2011, Version 4.0</b></p>
---

Trial Number	
Responsible Investigator	

Initial boxes to agree

1. I confirm that I have read and understood the information sheet dated **June 2011 (Version 5.0)** for the above study and have been given a copy to keep. I have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the Medical Research Council (MRC) Clinical Trials Unit (CTU) or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records, but understand that my confidentiality will be maintained.
4. I agree to take part in the above study.
5. I agree to my GP being informed that I am joining this study.
6. I give permission for my name and NHS number to be registered by the MRC CTU with the usual national register mechanisms (e.g. National Health Service Central Register – NHSCR) should I lose contact with my hospital doctor. I give permission for information about my health status to be obtained this way by the Medical Research Council if necessary. I understand that my confidentiality will be maintained. *(If you do not wish to give this permission, do not initial – you can still participate in the trial).*
7. I give permission for a copy of my consent form to be sent to the MRC CTU (where it will be kept in a secure location), to allow confirmation that my consent was given. *(If you do not wish to give this permission, do not initial – you can still participate in the trial).*
8. I give permission for my stored samples to be made available for future research where the samples would be stored appropriately and the research approved separately. *(If you do not wish to give this permission, do not initial – you can still participate in the trial).*

// continued

\_\_\_\_\_  
Signature of Patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Person taking consent  
(if different from Responsible Investigator)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Responsible Investigator

\_\_\_\_\_  
Date

*4 copies: 1 for patient, 1 for researcher, 1 to be kept with hospital notes and 1 to be sent to MRC Clinical Trials Unit (if box 7 initialled)*