

## **RADICALS**

### **Radiotherapy and Androgen Deprivation In Combination After Local Surgery**

#### **A randomised controlled trial in prostate cancer**

**Version:** 6.0  
**Date:** 14<sup>th</sup> December 2018

**MRC CTU ID:** PR10  
**ISRCTN #:** ISRCTN 40814031  
**NCT #:** NCT00541047  
**EUDRACT #:** 2006-000205-34  
**CTA #:** 00316/0223/001-0001  
**MREC #:** 07/Q0501/48

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**Role:** Chief Investigator  
**Date:** 14-December -2018  
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## GENERAL INFORMATION

This document was constructed using the MRC CTU Protocol Template Version 4.0. It describes the RADICALS trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the Cancer And Other Non-Infectious Diseases Group, MRC CTU at UCL, London, UK, to confirm they have the most up-to-date version.

## COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites will comply with the principles of GCP as laid down by the ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC (the European Directive 2001/20/EC [where applicable]) and applicable national regulations.

## SPONSOR

MRC: Medical Research Council, 2nd Floor, David Phillips Building, Polaris House, North Star Avenue, Swindon, SN2 1FL, UK

CCTG: Canadian Cancer Trials Group

On 01-Aug-2013, the MRC CTU became part of University College London (UCL). The MRC maintains sponsorship for the trial however UCL is the legal entity responsible for the running of the trial. This responsibility is delegated to the coordinating trial unit, the MRC CTU at UCL.

## FUNDING

Funder in UK: Clinical Trials Advisory Awards Committee (on behalf of Cancer Research UK) and Medical Research Council.

Funder in Canada: Canadian Cancer Society – Research Institute

## AUTHORISATIONS AND APPROVALS

The following persons are authorised to sign the final protocol and protocol amendments for the sponsor: Dr Chris Parker (Chief Investigator) and Matthew Sydes (Trial Statistician).

## **TRIAL REGISTRATION**

This trial has been registered with the ClinicalTrials.gov Clinical Trials Register, where it is identified as NCT00541047.

## INFORMATION FOR MRC INVESTIGATORS

### 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, 23<sup>rd</sup> April 2007

### REGULATORY APPROVAL

CTA reference 00316/0223/001-0001, 27<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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For full details of all trial committees, please see [Appendix A](#)

**RANDOMISATIONS**

To randomise, call MRC CTU at UCL, Monday to Friday 0900-1700  
excluding public holidays or dates when notice has been given by the CTU.  
Tel: +44 (0) 20 7670 4777

**SAE REPORTING**

Fax to 020 7670 4818 within 24 hours of becoming aware of the event

## INFORMATION FOR CCTG INVESTIGATORS

### SCIENTIFIC APPROVAL

Canadian Cancer Trials Group (CCTG)

### 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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SAEs must be reported on the Serious Adverse Event Form  
Tel: 613-533-4630    Fax: 613-533-2941

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## ABBREVIATIONS AND GLOSSARY

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

Abbreviation	Expansion
MHRA	Medicines and Healthcare Regulatory Authority
MLC	Multi-leaf Collimation
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NCIC CTG	NCIC Clinical Trials Group
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHS	National Health Service
NHSCR	National Health Service Central Register
ONS	Office for National Statistics
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Patient information Sheet
PSA	Prostate Specific Antigen
PTV	Planning Target Volume
QA	Quality Assurance
QL	Quality of life
RADICALS	Radiotherapy and Androgen Deprivation In Combination After Local Surgery
RADICALS-RT	RADICALS Radiotherapy Timing Randomisation
RADICALS-HD	RADICALS Hormone Duration Randomisation
RCT	Randomised Controlled Trial
RP	Radical Prostatectomy
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SAR	Serious adverse reaction
SF12	Short Form 12
SI	Superior/Inferior
SmPC	Summary of Product Characteristics
SOP	Standard operating procedures
SPC	Summary of product characteristics
SSA	Site specific assessment
STHT	Short Term Hormone Therapy
SUSAR	Suspected unexpected serious adverse reaction
SV	Seminal Vesicle
SWOG	South West Oncology Group
tds	Three times daily
TMG	Trial Management Group
TSC	Trial Steering Committee
TROG	Trans-Tasman Radiation Oncology Group
UAR	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.

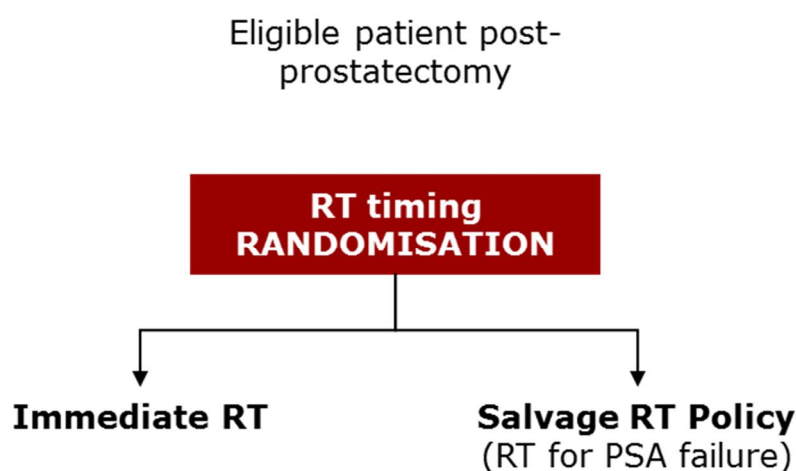
##### 1.1.3.A RADICALS-RT: RADIO THERAPY TIMING RANDOMISATION

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.B RADICALS-HD: HORMONE DURATION RANDOMISATION

See [Figure 2](#)

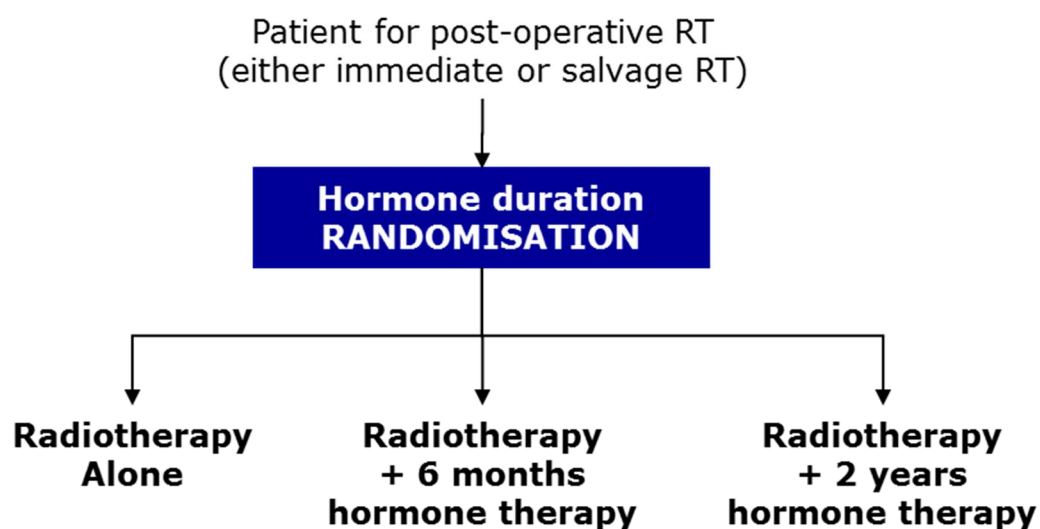
- No hormone therapy with RT
- Short-term hormone therapy (6 months) commencing shortly before RT
- Long-term hormone therapy (24 months) commencing shortly before RT

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:

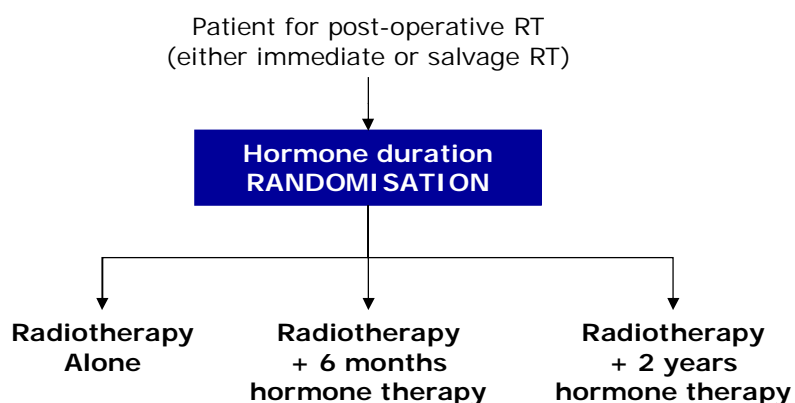
- RT + no hormone therapy vs RT + 6m hormone therapy vs RT + 24m hormone therapy
- RT + no hormone therapy vs RT + 6m hormone therapy
- RT + 6m hormone therapy vs RT + 24m hormone therapy

**Figure 2: Hormone Duration Randomisation**

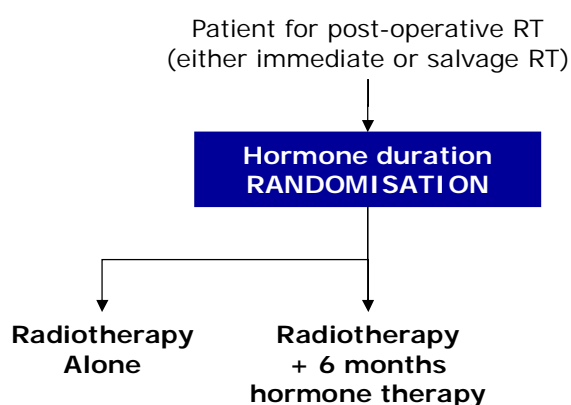


**Figure 3: Two- and three-arm Hormone Duration Randomisations**

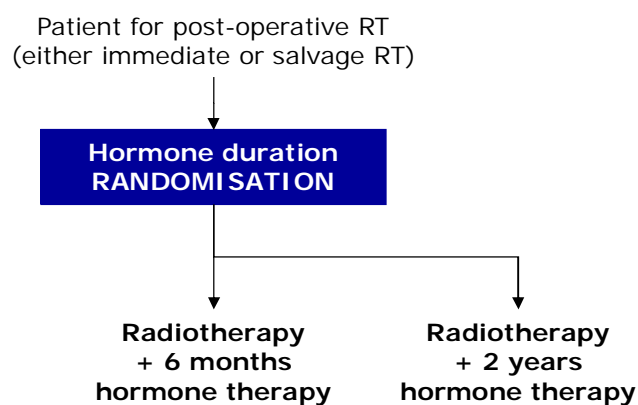
Three-arm randomisation  
(preferable)



Two-arm randomisation  
(none vs \_short)



Two-arm randomisation  
(short vs long)



#### 1.1.4 OUTCOME MEASURES

##### 1.1.4.A 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  
Freedom from biochemical progression

##### ARTISTIC META-ANALYSIS OF RADICALS-RT

The proposed outcomes of interest for the ARTISTIC meta-analysis (see also sections 2.5.1 and 9.6.1) are as follows:

- Event free survival
- Time to start of salvage hormone therapy
- Time free of metastases
- Prostate cancer specific survival
- Overall survival

##### 1.1.4.B 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

A total of 1396 patients were recruited into RADICALS-RT and 2840 patients into the RADICALS-HD. Many patients contributed to both randomisations. Patients were 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 was originally planned to address these questions over 12-13 years with 5½ to 6½ years of accrual and around 7 years of further Follow-up. The IDMC has advised that overall event rates have been much lower than anticipated. This prompted a change of primary outcome in the RADICALS-RT comparison (changed in protocol V4.0 from disease-specific survival to freedom from distant metastases). The IDMC subsequently advised that event rates are lower still (without reference to comparative data by arm).

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 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 or a substudy protocol will be developed.

## 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 (CCTG 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. This meta-analysis may be performed prior to the main outcome measure analysis of RADICALS-RT, as detailed in section 9.6. The meta-analysis will be based on up-to-date data from all trials. All RADICALS-RT randomised patients will be included in the analyses, which will be performed on an intention-to-treat basis. The meta-analysis will be conducted in stages, as data for each outcome matures, with analyses being carried out when reasonable power to detect treatment differences is achieved. Relevant information, for example accrual and follow-up durations, control arm event rates and patient retention rates, will be sought from each study to finalise the appropriate time point for the analysis of each outcome. Full details will be documented in the ARTISTIC protocol and statistical analysis plan.

### 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 AND 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**

TRIAL SECTION	INCLUSION	EXCLUSION
All Patients	<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<sup>*</sup></li> </ul>
RADICALS-RT	<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 <ul style="list-style-type: none"> <li>:: two consecutive rises in PSA and final PSA <math>&gt; 0.1</math>ng/ml OR</li> <li>:: three consecutive rises in PSA</li> </ul> </li> <li>• Ideally more than 22 weeks since radical prostatectomy<sup>#</sup></li> </ul>
RADICALS-HD	<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

<sup>\*</sup>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 2: Timing of Investigations**

COMPARISON	TEST	TIMING
RADICALS-RT	Bone scan <sup>*</sup>	16 weeks prior to randomisation
	PSA <sup>**</sup>	Within 30 days prior to randomisation AND At least 30 days after surgery
RADICALS-HD	Bone scan <sup>#</sup>	16 weeks prior to randomisation
	PSA <sup>**</sup>	Within 30 days prior to randomisation AND At least 30 days after surgery

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

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

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

## 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 1-3](#)). 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>	Tel: +44 (0)20 7670 4777
Monday-Friday	09.00 – 17.00 (GMT)
<b>CCTG Randomisations</b>	Tel: +1 613-533-6430
	Fax: +1 613-533-2941
Monday – Friday	08.00 – 18.00 (EST)

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](#).

If radiotherapy centres wish to use IMRT, they may do so with the exception of Canadian centres who will need to be credentialed for IMRT before they can use it for their RADICALS patients (full details are available in the Canadian Appendix). The prostate bed dose should be 66Gy in 2Gy fractions or 52.5Gy in 20 fractions. However, if it is intended to use IMRT to treat the pelvic lymph nodes in addition to the prostate bed, then treatment should be given over 33 fractions to a total nodal dose of 52-54Gy. Alternative schedules should be agreed with the RADICALS Trial Management Group.

#### 6.1.1 EARLY POST-OP RADIOTHERAPY

Patients allocated to early radiotherapy to the prostate bed will start treatment within approximately 2 months of entering into 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.A 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.D](#).

##### 6.1.3.B PHYSICAL FACTORS

Megavoltage equipment is required with effective photon energies >6MV. 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.C TREATMENT VOLUMES GUIDANCE

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

#### [A] 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 (% seminal vesicle (SV) involvement risk =  $PSA + 10 \times [GS - 6]$  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** = ≥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.

#### [B] 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.D 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 is recommended to be one of the following:

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

Other schedules should be discussed and approved by the TMG. 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.E 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**

STRUCTURE	DOSE	VOLUME OBJECTIVE
Bladder	50 Gy	< 80%
	60 Gy	< 50%
Rectum	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**

STRUCTURE	ISODOSE	VOLUME OBJECTIVE
Bladder	40 Gy	< 80%
	48 Gy	< 50%
Rectum	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) because bicalutamide monotherapy is not approved for use.

#### **6.2.2.A 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) because bicalutamide monotherapy is not approved for use.

#### **6.2.2.B 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, leuporelin). In this arm, the use of 3-month depot preparations (e.g. goserelin 10.8mg, leuporelin 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) because bicalutamide monotherapy is not approved for use.

#### **6.2.2.C 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) 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- or Post-randomisation
Co-morbidity form (CRF 2)	Within two weeks prior to randomisation
PSA History Log	Pre-randomisation
Randomisation forms (CRF 3 = RADICALS-RT and RADICALS-HD ) (CRF 4 = RADICALS-HD 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)	As needed
Serious adverse event form (CRF 8)	As needed
Death Report form (CRF 9)	As needed

\*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 for the duration of the trial. 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](#)). If follow-up visits are no longer possible according to the trial schedule, patients can be followed up by telephone or using information from other healthcare services, e.g. GP practice. These follow-ups should adhere to the timelines specified in the patient's schedule. If information reported on the follow-up CRF is not from a follow-up visit to a RADICALS investigator site please indicate this by completing question 1a. Where it applies, the consent of patients should be obtained for their names to be flagged for survival information through national registries, for example NHS Information Centre/Office of National Statistics (ONS) in England/Wales and General Register Office in Scotland, Hospital Episode Statistics (HES). If the clinician moves, appropriate arrangements should be made to arrange for trial follow-up to continue at the centre.

#### 7.5.1 MORTALITY DATA FROM ELECTRONIC HEALTH RECORDS

Death registration data for England and Wales became available to the trial in January 2018, to be updated quarterly thereafter. These will be provided through ONS or an appropriate alternative. This enables regular checking for completeness of the trial database, with specific data chases to sites in the event of unreported deaths becoming known. The data also enables more precise survival estimation, since patients without recent trial follow-up may be assumed to be alive approximately one month before the data extract if death has not been registered. Death registration also enables checking for unreported distant metastases, in the event of a prostate cancer death being registered

with ONS but no distant metastases previously recorded in the trial database. Data from other national registers may be used in the future if it becomes available to the trial team.

## **7.6 TRIAL CLOSURE**

All patients will be actively followed according to the trial schedule until end of funding unless the TMG considers appropriate to transition before then to a long-term follow-up stage. During the long-term follow-up stage participants will not be required to make any trial specific visits to the clinic but will be followed-up via retrospective data collection from the sites and national registries for which consent has been requested as part of the original consent process. During this follow-up period participants will have completed the interventional phase of the study and will not be on any trial mandated regimen so real time SUSAR and SAE reporting will cease but investigators will be asked to report events via national reporting systems such as the MHRA Yellow card system in the UK.

## 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. To document the transfer process the main contact person at both the current and receiving hospitals should complete and sign the Patient Transfer Confirmation form. A fully completed form must be returned to the CTU prior to the patient transfer and ideally any data queries for the patient should be completed prior to transfer.

On receipt of the completed transfer form a member of the RADICALS team will confirm the database has been updated and request confirmation of the name of the patient's new Clinician. Photocopies of the following documents may then be sent to the new hospital to complete the transfer and copies must be also retained at the original site for monitoring purposes:

- Consent form
- Completed CRFs
- Any documentation relating to the patient's participation in RADICALS (patient names must be removed from any documentation).

## 9 STATISTICAL CONSIDERATIONS

### 9.1 METHOD OF RANDOMISATION

Randomisation will be performed centrally at the MRC Clinical Trials Unit at UCL 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 distant metastases** (RADICALS-HD 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. Radiotherapy treatment planning data is required to understand the cause of treatment toxicity.
- **Patient reported outcomes:** See [Section 13.1](#) for details
- **Freedom from biochemical progression:** Where a biochemical progression event is defined as a PSA level of  $\geq 0.4$  ng/ml following radiotherapy or a PSA level of  $> 2.0$  ng/ml regardless of prior radiotherapy.

### 9.2.4 EARLY REPORTING OF BIOCHEMICAL OUTCOMES

In early 2018, based on the number of primary outcome events in the control arm of the RADICALS-RT comparison, the target number of events was not forecast to occur until 2025. This is several years later than originally expected due to the low event rate. Two other randomised controlled trials (RCTs), RAVES and GETUG 17, also address the question of deferred RT and are planning to report in 2018/2019. The ARTISTIC project is a pre-planned individual patient data meta-analysis, combining RAVES, GETUG-17 and RADICALS-RT. The RADICALS TMG therefore agreed, in February 2018, to publish the Freedom from biochemical progression results of RADICAL-RT to coincide with the other two trials, and enable a timely meta-analysis.

## 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 per month 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 SHT vs LHT 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 SHT and SHT vs LHT. 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.A 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.B 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 51/2 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 at UCL. 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

In collaboration with the two parallel trials to RADICALS-RT, RAVES and GETUG-17, and the Meta-analysis Group of the MRC-CTU at UCL, the ARTISTIC collaborative group has been formed in order to prospectively plan a meta-analysis. Pooling summary results and relevant statistics for event free survival from all three trials will facilitate a meta-analysis of almost 2000 patients in total. The resulting increase in power and precision that the meta-analysis provides will enable a timely and definitive assessment of the treatment effects of adjuvant RT in all patients as well as potentially enabling an assessment of treatment effects within subgroups of patients, defined for example by risk groups or by age at randomisation. In due course, as trial outcome data matures, the ARTISTIC

collaboration will undertake a full meta-analysis based on individual participant data to assess all outcome measures (see section 1.1.4.A).

#### 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.

## 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 Trials Quality Assurance (RTTQA) 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 [Section 6.1.3.A](#).

Data will be collected by the NCRI Radiotherapy Trials QA (RTTQA) Group for patients treated in the RADICALS trial. This includes: CT images, contours, plan and plan dose cubes along with DVHs. Data must be appropriately anonymised.

### 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.

## 10.5 PROTOCOL DEVIATIONS

If the site identifies a protocol deviation they should notify the PI within 24 hours. The PI and team should review the deviation and create a suggested corrective action plan. This corrective plan should be reported to the MRC CTU team, who will review it and the deviation. The site will keep a protocol deviation log and the completed corrective action plan in order to ensure, as far as possible, that the deviation does not reoccur.

## 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 at UCL 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
Adverse Event (AE)	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.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	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.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	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

SAEs related to disease progression, or death as a result of disease progression, are exempt from expedited reporting 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 patient's medical notes. Specific toxicities should be reported for the trial in the toxicity (symptoms) section of the Follow-up form (CRF 6) and sent to the MRC CTU at UCL within one month of the form being due. The specific toxicities reported for the trial are diarrhoea, proctitis, cystitis, haematuria, urethral stricture & rectal haemorrhage. SAEs/SARs should be notified to the MRC CTU at UCL as described below.

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be graded using the NCI CTCAE v3.0. The full list is available at [https://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.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 at UCL in the first instance.

#### 11.3.2 INVESTIGATOR ASSESSMENT

##### 11.3.2.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 6](#). If the event is serious and not exempt from expedited reporting, then an SAE form must be completed and the trials unit notified.

##### 11.3.2.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.

#### 11.3.2.C EXPECTEDNESS

The investigator should make an initial assessment of the expectedness of the event, however the sponsor has the final responsibility for determination of expectedness. 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. An unexpected adverse reaction is one not previously reported in the reference safety information (RSI) for that hormone treatment. For the purpose of this trial, the reference safety information will be section 4.8 of the relevant Summary of Product Characteristics (SPC) included in **Appendix C**.

The main expected short term side-effects which may occur during or after the radiotherapy treatment include tiredness, skin irritation, pubic hair loss, urinary frequency, decreased urinary stream, haematuria, need for urinary catheter, diarrhoea and bowel urgency. Late effects of radiotherapy treatment include bowel urgency, frequency or bleeding, urinary frequency, urinary urgency, erectile dysfunction, infertility, and increased risk of bladder or bowel cancer.

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

RELATIONSHIP	DESCRIPTION	EVENT TYPE
<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

#### 11.3.2.D NOTIFICATION

The MRC CTU at UCL should be notified within 24 hours of the investigator becoming aware of an event that requires expedited reporting. Investigators should notify the MRC CTU at UCL 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 at UCL until trial closure (i.e. no matter when they occur after randomisation).

#### 11.3.2.E NOTIFICATION PROCEDURE:

- 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 at UCL as soon as possible. The initial report shall be followed by detailed, written reports as appropriate.
- Send the SAE form by fax to the MRC CTU at UCL within 24 hours of the investigator's knowledge of the event.  
Fax Number: see box, below
- 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 at UCL 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 at UCL 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.

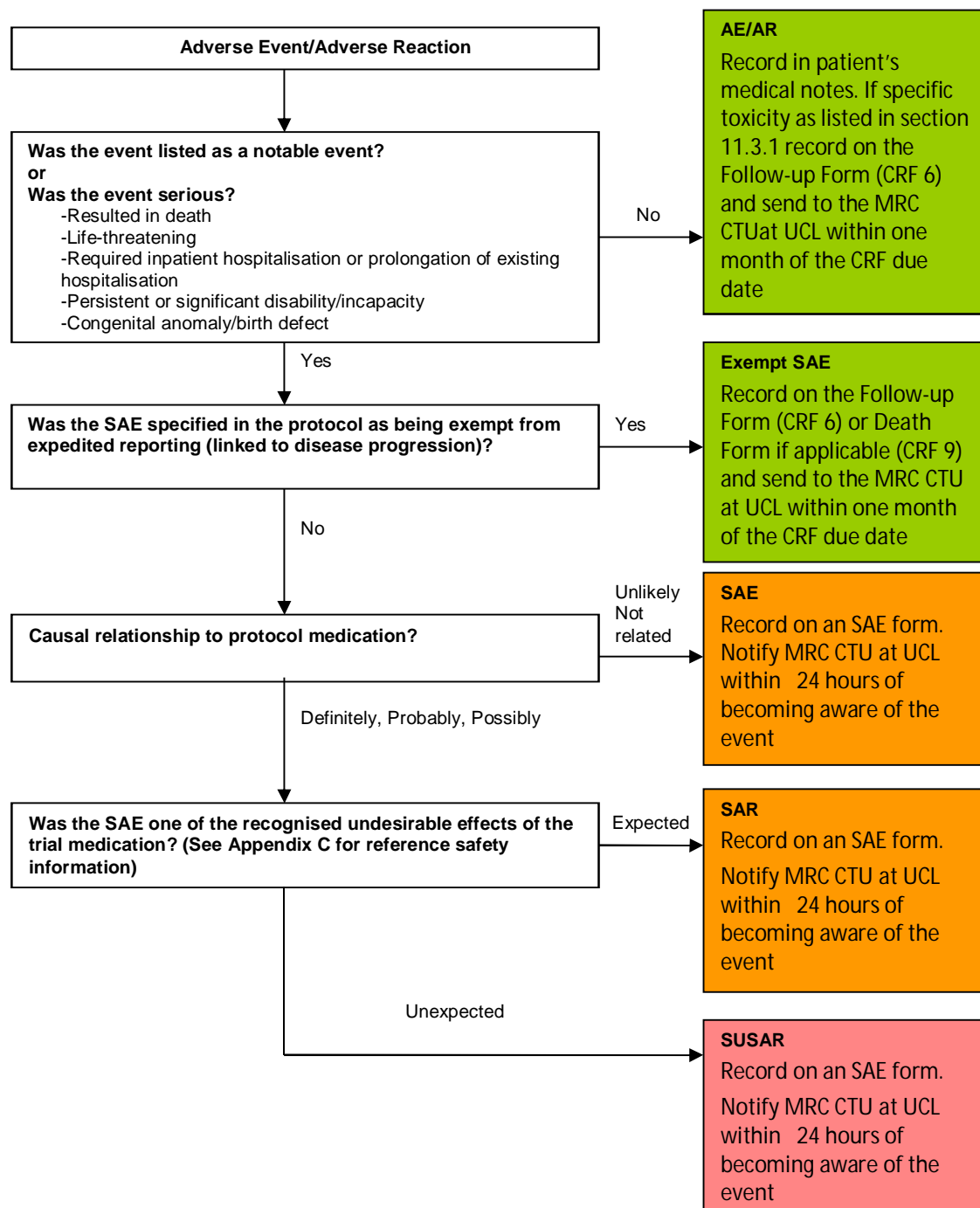
The MRC CTU at UCL is undertaking the duties of trial sponsor and is responsible for the reporting of all SUSARs and other SARs to the regulatory authorities and the research ethics committees as appropriate.

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

### **SAE NOTIFICATION**

**WITHIN 24 HOURS OF BECOMING AWARE OF AN SAE, PLEASE FAX A COMPLETED SAE FORM TO THE MRC CLINICAL TRIALS UNIT AT UCL ON:  
FAX: +44 (0)20 7670 4818**

## Safety Reporting Flowchart



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

## 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 (<https://mrc.ukri.org/research/policies-and-guidance-for-researchers/>).

## 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 at UCL 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.

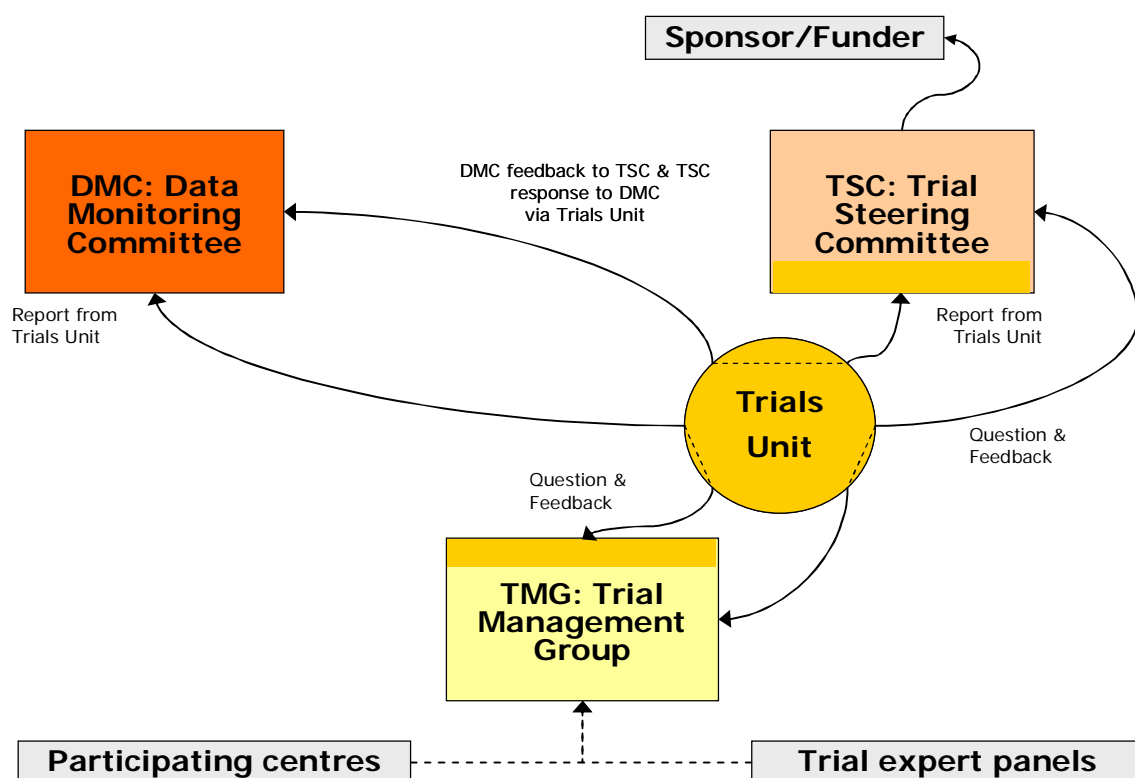
## 15.7 PATHOLOGY QUALITY ASSURANCE SUBGROUP

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 4: 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 4.1 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:  

Dose	Volume Objective
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 61/2 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  $\geq 8$  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.

#### 17.1.6 AMENDMENTS MADE TO PROTOCOL VERSION 4.0 JUNE 2011

This document was created using the MRC CTU Protocol Template Version 4.0, and as a result there are major formatting changes. The rationale to adopt this protocol template is to keep in line with the current style of documentation as recommended by the MRC CTU Protocol Review Committee. 'At UCL' has been added throughout protocol to reflect the organisational change.

1. Page i – Wording updated to reflect use of new protocol template.
2. Page i – Compliance section updated.
3. Page ii – Authorisations and Approvals section included.
4. Page ii – Trial Registration section included.
5. Page iii – Date of Ethics Approval added.
6. Page iii – Typographical correction: Regulatory approval date corrected from 17<sup>th</sup> April to 27<sup>th</sup> April.
7. Page iii – Email address has been amended.
8. Page iii – MRC CTU staff details updated.
9. Page iv – NCIC CTG contact details updated.
10. Section 1.1.1 – Typographical correction: space added between RADICALS-HD and alone.
11. Section 1.1.3.2 -Figure 3: Clarification added.
12. Section 1.1.5 – Years of further Follow-up updated to 7 years.
13. Section 4 – Table 1: Additional heading added.
14. Section 4.1 – Tables 2a and 2b merged as one table.
15. Section 4.1 – Table 2b: 4 weeks changed to 30 days for clarity and timing added.
16. Section 5.1.2 – Reference to see figures 1-4 corrected to figures 1-3.
17. Section 6.1 – Use of IMRT information added.
18. Section 6.1.3.4 – Updated to allow for other appropriate dose schedules.
19. Section 6.2.2 – Degarelix removed as an option for Canadian patients.
20. Section 6.2.2.1 – Degarelix removed as an option for Canadian patients.
21. Section 6.2.3 – Degarelix removed as an option for Canadian patients.
22. Section 6.2.3.1 - Degarelix removed as an option for Canadian patients.
23. Section 7.1 – Table 5: Two weeks prior to randomisation replaced by Within two weeks prior to randomisation for clarity.
24. Section 7.1 – Table 5: Randomisation forms details amended for clarity.
25. Section 7.5 – Details of national registries updated.
26. Section 7.6 – Trial closure information updated with current template.
27. Section 8.2 – Patient transfer procedure updated.
28. Section 9.2.3 – Requirement of radiotherapy treatment planning data added to treatment toxicity.
29. Section 9.3.2 – Clarification of number of patients randomised per month.
30. Section 10.2 – Typographical correction: hyphen added between RADICALS and RT.
31. Section 10.2 – 'the protocol' removed from last paragraph.
32. Section 10.2 – Information about data collection for RTTQA added.
33. Section 11.2 – Typographical correction: full stop added to end of 4<sup>th</sup> paragraph.
34. Section 11.3.2 (d) – Reporting period amended from one working day to 24 hours.
35. Section 11.3.2 – Notification procedure: Reporting period amended from one working day to 24 hours.

36. Section 11.4 - Reporting period amended from one working day to 24 hours.
37. Section 11.4 – Figure 4: Reporting period amended from one working day to 24 hours.

#### **17.1.7 AMENDMENTS MADE TO PROTOCOL VERSION 5.0 MARCH 2014**

1. Page i – Update to Canadian Sponsor name, Addition of information about sponsorship of the trial
2. Page ii – Update to MRC CTU address, update to MRC CTU staff
3. Page iii – Update to Canadian Sponsor name, update to CCTG staff
4. Section 1.1.3 – Update for Figure 1 and Figure 2
5. Section 1.1.4.A – Addition of 'Freedom from biochemical progression'; Addition of ARTISTIC meta-analysis outcomes
6. Section 1.1.4.B – Addition of number of recruited patients
7. Section 1.1.5 – Update to trial duration
8. Section 1.1.7 – Clarification of samples to be collected
9. Section 2.3 – Change of Canadian sponsor name
10. Section 2.5.1 – Details of ARTISTIC meta-analysis
11. Section 3 – Addition of a Bullet Point for point 4
12. Section 5.2 - Update to Canadian Sponsor name
13. Section 6.1.1 – addition of 'entering into' RADICALS-RT
14. Section 6.1.3.A – change Section 6.1.3.4 to Section 6.1.3.D
15. Section 7.2.2 – clarification of length of follow up
16. Section 7.5 – Addition of guidance for conducting visits with patients on long term follow-up
17. Section 7.5.1 – Addition of inclusion of ONS mortality data
18. Section 7.6 – Clarification of when trial closure will occur
19. Section 9.2.3 – Addition of 'Freedom from distant metastases (RADICALS-HD only); Addition of 'Freedom from biochemical progression (RADICALS-RT only)
20. Section 9.2.4 – Addition of details of early reporting of biochemical outcomes
21. Section 9.6.1 – Update to the plans for ARTISTIC collaborative group
22. Section 10.5 – Addition of guidance for sites regarding protocol deviations
23. Section 11.3 – clarification of SAE reporting
24. Section 11.3.1 - clarification of adverse event reporting, update to link of CTCAE V3.0
25. Section 11.3.2.A – change Table 5 to Table 6
26. Section 11.3.2.C – Addition of how to find RSI for investigators, addition of responsibility of assigning expectedness
27. Section 11.3.2.D – Clarification of reporting timelines for SARs and SUSARs
28. Safety Reporting Flowchart – Updated
29. Section 12 – change website address

## **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.

#### **17.2.10 AMENDMENTS MADE TO APPENDIX A VERSION 4.0 JUNE 2011**

1. Section Aiii – Urethral stricture removed from the RTOG toxicity table
2. Section Avii – Trial Committee Members list updated

#### **17.2.11 Amendments made to Appendix B version 4.0 June 2011**

1. Section Bii – MRC CTU trial email address updated
2. Section Biv – Date and version of GP letters updated
3. Section Bvi – Insurance arrangements have changed
4. Section Bviii – Patient Information Sheets have been removed from this appendix and will be kept as a separate document
5. Section Bix – Consent Forms have been removed from this appendix and will be kept as a separate document

#### **17.2.11 AMENDMENTS MADE TO APPENDICES VERSION 5.0 MARCH 2014**

1. Appendix A, Section A VII – update of trial committee members
2. Appendix B, Section B II – update of MRC CTU contact address
3. Addition of APPENDIX C: Reference Safety Information

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