RADICALS

Radiotherapy and Androgen Deprivation In Combination After Local Surgery

A randomised controlled trial in prostate cancer

ISRCTN 40814031
EUDRACT 2006-000205-34

MRC PR10, NCIC CTG PR13

STATISTICAL ANALYSIS PLAN

Version 7.0; 23-May-2022

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This template and all preceding versions will be stored in the Statistical Analysis Master File for this trial held by the Trial Statistician

Major changes to previous versions

V2.0	Update primary outcome for RT to FFDM Update sample size calculations Add early reporting of biochemical PFS for RADICALS-RT Use of ONS mortality data
V3.0	Define outcome to be used for early analysis of biochemical failure Introduce method for non-proportional hazards analysis of survival data
V4.0	Update primary outcome measure to MFS for RADICALS-HD
V5.0	Add death review criteria
V6.0	Add power calculations for subgroup analyses
V7.0	Add rationale for RT and HD having different primary endpoints.

CONTENTS

ABBREVIATIONS

Abbreviation	Expansion
bPFS	Biochemical progression-free survival
CI	Confidence interval
COD	Cause of death
CONSORT	Consolidated standards for reporting trials
CRD	Civil registration of death
CRF	Case report form
DSS	Disease-specific survival
FFDM	Freedom from distant metastasis
GnRHa	Gonadotrophin-releasing hormone analogue
Gy	Gray
HE	Health economics
HR	Hazard ratio
HT	Hormone therapy
ICH	International Conference Harmonisations
IDMC	Independent Data Monitoring Committee
IIEF	International Index of Erectile Function
LTHT	Long-term hormone therapy
MRC	Medical Research Council
MRC CTU	MRC Clinical Trials Unit at UCL
NCIC	National Cancer Institute of Canada
NCIC CTG	NCIC Clinical Trials Group
NHS	National Health Service
NHSCR	NHS central register
ONS	Office for National Statistics
PFS	Progression-free survival
PRO	Patient-reported outcome
PSA	Prostate specific antigen
RADICALS	Radiotherapy and Androgen Deprivation In Combination After Local Surgery
RP	Radical prostatectomy
RT	Radiotherapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SF-12	Short-form 12
SOP	Standard operating procedure
STHT	Short-term hormone therapy
SUSAR	Suspected Unexpected Serious Adverse Reaction

1 INTRODUCTION

RADICALS is an international, multi-centre, open-labelled, randomised controlled trial for men with prostate cancer. Full details of the background to the trial and its design are presented in the protocol.

This statistical analysis plan details the presentation and analysis for the RADICALS trial. It is intended that the clinical results reported in the main paper will follow the broad principles set out in this document and it is intended that these guidelines will be followed, as closely as possible, when analysing and reporting the trial. However, the final analysis may be determined by unpredictable aspects of the data.

2 STUDY METHODS

2.1 TRIAL DESIGN

The RADICALS trial has two separate randomisations. The first randomisation was performed immediately after radical prostatectomy for those patients where there was clinical uncertainty about the use of adjuvant post-operative radiotherapy (**Radiotherapy Timing Randomisation: RADICALS-RT**). In RADICALS-RT, patients were randomised between adjuvant post-operative radiotherapy and a policy of salvage radiotherapy (for PSA failure). The second randomisation was performed shortly before the administration of post-operative radiotherapy and concerns the addition of hormone therapy (**Hormone Duration Randomisation: RADICALS-HD**). In RADICALS-HD, patients were allocated to no hormone therapy, short-course (6 months) or long-course (24 months).

Patients entering RADICALS-RT and allocated adjuvant radiotherapy were encouraged to also enter RADICALS-HD at the same time; however, in practice this rarely happened. Patients entering RADICALS-RT and allocated the salvage radiotherapy policy could also join RADICALS-HD when PSA failure occurred, provided they were re-consented and the comparison was still open to recruitment. Patients who did not take part in RADICALS-RT could also enter RADICALS-HD if post-operative radiotherapy was clinically indicated, either immediately post-surgery or in the salvage setting for PSA failure.

2.1.1 DISEASE/PATIENTS STUDIED

Patients with non-metastatic adenocarcinoma of the prostate who had a radical prostatectomy were eligible for RADICALS-RT provided there was uncertainty, in the opinion of the clinician and patient, regarding the need for adjuvant post-operative radiotherapy (RT). Patients who were due to receive post-operative RT were eligible for RADICALS-HD.

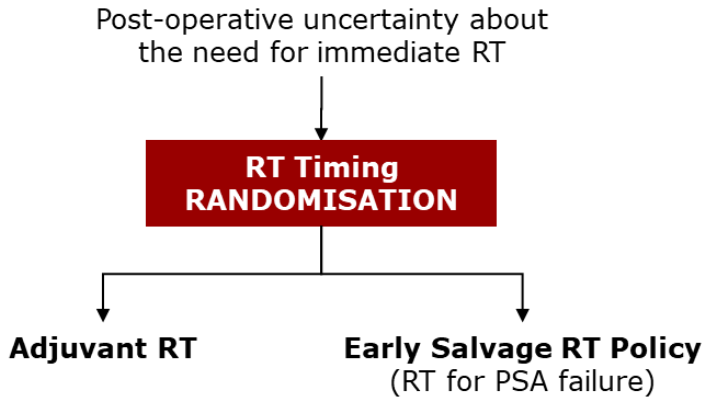
2.2 TRIAL INTERVENTIONS – RESEARCH AND CONTROL

There are two trial interventions in the RADICALS trial overall: radiotherapy and hormone therapy.

2.2.1 RADICALS-RT (RADIOTHERAPY TIMING RANDOMISATION)

- Adjuvant post-operative RT to prostate bed
- Salvage RT policy: RT to prostate bed given in the event of PSA failure.

Figure 1: RADICALS-RT overview



2.2.2 RADICALS-HD (HORMONE DURATION RANDOMISATION)

- No hormone (0 months) therapy with RT [No-HT]
- Short-term hormone therapy (6 months) commencing shortly before RT [STHT]
- Long-term hormone therapy (24 months) commencing shortly before RT [LTHT]

Patients were encouraged to be randomised between all 3 arms, but could be randomised between 0 and 6 or 6 and 24.

Figure 2: RADICALS-HD overview

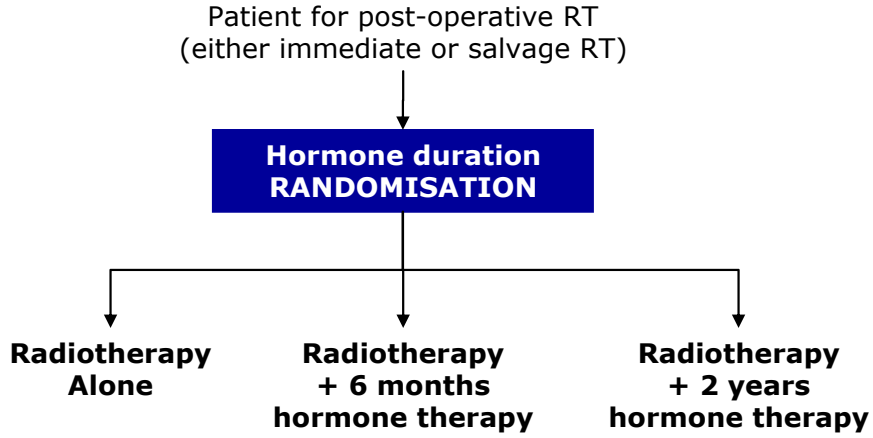
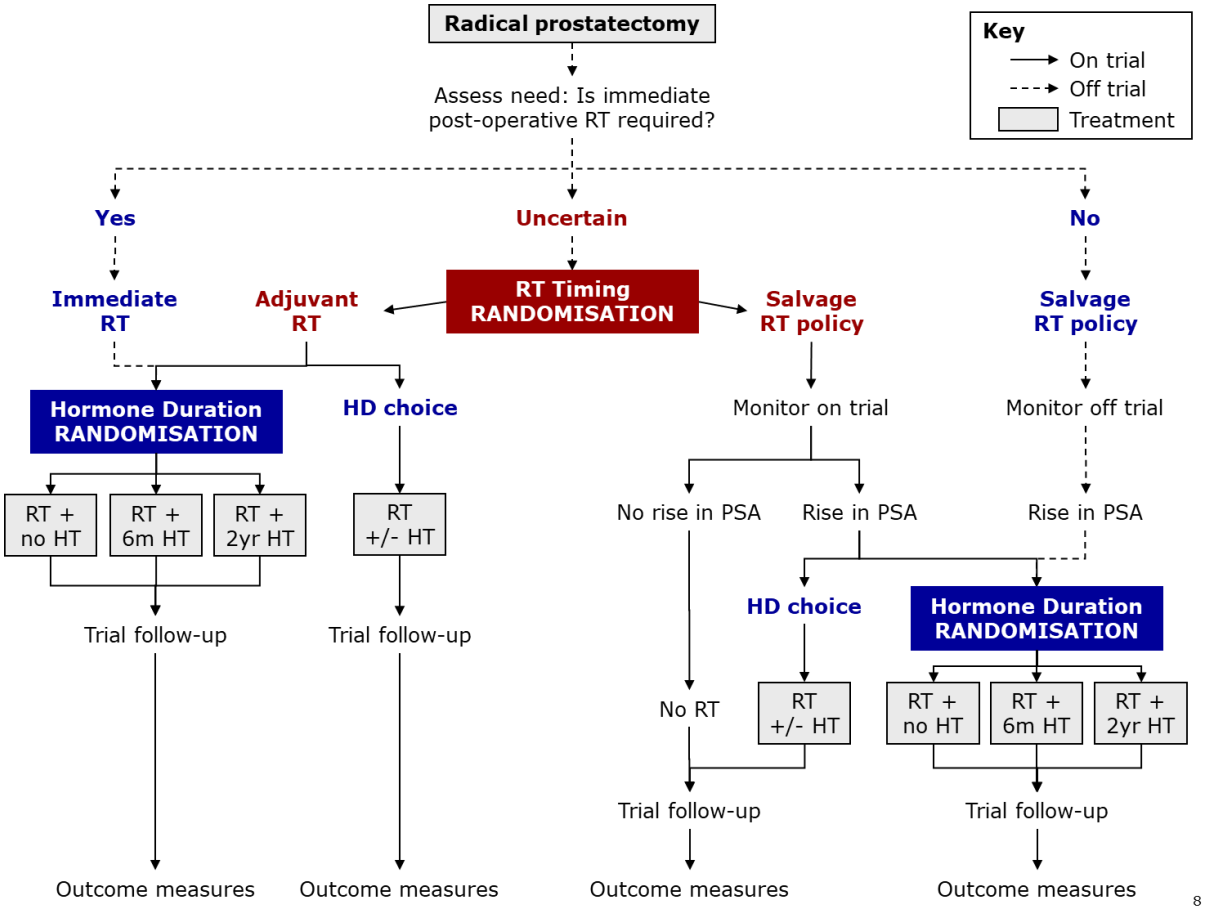


Figure 3: Overall trial design



2.2.3 DURATION

The trial was planned to address these questions over 12-13 years with $5^1/_2$ years of accrual and 7 years of further follow-up. The patient group is men with non-metastatic adenocarcinoma of the prostate who have had a radical prostatectomy. Treatment duration within the trial will range from zero months (i.e. a proportion of patients, maybe 60%, allocated to salvage 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 6.6 below.

2.3 RANDOMISATION

Randomisation was performed centrally at the MRC Clinical Trials Unit at UCL using computer-based algorithms. It was possible for patients to be randomised between two of

the three RADICALS-HD arms; therefore, there were separate implementations of the randomisation program to account for this.

The method of minimisation-with-a-random-element was employed where the minimising treatment is determined and treatment is allocated at random with an 80% probability of allocation to the minimising treatment. Stratification was used to help ensure balance over important clinical and practical factors. The stratification factors are presented in the table below.

Table 1: Stratification factors for trial randomisations

		Randomisation	
Stratification Factor	**Levels**	**RADICALS-RT**	**RADICALS-HD**
Gleason sum score	• <7 • 7 • >7	Stratification factor	Stratification factor
Margin status	• Positive • Negative	Stratification factor	Stratification factor
RT schedule	• 66Gy / 33f • 52.5Gy / 20f	Stratification factor	Stratification factor
Randomising centre	• Site	Stratification factor	Stratification factor
Timing of radiotherapy	• Adjuvant • Early salvage	No	Stratification factor
Choice of long-term HT	• GnRHa • Bicalutamide	No	Stratification factor

2.4 SAMPLE SIZE

2.4.1 BASIC ASSUMPTIONS (FROM PROTOCOL V1.0)

The sample size calculations were performed using the -art- package in Stata 9.(28) In terms of accrual and follow-up, these assumed 5½ years of recruitment, attaining a constant rate of accrual by 18 months after initiation of the trial in RADICALS-RT; a constant rate of accrual would be reached slightly later in time in RADICALS-HD as the rate may not peak until patients allocated to the early salvage radiotherapy policy in RADICALS-RT started to experience biochemical failure. After recruitment, the trial assumed a further 7 years of follow-up. Clinically, it assumed that the clinical community should only be interested in treatment options with an absolute increase in 10-year disease-specific survival of at least 5%.

The sample sizes have been calculated separately for the two randomisations because of potential variation in the underlying assumptions, unknown levels of overlap in both randomisations and some uncertainty about accrual rates. A number of scenarios relating to

trial recruitment and assumptions were calculated and are reported elsewhere; these are available upon request. Selected scenarios are reported here.

2.4.2 RADICALS-RT Sample Size

In the patients suitable for randomisation in RADICALS-RT, the control arm was assumed to be the salvage radiotherapy policy i.e. radiotherapy at PSA relapse. There was some uncertainty in the baseline disease-specific survival (DSS) rate. However, a total of 2600 patients could detect an increase in 10-year DSS:

- from 70% to 75% (HR=0.81) with 80% power (679 events) or
- from 80% to 85% (HR=0.73) with 90% power (423 events)

each with 5% two-sided significance level. This recruitment target could be achieved with a recruitment rate of approximately 500 patients per year (42 patients per month) from 18 months onwards.

2.4.3 RADICALS-RT: Change of Primary Outcome to FFDM (protocol v4.0 Onwards)

From data that became available from the SWOG 8794 and EORTC 22911 trials after recruitment began to RADICALS-RT, the proportion of patients free of distant metastases at 10 years was estimated to be 90%, an event rate much lower than previously anticipated. The trial would look to test whether adjuvant RT could improve this to 95% (hazard ratio 0.487), which was seen as the minimum, clinically-significant absolutely 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, the trial would need to recruit 1,063 patients in order to observe 66 distant metastases events. This sample size assumed that 30% of patients would be lost to follow-up after 5 to 10 years in the trial, and accrual rates of around 30 patients/month randomised from 30 months onward. Therefore, the target sample size was reduced from 2,600 to around 1,063 patients. If the peak accrual was 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.

2.4.4 RADICALS-HD Sample Size (protocol v1.0 Onwards)

Patients would be suitable for this randomisation in RADICALS-HD at the time they were planned for post-operative radiotherapy, whether adjuvant or early salvage. When RADICALS was launched, patients randomised to receive adjuvant radiotherapy in RADICALS-RT had to take part in this randomisation as well. There is some uncertainty in the baseline disease-specific survival rate for patients allocated to adjuvant RT *and* for patients allocated to the early salvage RT policy. It was assumed that patients allocated adjuvant radiotherapy do at

least as well as patients allocated to the salvage radiotherapy policy. There was also uncertainty over the proportion of adjuvant and early salvage patients that would join the trial; it was assumed that at least as many patients following an early salvage RT policy would be randomised, if not two to three times more. A total of 2035 patients (305 events) in a two-way comparison of No-HT vs either duration arm would allow for 80% power to detect an increase in 10-year DSS from 82% to 87% (HR=0.71). The long-term hormone therapy (LTHT) and short-term hormone therapy (STHT) arms would be separately compared to the No-HT. Therefore, a 3% two-sided significance level would be used to allow for the repeated use of the No-HT arm. Therefore, if all patients are randomised between all three hormone duration arms, a total of 3053 patients would be required. This could be achieved in $5^1/_2$ years with 54 patients randomised each month from 18 months onwards.

Patients were permitted to be randomised between two of the three HT duration randomisation arms during the pilot phase and this was continued in the long-term to facilitate randomisation: Patients could be randomised between No-HT and STHT, or between STHT and LTHT, or, ideally, between all three arms. It is accepted that the required sample size increases with each patient randomised between two arms. If both STHT and LTHT were each better than No-HT, a comparison of STHT and LTHT would be undertaken. If both were advantageous over No-HT, the difference between these arms would be smaller and there would likely be insufficient events to adequately power the comparison between the durations. However, the results of the comparison would be indicative and still be useful.

2.4.5 UPDATE TO RADICALS-HD DESIGN IN 2011 (PROTOCOL V4.0 ONWARDS)

It became apparent the three-way randomisation was less well supported than either of the two separate potential two-way randomisations: No-HT vs STHT and STHT vs LTHT. These were each clinically important questions and it was agreed that RADICALS-HD should address both. This meant it would 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 became:

1. RT without hormone therapy (No-HT) vs RT + short-term hormone therapy (STHT), often referred to as "None vs Short"
2. RT+ short-term HT (STHT) vs RT + long-term HT (LTHT), often referred to as "Short vs Long"

It was assumed that patients who joined the "STHT vs LTHT comparison" would have a slightly higher risk of a disease event than patients who enter "No-HT vs STHT comparison" because the clinician assumed that some hormone therapy was required; therefore, their 10-year DSS rate was estimated as being lower.

2.4.6 UPDATE: NO-HT VS STHT (PROTOCOL V4.0 ONWARDS)

It was estimated that DSS would be 85% at 10 years in patients allocated to No-HT. This superiority trial would be testing whether addition of STHT to RT could 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 of those patients who join the three-way randomisation).

2.4.7 UPDATE: NO-HT VS STHT (PROTOCOL V7.0 ONWARDS)

The primary outcome measure of RADICALS-HD was amended from disease-specific survival (DSS) to metastatis-free survival (MFS) after independent peer review of a proposal by the Trial Management Group in 2019 without any reference to accumulating, comparative data. This followed the work of the ICECAP group to show that MFS was a good earlier outcome measure in this disease setting. At this point, recruitment was already completed with 1480 patients in this No-HT vs STHT comparison. It was estimated that MFS would be approximately 80% at 10 years in patients allocated to the No-HT group. The No-HT vs STHT comparison would have >80% power, with a two-sided 5% alpha, to detect an absolute increase in MFS of 6%, from 80% in the No-HT group to 86% (HR=0.67) in STHT. Approximately 200 MFS events were anticipated for this analysis.

2.4.8 UPDATE: STHT VS LTHT (PROTOCOL V4.0 ONWARDS)

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

2.4.9 UPDATE: STHT VS LTHT (PROTOCOL V7.0 ONWARDS)

The primary outcome measure of RADICALS-HD was amended from disease-specific survival (DSS) to metastatic-free survival (MFS) after independent peer review of a proposal by the Trial Management Group in 2019 without any reference to accumulating, comparative data. This followed the work of the ICECAP group to show that MFS was a good earlier outcome measure in this disease setting. At this point, recruitment was already completed with 1524 patients in this "STHT vs LTHT comparison". It was estimated that MFS would be approximately 75% at 10 years in patients in patients allocated to STHT in this comparison; it was expected that patients in this comparison would be at higher risk of an event than those in "No-HT vs comparison". The "STHT vs LTHT comparison" should have over 80%

power, with a two-sided 5% alpha, to detect an absolute increase in MFS of 6%, from 75% in the short HT group to 81% in the long-HT group (HR=0.72). Approximately 300 MFS events are anticipated for this analysis.

2.4.10 OVERALL SAMPLE SIZE (PROTOCOL V1.0 ONWARDS)

The overall sample size for the RADICALS protocol would depend on how many patients are recruited to both the RADICALS-RT and the RADICALS-HD , and how many patients joined the three-arm RADICALS-HD. It was anticipated that, of patients who have undergone radical prostatectomy, 10% would have a definite indication for non-randomised adjuvant radiotherapy and 50% would have a definite indication for following an policy of early salvage radiotherapy. The value of adjuvant radiotherapy will would be uncertain in the remaining 40% who, if they met the eligibility criteria, should be randomised in RADICALS-RT. Therefore, if accrual to RADICALS-RT ran at 42 patients per month, 21 of these patients certainly would also be in the RADICALS-HD i.e. those who are allocated adjuvant RT. The remaining 33 patients per month targeted for the RADICALS-HD would be patients currently monitored off-trial whose PSA is rising and, increasingly over time, patients randomised to early salvage radiotherapy whose PSA is starting to rise.

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

Subsequently, on the advice of the IDMC, the TMG and TSC decided to de-couple randomisation to RADICALS-RT and RADICALS-HD, as explaining both comparisons was causing some sites difficulty. At this point, the concept of an overall sample size for RADICALS disappeared, replaced by the sample size for each comparison separately.

3 OUTCOME MEASURES

As explained in Section 2, RADICALS was originally designed with the same outcome measures in both randomisations. Emerging data external to RADICALS showed that, for RADICALS-RT, an absolute improvement of 5% in disease-specific survival was not an achievable improvement, and in 2011 the primary outcome measure for RADICALS-RT was amended, after independent peer review, to **freedom-from-distant-metastases**. By 2019, it was also apparent that RADICALS-HD would not reach maturity for its original primary outcome measure in a realistic timeframe, and new evidence from the ICECAP meta-analysis of similar trials [1] showed that **metastasis-free-survival** could serve as a suitable surrogate, and so the primary outcome was formally amended, after independent peer review, to metastasis-free survival. The Trial Management Group considered it appropriate to use different primary outcome measures for RADICALS-RT and RADICALS-HD parts of RADICALS. The primary outcome measure for RADICALS-RT excludes death from other causes. However, the TMG considered it important the primary outcome measure for RADICALS-HD also include deaths from any cause because hormone therapy may increase the risk of death from other causes.

3.1 RADICALS-RT

3.1.1 PRIMARY OUTCOME MEASURE

- Freedom-from-distant-metastasis (any distant metastasis or prostate cancer death)

3.1.2 SECONDARY OUTCOME MEASURES

- Disease-specific survival (Death due to prostate cancer)
- Metastasis-free survival (any distant metastasis or death from any cause)
- Freedom-from-treatment-failure (PSA progression when on HT)
- Clinical progression-free survival (Clinical progression of PCa, initiation of non-protocol HT, PCa death)
- Overall survival (Death from any cause)
- Non-protocol hormone therapy (Initiation of HT other than that randomised)
- Treatment toxicity (Grade 3+ AE or SAE)
- Patient-reported outcomes (Focused on key functional issues)
- Freedom from biochemical progression

3.2 RADICALS-HD

3.2.1 PRIMARY OUTCOME MEASURE

- Metastasis-free survival (any distant metastasis or death from any cause)

3.2.2 SECONDARY OUTCOME MEASURES

- Freedom-from-distant-metastasis (any distant metastasis or PCa death)
- Freedom-from-treatment-failure (PSA progression when on HT)

- Clinical progression-free survival (Clinical progression of PCa, initiation of non-protocol HT, PC death)
- Overall survival (Death from any cause)
- Non-protocol hormone therapy (Initiation of HT other than that randomised)
- Treatment toxicity (Grade 3+ AE or SAE)

Patient-reported outcomes (Focused on key functional issues)

1. Metastasis-free survival is a strong surrogate of overall survival in localised prostate cancer. Xie W, Regan M, Buyse M, et al. J Clin Oncol 2017; 35(27)3097-3104.

4 DATA

4.1 CRFS AND VARIABLES

The data collection schedule is detailed below. Full details of data collection and timing are described in the protocol.

Table 2: Timing of assessments and CRFs completed

Timing	Case report form										Timing
	1	2	3	4	5	6	7	8	9	PRO	
Before rand[n]	X	X									Before rand[n]
At rand[n]			X	X						X	At rand[n]
After RT					X						After RT
Month 4						X					Month 4
Month 8						X					Month 8
Year 1						X				X	Year 1
Month 16						X					Month 16
Month 20						X					Month 20
Year 2						X					Year 2
Month 30						X					Month 30
Year 3						X					Year 3
Month 42						X					Month 42
Year 4						X					Year 4
Month 54						X					Month 54
Year 5						X				X	Year 5
Year 6						X					Year 6
Year 7						X					Year 7
Year 8						X					Year 8
Year 9						X					Year 9
Year 10						X				X	Year 10
Year 11						X					Year 11
Year 12						X					Year 12
Year 13						X					Year 13
Year 14						X					Year 14
Year 15						X					Year 15
At event						X	X				At event
At SAE								X			At SAE
At death									X		At death

Table 3: Key to Table 2

CRF	Description
1	Baseline Information form
2	Co-morbidity form
3	RT Timing & RADICALS-HD
4	RADICALS-HD alone
5	Radiotherapy forms
6	Follow-up forms
7	Disease Event form
8	Serious adverse event form
9	Death Report form
PRO	Patient Reported Outcome forms*
Other	**Description**
SAE	Serious adverse event
Timing	Relative to most recent randomisation**

* RADICALS-RT only

** Follow-up schedule is reset for patients at randomisation in RADICALS-HD if having RT as part of the early salvage RT policy in RADICALS-RT

4.2 MANAGEMENT OF DATASETS

A clinical trial database was established in Macro and this will be used as the repository for all trial data (see separate Trial Management SOPs). At the time of analysis:

- The responsible statistician or allocated DMS Programme will file out from Macro a dataset of all data stored in the database. This will act as the frozen dataset. It is the responsibility of the statistician to accurately record the date of freezing
- A copy of the database will be warehoused at this point
- New data can continue to be entered onto the Macro database unless otherwise agreed (Database Lock)
- If any outstanding data queries are resolved during the analysis that relate to data in the frozen dataset (e.g. problems that are found during analysis or amended CRFs that are returned to MRC CTU), the main Macro database should be changed under the oversight of the Trial Manager

4.3 DATASETS AND DATA COLLECTION

Datasets for analysis will be constructed at CTU using programmable Stata analysis files (*.do). Every care will be taken in constructing and connecting these datasets. Stata 15 or a later version will likely be used for the analyses as this would allow for interim analysis files to be used to form the basis of the final analysis files.

Additional information may be drawn from outwith the clinical storage databases e.g. trial patients from Engand and Wales are flagged with the Office for National Statistics to supplement survival data and death review.

4.4 DATA VERIFICATION

Data verification, consistency and range checks will have been performed at the data entry stage by the MRC CTU, as well as checks for missing data. Additional range, consistency and missing data checks will be performed, as appropriate, when the datasets for analysis are constructed. All variables will be examined for unusual, outlying, unlabelled or inconsistent values.

Given the thorough nature of our follow-up procedure and the intentional simplicity of the requested data, the issue of missing data is expected to be minimal. We anticipate high compliance with initial data collection as this is close to the time of patient registration. If any data is missing no imputation will be done.

Any problems with trial data would be queried with the Trial Managers, Data Managers, or statisticians, as appropriate. If possible, data queries will be resolved, although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist. This will be minimised.

4.5 DATA CODING

4.5.1 CODING OF FREE-TEXT VARIABLES

The trial case report forms (CRFs) present some questions whose responses require categorisation prior to summarisation. In many of these cases, a limited number of categories are presented but the option to provide an answer outwith these categories is usually offered. Therefore, the appropriate grouping for these responses will need to be undertaken prior to analyses. These have been classified by statistical/trial management staff for the purposes of interim analyses, but will be reclassified by the appropriate clinically qualified staff at CTU, and offered to the Principal Investigators prior to analyses. Indeed, such categorisation will be honed during interim and administrative analyses performed throughout the trial.

The variables requiring such categorisation may include (but are not limited to):

- Reason for permanently stopping protocol treatment
- Treatment after disease events
- Suspected event (adverse event data)

4.5.2 END OF FOLLOW-UP

Follow-up in the trial ended on 31st December 2021. For each patient, follow-up time is calculated as the period from randomisation to the date last seen prior to 31 December 2021. For data received after 31st December 2021 and before database lock, outcome events and follow-up time will not be included in analyses unless they occurred prior to 31st December 2021.

4.5.3 REVIEW OF CAUSES OF DEATH

For disease-specific survival (DSS), 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 Office for National Statistics (ONS) for mortality data to support the data collected on the case report forms (CRFs).

Prior to analysis, reported deaths may be reviewed by a clinician to confirm whether the death was due to prostate cancer. The cause of death will be considered uncertain for deaths

not meeting one of the criteria listed in table 4, all such deaths will then be clinically reviewed.

Table 4. Criteria for deaths that do not require clinical review

Patients with ONS flagging (E&W)	Death CRF reports primary COD to be prostate cancer. No other factor reported as first, second or third contributory cause. Prostate cancer recorded as primary or underlying COD on death certificate.	Probably prostate cancer
	Death CRF reports primary COD to be other primary malignancy. No other factor reported as first, second or third contributory cause. Other cancer type recorded as primary or underlying COD on death certificate.	Probably ***not*** prostate cancer
	Death CRF has primary cause and first, second, third contributory causes as non-cancer. Death certificate has underlying and first, second, third contributory causes as non-cancer.	Probably ***not*** prostate cancer
Patients without ONS flagging	Death CRF reports primary COD to be prostate cancer. No other factor reported as first, second or third contributory cause. Clinical or biochemical progression reported, no secondary primary cancer reported.	Probably prostate cancer
	Death CRF reports primary COD to be other primary malignancy. No other factor reported as first, second or third contributory cause. No clinical or biochemical progression reported, secondary primary cancer reported.	Probably ***not*** prostate cancer
	Death CRF has primary cause and first, second, third contributory causes as non-cancer. No clinical or biochemical progression reported, no secondary primary cancer reported.	Probably ***not*** prostate cancer

For deaths which are clinically reviewed, cause of death will be classified using the categories:

1. Definitely prostate cancer
2. Probably prostate cancer
3. Possibly prostate cancer
4. Probably not prostate cancer
5. Definitely not prostate cancer
6. Insufficient data to assign cause of death.

For the main analyses, categories 1 and 2 will be taken to indicate a prostate cancer death.

4.6 CIVIL REGISTRATION OF DEATH DATA

Civil registration of death (CRD) data (Healthcare Systems Data) for England and Wales became available to the trial in Jan-2018, to be updated quarterly thereafter. This enables regular checking for completeness of the trial database, with specific data chases to sites in the event of unreported deaths becoming known. Restrictions placed by ONS, later NHS Digital, means that that this death data could not be relied on in the long-term, an issue being resolved outside of RADICALS, and the trial team could not rely on this in the long-

term. Therefore, deaths reported from Healthcare System Data were used to verify the clinical database with the participating site.

Death data from Healthcare Systems Data also enables checking for unreported distant metastases, in the event of a prostate cancer death being registered in the CRD dataset without distant metastases being previously recorded in the trial database.

Queries were sent to sites if any of the following three criteria were met:

1. Underlying COD is prostate cancer in CRD dataset, but not in the database – checking for unreported prostate cancer deaths
2. Underlying COD is prostate cancer in CRD dataset, but no mets reported in the database – checking for unreported mets
3. Mets are reported, cause of death is not "prostate cancer" in CRD dataset or the database and the cause of death differs between CRD dataset and the database – checking for unreported prostate cancer deaths

5 DEFINITIONS OF TERMS

The table, below, defines some terms that may be used in the analysis.

Table 4: Definition of terms

Term	Definition
PSA progression (criteria for RT in deferred arm of RT randomisation)	Two consecutive rises in PSA and final PSA > 0.1 ng/ml OR three consecutive rises in PSA after radical prostatectomy.
Biochemical progression (criteria for failure in early reporting of biochemical outcomes)	PSA≥0.4 ng/ml following RT, or PSA>2.0 ng/ml at any time.
Case report form (CRF)	Pro forma for collecting data, also known as Clinical Record Form
Date last seen	This is the date on which the patient was last seen (alive or dead) and will be taken as the maximum of date of randomisation, date of follow-up (except on forms where the patient died), date of death, date of onset or resolution of an adverse event.
Loss to follow-up	No data for more than 2 years or site reports as lost
Overall survival	Time from randomisation to death from any cause
Progression-free survival (PFS)	First clinical failure event including local progression, lymph node mets, bone mets, other mets and death
Prostate cancer death	Death from prostate cancer or death from treatment for prostate cancer
Clinical progression of prostate cancer	Local progression, pelvic nodal disease, lymph node mets, bone mets, other mets, initiation of non-protocol HT, prostate cancer death

6 STATISTICAL PRINCIPLES

All analyses will be performed on an intention-to-treat basis; no per-protocol analyses are planned. All patients will be included in analyses, including those patients who do not start any allocated trial treatment and those who cross-over immediately to the management approach described by another trial arm. Patients with any major ineligibility criterion and who were randomised in error will be included to the extent that sites permit follow-up.

All statistical tests will be at the 2-sided p-value of 0.05, unless otherwise specified. There will be no formal adjustment of p-values for interim analyses performed or for multiple testing. In the original design the significance level was adjusted for testing two treatment durations against no treatment, but following the way that randomisation developed the design now compares no treatment with short duration, and short duration with long duration. Comparability at baseline of the randomised groups will be examined but significance testing will not be performed as this is not appropriate in such comparisons.

Continuous variables will be summarised as (at least) the minimum, quartiles, maximum, mean, standard deviation and number of values, and would be tested with an appropriate parametric or non-parametric test (possibly with an appropriate, prior transformation of the values). Categorical data will be presented as numbers and percentages, and tested using a χ^2 test or Mann-Whitney U-test, as appropriate.

Time-to-event data will be presented using Kaplan-Meier plots with appropriately scaled x-axes with labels at appropriate intervals and the number of patients at risk displayed; if possible this will be supplemented with the number of events. In time-to-event analyses, patients that have not experienced the event in question (e.g. progression) will be censored on the date last seen. Time-to-event data will be tested using a log-rank χ^2 test. The number of events observed and the log-rank expected number of events will be presented. Unadjusted hazard ratios (HR) will be calculated with Cox regression models in order to express the differences between the treatment arms; 95% CIs will be presented. Regression models will be stratified by randomisation stratification factors (primary analysis). Adjusted models will also be presented, adjusting for characteristics that may be of prognostic significance such as nodal stage. Kaplan-Meier plots will be presented in the KMunicate format with confidence intervals around the lines and an extended risk table.

PFS and OS will be evaluated according to the following process to take into account potential non-proportional hazards:

1. Test the treatment effect using the log rank test
2. Test the treatment effect for non-proportional hazards using the Grambsch-Therneau test. A graphical plot of the hazard ratio over time will also be plotted, as estimated from a flexible parametric model with a time-dependent treatment effect.

3. If no evidence of proportional hazards is shown (P≥0.1), then the hazard ratio and associated confidence interval will be presented as the primary summary of the treatment effect.
4. If non-proportional hazards are evident (P<0.1), then the primary measure of treatment effect that will be used is the difference in the restricted mean survival time, and its associated 95% confidence interval, at a salient timepoint to maximise power.

Together with the HR, the proportion of patients event-free at set times by treatment group and the difference between these figures will be described at clinically salient timepoints. The estimate of these figures for both groups will be taken from smoothed fitted curves or the figure for the reference group will be taken from the life table and the estimate for the research group be calculated using the reference figure and the HR. The difference between the treatment groups will be calculated using these two figures, and the 95% CI of the difference will be calculated. Similarly, the median time-to-event will be presented for each group using the same principle, if the median time has been reached.

To assess whether any treatment is more or less effective in well-defined subgroups, χ^2 tests for heterogeneity or, when appropriate, trend will be performed. Forest plots will be presented to more visually summarize the consistency of effect in each subgroup. Subgroups are defined in 6.3 below.

Median follow-up time will be calculated using a Kaplan-Meier approach, taking date last seen (if alive) to be an event and death as the time of censorship.

Only randomised groups will be compared. There is no intention to compare groups that were not randomised directly, unless there are unusual and specific circumstances during which such analyses would be performed in an exploratory fashion, clearly labelled as such and interpreted with caution.

6.1 INTERIM ANALYSES

The data were reviewed and interim analyses performed at regular intervals (approximately annually) for a review by an Independent Data Monitoring Committee (IDMC) who will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment and follow-up of further patients (see the IDMC Charter). No formal stopping rules are planned. The feasibility of the trial was be reviewed at 18 months from the start of the trial.

6.2 EARLY REPORTING OF BIOCHEMICAL OUTCOMES

In early 2018, based on the number of primary outcome events in the control arm of RADICALS-RT, data maturity was not forecast to occur until 2025. This was several years

later than originally expected due to the low event rate. Two RCTs asking complementary questions, RAVES and GETUG-17, were planning to report in 2019. Working with the ARTISTIC group, a meta-analysis was prospectively planned using the FAME approach. This planned to combine RAVES, GETUG-17 and RADICALS-RT with aggregate data, and individual patient data (IPD) meta-analysis if required. The RADICALS TMG therefore agreed in Feb-2018, and with the agreement of the IDMC and TSC, to publish the biochemical PFS (bPFS) results of RADICAL-RT to coincide with the other two trials, and enable a timely meta-analysis. bPFS had not previously been an outcome measure of interest in RADICALS-RT.

As part of the early reporting, interim data was presented on freedom-from-distant-metastases (primary outcome measure) for the control arm only of RADICALS-RT. This was considered informative as it would indicate how much room for improvement existed, but would not compromise the main analysis by inappropriate disclosure of accumulating comparative data.

Early reporting of RADICALS-RT took place, as described above, with presentation at ESMO in 2019 and a subsequent Lancet publication in 2020.

6.2.1 Definition of Endpoint for Biochemical PFS

Biochemical progression is defined as PSA≥0.4 ng/ml following RT, or PSA>2.0 ng/ml at any time (Table 5). The higher value is intended to capture patients allocated to the early salvage RT policy who experienced a PSA rise but who, for some reason, did not then have RT. A further criterion for defining biochemical progression is that PSA must be rising relative to the previous measurement, to allow for slow decline following RT in any setting.

In order to capture patients where biochemical progression goes unreported the following events would also be counted as endpoints:

- Clinical progression
- Initiation of non-protocol hormone therapy
- Death from prostate cancer

The number of additional events identified by these outcomes was expected to be small as each should always be preceded by PSA progression.

Clinical progression is reported on disease event CRF as evidence of local progression, new pelvic nodal disease or distant metastases. Distant metastases comprise distant node, bone, liver, lung or other metastatic disease. Suspicion of local progression or distant metastases may also be reported. This should be followed by a reported event; if suspicion is reported with no subsequent event this will be queried, but if confirmation is not received in time suspicious events will be included in the analysis.

Initiation of non-protocol hormone therapy is reported on disease event forms.

Deaths are reported on disease event forms and death forms; ONS data is used to check completeness of death reporting.

A modified version of the above bPFS definition, using deaths from any cause, will also be presented although the addition of all-cause deaths is expected to dilute the treatment effect since most deaths will not be from prostate cancer.

6.3 SUBGROUP ANALYSES

a. The effect of randomised treatment will be analysed within groups defined by stratification factors, with the exception of centre. As exploratory interaction analyses it is recognised that these pre-specified analyses will have low power. To detect the target HR of 0.67 for "none vs short" in adjuvant and salvage subgroups, power would be approximately 28% and 75% respectively. For the target HR of 0.72 for "short vs long" in adjuvant and salvage subgroups, power would be approximately 47% and 56% respectively.
b. The effect of co-morbidities will be investigated in a proper subgroup analysis using the Charlson comorbidity score at randomisation. Strata will be 0, 1, ≥2 comorbidities, with the prior expectation that the benefit of longer-term HT is greater in men with less comorbidity.
c. Among patients following a salvage RT policy, it has been suggested from the RTOG 9601 trial that pre-RT PSA is predictive of hormone therapy benefit, with greater benefit of ADT in men with higher PSA. A proper subgroup analysis with a stratified analysis of both RADICALS-HD comparisons will therefore be undertaken, stratifying patients by their pre-RT PSA <0.3ng/ml, ≥0.3 and <0.5ng/ml, ≥0.5ng/ml. These pre-specified analyses wi would ll also have low power. To detect the target HR of 0.67 for "none vs short" in <0.3, 0.3-0.5 and >0.5 subgroups, power will be approximately 46%, 29% and 24% respectively. To detect the target HR of 0.72 for "short vs long" in <0.3, 0.3-0.5 and >0.5 subgroups, power would be approximately 27%, 16% and 25% respectively.

6.4 SENSITIVITY ANALYSES

Healthcare systems data on death, available only for patients in England and Wales, is used primarily to verify the clinical database. To explore the effect of this restriction a sensitivity analysis will be undertaken in which patients will be assumed alive at the date of the most recent NHSD data extract – patients with no death reported can be assumed to be alive 8 weeks before the data freeze.

6.5 ANALYSIS DETAILS

The results of the analyses will be reported following the principles of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports. Overall, the flow of patients through the trial will be presented in a CONSORT diagram, which will be developed in future versions and may be based on the overall trial schema presented in
Figure 3: Overall trial design

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6.6 ANALYSIS POPULATIONS

6.6.1 RADICALS-RT – EFFICACY ANALYSES

All patients randomised into RADICALS-RT will be included.

6.6.2 RADICALS-RT – SAFETY ANALYSES

All patients randomised into RADICALS-RT will be included. It is accepted that some patients will cross-over. One arm involves not having additional treatment (at least, not immediately) so it is inappropriate to perform safety analyses only on the group of patients which start treatment.

6.6.3 RADICALS-HD: "NONE VS SHORT"– EFFICACY ANALYSES

All patients randomised between No-HT and STHT in RADICALS-HD will be included.

6.6.4 RADICALS-HD: "NONE VS SHORT" – SAFETY ANALYSES

All patients randomised between No-HT and STHT in RADICALS-HD will be included. One arm involves no additional treatment so it is inappropriate to limit to patients starting treatment. It is accepted that some patients will cross-over.

6.6.5 RADICALS-HD: "SHORT VS LONG" – EFFICACY ANALYSES

All patients randomised between STHT and LTHT in RADICALS-HD will be included.

6.6.6 RADICALS-HD: "SHORT VS LONG" – SAFETY ANALYSES

All patients randomised between STHT and LTHT in RADICALS-HD will be included. Analysis is not limited to patients starting treatment, for consistency with the other comparisons. It is accepted that some patients will cross-over.

6.6.7 RADICALS-HD: "NONE VS LONG" – EFFICACY ANALYSES

All patients randomised between No-HT and LTHT in RADICALS-HD will be included (i.e. only those patients joining the 3-way RADICALS-HD).

6.6.8 RADICALS-HD: "NONE VS LONG" – SAFETY ANALYSES

All patients randomised between No-HT and LTHT in RADICALS-HD will be included (i.e. only those patients joining the 3-way RADICALS-HD). One arm involves no additional treatment so it is inappropriate to limit to patients starting treatment. It is accepted that some patients will cross-over.

6.7 SUMMARY OF PLANNED ANALYSES

Table 66 presents the planned analysis. The table is broken down by CRF (broadly), item of analysis, method of presentation, how data will be split, when analyses will be performed (be that interim or final) and the patient group considered in the analysis. Additional information may be provided in an extra section after this table in later versions.

Table 6: Planned comparisons

Data set	Comparison							
	RADICALS -RT		RADICALS-HD "None vs Short"		RADICALS-HD "Short vs Long"		RADICALS-HD "None vs Short"	
	Interim	Final	Interim	Final	Interim	Final	Interim	Final
Recruitment details								
Observed vs expected over time	I	F	I	F	I	F	I	F
Choice of RADICALS-HD arms			I	F	I	F	I	F
Recruitment by centre, and by country	I	F	I	F	I	F	I	F
Data returns								
Forms returned	I	F	I	F	I	F	I	F
Forms returned compared to expectations	I	F	I	F	I	F	I	F
Loss to follow-up	I	F	I	F	I	F	I	F
Randomisation and baseline form data								
All inclusion criteria satisfied	I	F	I	F	I	F	-	F
All exclusion criteria satisfied	I	F	I	F	I	F	-	F
All baseline data summarised including disease staging	I	F	I	F	I	F	-	F
Time from RP to randomisation	I	F	I	F	I	F	-	F
Co-morbidity scores	-	F	-	F	-	F	-	F
Radiotherapy								
Administration of radiotherapy	I	F	I	F	I	F	-	F
Time from randomisation to radiotherapy or censoring	I	F	I	F	I	F	-	F
Time from RP to radiotherapy or censoring	I	F	I	F	I	F	-	F
Dose of radiotherapy given	I	F	I	F	I	F	-	F
Schedule of radiotherapy	I	F	I	F	I	F	-	F
Radiotherapy toxicity data	I	F	-	F	-	F	-	F
Hormone therapy								
Time from randomisation to starting hormone therapy			I	F	I	F	-	F
Time from randomisation to stopping hormone therapy			I	F	I	F	-	F

Data set	Comparison							
	RADICALS -RT		RADICALS-HD "None vs Short"		RADICALS-HD "Short vs Long"		RADICALS-HD "None vs Short"	
	Interim	Final	Interim	Final	Interim	Final	Interim	Final
Reason for stopping or changing hormone therapy			I	F	I	F	-	F
Type of protocol hormone therapy			I	F	I	F	-	F
Time from randomisation to starting non-protocol hormone therapy	I	F	I	F	I	F	-	F
Type of non-protocol hormone therapy	-	F	-	F	-	F	-	F
Follow-up & toxicity data								
Incidence of toxicities from treatment	I	F	I	F	I	F	-	F
Time from randomisation to severe toxicity	I	F	I	F	I	F	-	F
Trial events (progression form and death)								
Incidence of death (all cause)	I	F	I	F	I	F	-	F
Time from randomisation to death (all cause)	I	F	I	F	I	F	-	F
Main cause of death	I	F	I	F	I	F	-	F
Other contributing causes of death	-	F	-	F	-	F	-	F
Place of death	-	F	-	F	-	F	-	F
Death within 4 weeks of trial treatment	I	F	I	F	I	F	-	F
Death related to trial treatment	I	F	I	F	I	F	-	F
Incidence of prostate cancer death	I	F	I	F	I	F	-	F
Incidence of treatment failure	I	F	I	F	I	F	-	F
Time from randomisation to treatment failure	I	F	I	F	I	F	-	F
Incidence of biochemical recurrence[1]	I	F	I	F	I	F	-	F
Time from randomisation to biochemical recurrence	I	F	I	F	I	F	-	F
Incidence of bPFS event[2]	I	F	I	F	I	F	-	F
Time from randomisation to bPFS event	I	F	I	F	I	F	-	F
Incidence of any non-prostate cancer death	-	F	-	F	-	F	-	F
Time from randomisation to non-prostate cancer death	-	F	-	F	-	F	-	F
Incidence of lymph node progression	I	F	I	F	I	F	-	F
Incidence of distant metastases	I	F	I	F	I	F	-	F
Site of first distant metastases	I	F	I	F	I	F	-	F
Incidence of each of bone, liver, lung, distant node mets	I	F	I	F	I	F	-	F
Incidence of skeletal related events and type	I	F	I	F	I	F	-	F
Time to treatment with any therapy for progression	I	F	I	F	I	F	-	F
Time to treatment with each type of therapy for	-	F	-	F	-	F	-	F

[1] PSA≥0.4ng/ml after RT, or >2.0ng/ml at any time
[2] Biochemical recurrence; clinical progression; initiation of non-protocol HT; death from any cause

Data set	Comparison							
	RADICALS -RT		RADICALS-HD "None vs Short"		RADICALS-HD "Short vs Long"		RADICALS-HD "None vs Short"	
	Interim	Final	Interim	Final	Interim	Final	Interim	Final
progression								
Serious adverse events (SAE) & reactions (SAR)								
Type of SAE	I	F	I	F	I	F	-	F
Attribution of SAE	I	F	I	F	I	F	-	F
Outcome of SAE	I	F	I	F	I	F	-	F
Time from randomisation to first SAE	I	F	I	F	I	F	-	F
Type of SAR	I	F	I	F	I	F	-	F
Attribution of SAR	I	F	I	F	I	F	-	F
Outcome of SAR	I	F	I	F	I	F	-	F
Time from randomisation to first SAR	I	F	I	F	I	F	-	F
Patient reported outcomes								
General health (SF-12) baseline	I	F	I	F	I	F	-	F
General health (SF-12) over time	-	F	-	F	-	F	-	F
General health for HE (EQ-5D) baseline	-	F	-	F	-	F	-	F
General health for HE (EQ-5D) over time	-	F	-	F	-	F	-	F
Urinary symptoms (ICSmale) baseline	I	F	I	F	I	F	-	F
Urinary symptoms (ICSmale) over time	-	F	-	F	-	F	-	F
Bowel symptoms (Vaisey) baseline	I	F	I	F	I	F	-	F
Bowel symptoms (Vaisey) over time	-	F	-	F	-	F	-	F
Sexual function (IIEF) baseline	I	F	I	F	I	F	-	F
Sexual function (IIEF) over time	-	F	-	F	-	F	-	F
Time from randomisation to patient assessments	I	F	I	F	I	F	-	F

6.8 RECRUITMENT AND FOLLOW-UP PATTERNS

Recruitment figures and accrual duration will be presented, including recruitment by centre and clinician. Graphs of recruitment over time will be presented, annotated by the timing of important trial events (eg IDMC reviews of data, protocol revisions, and sample size amendments). If any patients are found to be ineligible the reasons for ineligibility will be described, and the patients will continue to be included in analyses. The number of forms returned will be detailed. For surviving patients, the time since last follow-up form received will be listed e.g. by centre. The median follow-up time from randomisation will be presented.

6.9 RECONCILIATION OF ROUTINE TOXICITY DATA AND SERIOUS ADVERSE EVENT DATA

Routine toxicity data will be reported separately from serious adverse event data and the systems will be separately maintained and separately reported. However, every effort will be made to ensure that serious events that are also severe are reported as routine toxicities if they are one of the routinely reported toxicities.

SIGNATURES OF APPROVAL

Date: 23-May-2022
Version: 7.0

Signatures:

Name	Trial Role	Signature	Date
Mahesh Parmar	Director, MRC CTU at UCL	DocuSigned by: Max Parmar 47F3FE2126EF4EE...	26-May-2022
Matthew Sydes	RADICALS Trial Statistician	DocuSigned by: Matthew Sydes 2DB2A83EA918404...	26-May-2022
Adrian Cook	Delegated Statistician	DocuSigned by: Adrian Cook 81F44B750145464...	26-May-2022
Chris Parker	RADICALS Chief Investigator	DocuSigned by: Chris Parker 513B0A6947FD4F3...	26-May-2022

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