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STAR:
Standard vs Modified Sunitinib Treatment in Renal Cancer

A Randomised Multi-Stage Phase II/III Trial of Sunitinib Comparing Temporary Cessation with Allowing Continuation, at the Time of Maximal Radiological Response, in the First-line Treatment of locally advanced and/or metastatic Renal Cancer

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Contents

1. Trial Summary

Trial Title	A randomised multi-stage phase II/III trial of Sunitinib comparing Temporary cessation with Allowing continuation, at the time of maximal response, in the first-line treatment of locally advanced/metastatic Renal cell carcinoma
Trial Acronym	STAR
Trial Background	The National Institute for Health and Clinical Excellence (NICE) approval of sunitinib (February 2009) signalled a step change in management of incurable locally advanced/metastatic renal cell cancer (RCC). A significant survival advantage has been demonstrated with sunitinib over previous therapies and sunitinib is now standard therapy. It is however associated with significant toxicities and is expensive. The objectives of this proposed trial are to determine in the first line treatment of locally advanced/metastatic RCC with sunitinib, whether the utilisation of a drug-free interval strategy (DFIS) is non-inferior to the current standard of using a conventional continuation strategy (CCS), both in terms of overall survival (OS) and of quality adjusted life years (QALYs) averaged over treatment and follow up, whilst yielding significant benefits in terms of quality of life (QoL) for patients and cost effectiveness for the NHS, with a potential saving of approximately £16 million annually. A DFIS may also prolong response by reducing development of resistance.
Trial design	A phase II/III randomised (1:1) controlled, multicentre (UK) 3-stage trial is proposed. All 3 stages will be conducted to the same criteria to enable all patients to contribute to the final phase III analysis. Stages A and B (phase II) will be conducted in approximately 13 large renal cancer trial sites and are designed to confirm an adequate recruitment rate and early indication of non-inferiority in terms of efficacy (time to strategy failure [TSF][1]), with pre-defined objectives determining continuation to stage C (which will be expanded to 38 trial sites).
Trial Objectives	Overall to compare a sunitinib conventional continuation strategy (CCS) with a drug-free interval strategy (DFIS), at the time of maximal radiological response. The co-primary outcome measures are 2 year overall survival (OS) and Quality Adjusted Life Years (QALYs) averaged over trial recruitment and follow up.
Trial Endpoints	Primary endpoints: • Stage A: Recruitment rate/month • Stage B: Time to Strategy Failure (TSF) • Stage C/Overall: 2 year OS and averaged QALY (over recruitment and follow up) Secondary endpoints: • TSF

[1] See section 16.4 for definition of TSF

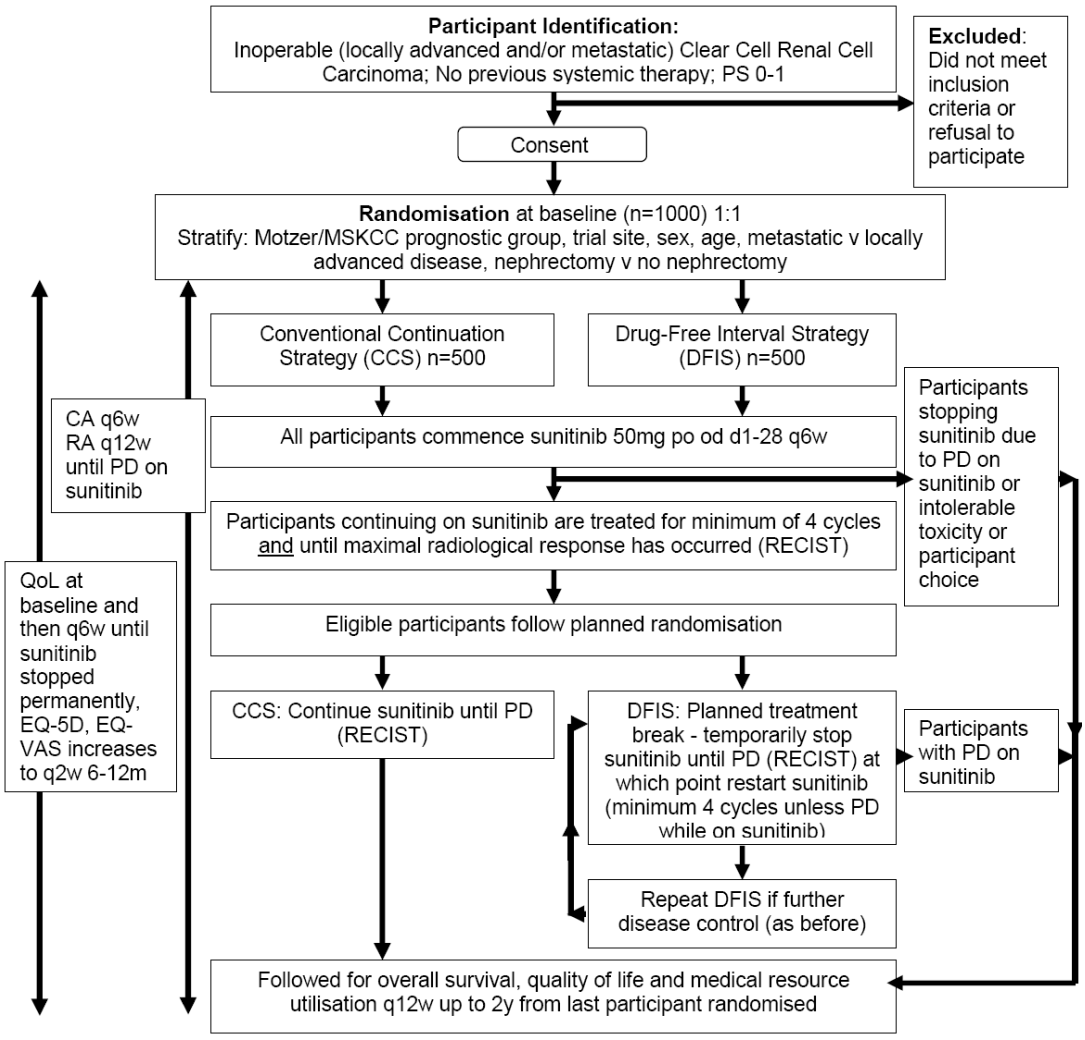
	• Summative progression free interval (SPFI) • Cost effectiveness (health economic endpoints) • Toxicity • Quality of Life (FACT-G, FSKI-15, EQ-5D and EQ-VAS) • Progression free survival *Ancilliary studies*: • Translational: Tissue and imaging[2]
Trial Population:	Phase II (stages A/B): 210 Overall Phase II+III (stages A/B/C): 1000 patients with locally advanced or metastatic clear cell renal cell carcinoma having received no prior systemic therapy for their locally advanced/metastatic disease.
Randomisation	Randomisation (1:1) to the control (CCS) arm or the research (DFIS) arm will be carried out by the Clinical Trials Research Unit (CTRU), Leeds at baseline prior to starting sunitinib.
Trial Treatment:	Sunitinib. One cycle of treatment refers to 50mg (starting dose) on, days 1-28, repeated every 42 days. All patients are planned to receive at least 24 weeks (4 cycles) of sunitinib treatment, assuming clinically appropriate to continue. After 4 cycles of treatment those patients that have stable disease (SD) (RECIST) will take up their allocated treatment arm (randomised at baseline). Those patients that continue to demonstrate an improvement in response will continue sunitinib until maximal radiological response (defined as stable disease [SD]/complete response [CR] for at least 10 weeks as per RECIST) and be randomised at that later point. *Control arm: Conventional continuation strategy (CCS)* Patients continue sunitinib with regular radiological assessments every 12 weeks until protocol-defined progressive disease [3] (PD) (RECIST), unacceptable cumulative toxicity or patient decision to stop treatment or withdraw from the study. *Research arm: Disease-free interval strategy (DFIS)* Patients stop treatment and continue 6 weekly active surveillance (clinical assessment) and 12 weekly radiological assessment, with planned recommencement of sunitinib at the time of PD (RECIST). Assuming further disease control, sunitinib is then continued again until the time of maximal radiological response and for a minimum of 4 cycles. At this point, assuming ongoing disease control, sunitinib

[2] Pending successful funding applications

[3] For patients on the DFIS arm sunitinib should be continued for a minimum of 10 weeks before confirming disease progression, e.g. if cross-sectional imaging is initially performed after the patient has had <10 weeks of sunitinib after re-commencing treatment, and the scan demonstrates PD (RECIST) then sunitinib should be continued and the decision regarding stopping sunitinib made with the results of the next imaging ≥10 weeks after re-commencing sunitinib

	can be again temporarily stopped until evidence of PD (RECIST) when again sunitinib is restarted This DFIS (planned treatment break strategy) is continued until PD occurs during sunitinib treatment, cumulative toxicity or patient decision to stop treatment or withdraw from the study.
Duration:	Stage A/B: 21 months Stage C: Further 33 months recruitment followed by 2 years of follow up
Evaluation of outcome measures	Patients will be clinically assessed every 6 weeks and radiologically assessed (RECIST) every 12 weeks during treatment as per protocol strategy (CCS or DFIS). Quality of life will be assessed using the FKSI-15 and FACT-G, along with the EQ-5D^{TM} and EQ-VAS. Adverse events and medical resources will be documented during trial treatment and follow up.

2. Trial Schema



Primary Endpoints:

- Stage A: Recruitment rate
- Stage B: Time to Strategy Failure (TSF)
- Stage C: 2 year overall survival AND QALY (co-primary)

Secondary endpoints:

- Quality of Life (FKSI, FACT-G, EQ-5D, EQ-VAS) and cost-effectiveness (health economic analysis)
- Time to Strategy Failure, Summative Progression free Interval, Toxicity, PFS
- Patient Preference and Understanding study (qualitative and quantitative)
- Bolt on translational studies

CA clinical assessment; CCS conventional continuation strategy; DFIS drug free interval strategy; PD progressive disease; PS performance status; QALY quality-adjusted life year; QoL Quality of Life; RA Radiological assessment; SD stable disease; d day; w week: m month; y year; q every

3. Abbreviations

ACRONYM	DEFINITION
AE	Adverse Events
CCS	Conventional Continuation Strategy
CR	Complete Response
CR-UK	Cancer Research UK
CSG	Clinical Studies Group
CTCAE v4.0	Common Terminology Criteria for Adverse Events version 4.0
CTIMP	Clinical Trial of an Investigational Medical Product
CTRU	Clinical Trials Research Unit
DCE-MRI	Dynamic Contrast Enhanced-MRI
DFIS	Drug Free Interval Strategy
DMEC	Data Monitoring and Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	Euro-Quality of Life 5D utility score
EQ-VAS	Euro-Quality of Life Visual Analogue Scale
EVPI	Expected Value Of Perfect Information
FACT-G	Functional Assessment of Cancer Therapy - General
FBC	Full blood count
FKSI-15	Functional Assessment of Cancer Therapy–Kidney Symptom Index-15 item
GCP	Good Clinical Practice
ICER	Incremental Cost Effectiveness Ratio
IFNα	Interferon-α
ITT	Intention to Treat
LDH	Lactate dehydrogenase
LFT	Liver Function Tests
mRCC	Metastatic Renal Cell Carcinoma
MRU	Medical Resource Utilisation
MUGA	Multiple Gated Acquisition
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NRES	National Research Ethics Service
OS	Overall Survival
PFS	Progression Free Survival
PIS	Patient Information Sheet
Plts	Platelets
PP	Per Protocol
PPI	Patient Public Involvement
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PR	Partial Response
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCC	Renal Cell Carcinoma

RECIST	Response Evaluation Criteria in Solid Tumours
RFA	Radiofrequency ablation
SAE	Serious Adverse Event
SDM	Senior Data Manager
sd	Standard deviation
SD	Stable disease
SOP	Standard Operating Procedure
SSOP	Study Site Operating Procedure
SPFI	Summative Progression Free Interval
STAR	Clinical trial short title
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFT	Thyroid function test
TKI	Tyrosine kinase inhibitor
TMG	Trial Management Group
TSF	Time to Strategy Failure
TSC	Trial Steering Group
UE	Urea and Electrolytes
WBC	White blood cell
WBBS	Whole body bone scan
YCRN	Yorkshire Cancer Research Network

4. Introduction

4.1 Background

Renal cell carcinoma (RCC) constitutes 3% of adult malignancies and 90% of kidney cancers. It is however the 6th leading cause of cancer-related death due to the lack of effective therapy for locally advanced or metastatic disease. It is estimated that RCC affected over 190,000 people worldwide in 2005 and was responsible for 95,000 deaths. The annual incidence of RCC in the UK is approximately 7,800 cases, with around 3,800 deaths [1].

The prevalence of RCC is continuing to increase with an annual worldwide increase of 1.5%-5.9%. Approximately 60% of cases present with localised disease (Stage I/II) at diagnosis, 20% with locally advanced disease (Stage III) and 20% with metastatic disease (Stage IV) [2]. Additionally, between 30-50% of patients with apparent localised and locally advanced disease at the time of diagnosis will subsequently develop metastatic disease. The 5 year survival for metastatic RCC (mRCC) is only around 10%, in part due to inherent resistance to systemic therapies.

Until recently IFNα was the UK standard of care for treatment of mRCC, but has only a 11 – 15% objective response rate in appropriately selected individuals. Responses are rarely complete or durable, but the results of two randomised studies suggest that IFNα does improve survival by about 4 months, compared with no active treatment [2, 3].

4.2 Sunitinib

The strategy of targeting angiogenic pathways has produced very positive results in advanced RCC. Tyrosine kinase inhibitors (TKIs) e.g. sunitinib and sorafenib and monoclonal antibodies (e.g. bevacizumab with IFNα) have produced improvements in terms of progression free survival (PFS) and also clinical Overall Survival (OS) for sunitinib [4-11]. Sunitinib selectively targets multiple protein receptor tyrosine kinases including vascular endothelial growth factor receptor and platelet-derived growth factor receptor. TKIs are thought to 'starve' tumours of blood and nutrients needed for growth, which leads to death of the cancer cells. These drugs also potentially have a direct effect on the tumour cells [12]. Sunitinib is therefore one of the confirmed successes of strategies to target specific features of cancer cells.

The landmark randomised controlled first-line trial of 750 patients (ECOG performance status 0 or 1) with metastatic RCC directly compared sunitinib and IFNα, with PFS as the primary endpoint [4]. The trial was unblinded after a second interim analysis and demonstrated significant benefit in patients treated with sunitinib and this led to cross over of a number of patients from IFNα to sunitinib. Updated results were published in 2009 [5] and in the intention to treat (ITT) population, median PFS was 11 months with sunitinib and 5 months with IFNα ($p<0.001$). Adverse events (AEs) were in keeping with what are currently recognised including hypertension (12%), fatigue (11%), diarrhoea (9%) and hand-foot syndrome (9%). OS was 26.4 months with sunitinib and 21.8 months with IFNα (HR 0.821; 95% CI, 0.673-1.001, p=.051), although this is likely to be an underestimation of the true OS benefit due to the significant cross over that occurred in the study population. Sunitinib was also associated with improved response rates over IFNα with 3% v 1% complete response (CR), 44% v 11% partial response (PR) and 40% v 54% stable disease (SD) as the best responses seen.

Early in 2009, sunitinib was approved in the UK by NICE for use in the first line treatment of advanced and/or metastatic RCC in patients with a good performance status (Eastern Cooperative Oncology Group, ECOG 0 or 1) until evidence of disease progression or unacceptable toxicity [13]. This was after reappraisal under the 'end-of-life' criteria with assessment of the value of the health gain to meet conventional cost effectiveness criteria. This has changed the standard of care in RCC and increased the use of sunitinib significantly.

The recommended cycle of sunitinib is 50 mg orally once daily on days 1-28, followed by a 14 day period treatment-free. Standard practice dictates that these cycles are repeated without interruption (with regular radiological assessment) until disease progression or unacceptable toxicity (the approach in the conventional continuation strategy [CCS] arm of the STAR trial). Sunitinib is however associated with a significant side-effect burden. The landmark first line trial reported that 8% of patients discontinued sunitinib due to AEs and 32% of patients required a dose reduction and 38% a dose interruption [5]. In the sunitinib open access program 8% of patients discontinued drug due to serious adverse events (SAEs); a further 33% had a dose reduction to 37.5 mg, with a further 13% requiring a subsequent dose reduction to 25 mg due to toxicity [14]. The longer-term impact of sunitinib-associated toxicities are recognised to be increasingly important as patients are living longer; individualised treatment strategies are necessary to optimise benefit and cost effectiveness whilst minimising toxicity [15].

The average cost per cycle is £3,700 per 6 week cycle with average cost per patient £47,000 and total NHS costs estimated at around £75 million for around 1600 patients. Estimates from our simulation show a likely reduction of approximately 21% in duration of sunitinib treatment with a DFIS. This would correspond to a saving of approximately £9,870 per patient, which when extrapolated to annual NHS costs in England produces a simulated annual saving of approximately £16 million.

4.3 Pazopanib

Pazopanib, another TKI which works in a similar way to sunitinib, has recently been recommended by NICE as a first-line treatment option for patients with advanced RCC, conditional on pricing. There is no evidence that pazopanib is more effective than sunitinib and it could be less clinically effective. However, the two drugs are currently being directly compared in the COMPARZ trial, which is due to report in mid 2012. Sunitinib is the only drug permitted for use in Phase II of the STAR trial, but a decision will be made on the basis of the results of the COMPARZ trial as to whether patients treated with pazopanib will be eligible for Phase III of the STAR trial.

4.4 Other agents in development

Other new agents for the treatment of kidney cancers such as mammalian target of rapamycin (mTOR) inhibitors and other TKIs are licensed or in development. However, there is a widespread consensus opinion amongst international renal cancer experts that these are very unlikely to be more effective than sunitinib and therefore will not replace sunitinib as first line therapy in the foreseeable future.

4.5 Intermittent treatment strategies in other cancer types

There is increased interest in drug-free interval strategies (DFIS) in oncology with evidence that these approaches are associated with reduced toxicity and increased QoL, without compromising previously demonstrated survival benefits.

This approach is most studied in colorectal cancer (CRC), where there is a considerable evidence base that treatment breaks can be introduced (utility of a DFIS) without a clinically significant survival deficit, but with evidence of a QoL advantage [16-19]. In one trial, 354 patients with metastatic CRC were treated with 5-fluorouracil (5FU) and folinic acid (FA) (de Gramont schedule) or continuous infusional 5FU or raltitrexed. Those who had stable or responding disease at 12 weeks were then randomised to continue therapy until progression or to stop, with the option to restart the same chemotherapy on progression. There was no evidence of a difference in OS between the two groups (intermittent or continuous chemotherapy), with both groups having a 1-year survival rate of approximately 45% [16]. There was however evidence of a quality of life advantage for those patients having intermittent chemotherapy.

Other trials have also demonstrated equivalence between intermittent and continuous therapy. OPTIMOX1 [17] compared 6 cycles of FOLFOX7 (three weekly bolus oxaliplatin, FA and 5FU) followed by continuous 5FU/FA alone (for a maximum of 24 weeks) before re-introduction of FOLFOX7 to FOLFOX4 (two weekly bolus oxaliplatin, 5FU and FA) until progression in 623 patients with metastatic CRC. The indication to restart oxaliplatin in the intermittent arm was evidence of progression compared to baseline scan, not progression compared to best response. Duration of disease control was similar between both arms (10.6 and 9.0 months respectively), as was PFS and OS. Of note almost 60% of patients on the intermittent arm did not have oxaliplatin reintroduced (protocol violations) but those that did tended to have a better prognosis [20].

Leading on from this the OPTIMOX2 trial compared FOLFOX7 for 12 weeks and then continued 5FU/FA until progression, at which point oxaliplatin was re-introduced, to FOLFOX7 for 12 weeks and then a complete break from chemotherapy until progression. The trial recruited 216 patients, but was curtailed as bevaciuzimab became available. The median duration of disease control was 13.1 months in the maintenance arm and 9.2 months in the intermitted arm, with OS in the arms 23.8 months and 19.5 months, respectively [21]. There were however significant design issues within this trial and the results are not clear cut. The primary endpoint of duration of disease control has been criticised as treatment was not mandated to be restarted until the disease reached baseline size, hence introducing variation in the time of restarting treatment. The statistical plan was also not adapted to account for the reduced sample size from 600 to 216. The extensive criticism of this trial has meant that definitive conclusions cannot be drawn and a DFIS is still practised by a number of leading clinicians [22].

An ongoing trial (DREAM/OPTIMOX3) is looking at a similar intermittent treatment strategy but comparing FOLFOX7 or XELOX4 (a capecitabine containing regimen) plus bevacizumab for 6 cycles followed by bevacizumab or bevacuzimab and erlotinib as maintenance therapy. There is also a trial [23] which has demonstrated that irinotecan first line therapy treatment can be used in an intermittent manner (in 2 month blocks in this trial). OS was identical in both arms (17.5 months).

In the UK, this concept was further investigated with the large randomised COIN trial [24]. In this study 1639 patients receiving oxaliplatin plus fluoropyrimidine-based chemotherapy were randomly assigned (1:1) to continuous chemotherapy until progression (arm A) or intermittent chemotherapy (arm C). In arm C, patients at 12 weeks who were responding, or who had stable disease, stopped chemotherapy until evidence of clinical or radiological disease progression. Whilst the results demonstrated an increased OS of 6 weeks in the

continuous arm, it was concluded that intermittent treatment is not an unreasonable option in fully informed patients. Treating patients with colorectal cancer with pre-planned chemotherapy breaks remains standard practice in many centres.

4.6 Evidence supporting an intermittent treatment strategy with tyrosine kinase inhibitors

Similar data for the use of TKIs are very sparse. There is only one randomised phase III trial that is informative and this is in gastrointestinal stromal tumours (GISTs) treated with imatinib mesylate. It was found that patients given a DFI generally progressed, however, 24 of 26 patients who progressed and were re-exposed to imatinib mesylate responded for a second time and there was no OS deficit found [25]. Imatinib mesylate is however associated with a minimal toxicity profile hence there was little incentive to adopt an intermittent scheduling approach in this setting.

Sunitinib however is associated with a significant side-effect burden and currently is recommended only for fitter patients. The initial first line trial reported 8% of patients discontinued treatment due to adverse events and in the reported sunitinib open access program 8% of patients discontinued drug due to serious adverse events (SAEs) and a further 33% had at least one dose reduction (13% had 2 dose reductions) [14]. A treatment strategy incorporating a DFI, assuming no survival disadvantage, would potentially give patients periods of time when symptoms attributable to sunitinib would be alleviated and would therefore have the potential to improve overall QoL and also cost-effectiveness.

Several studies add confidence to our rationale for the DFIS with sunitinib. In the USA, patients who progress during treatment with sunitinib are typically treated with multiple sequential therapies. Twenty three patients with advanced RCC who had initially responded to sunitinib then progressed (because of development of resistance), were treated with other therapies (median duration 6.7 months) and then re-challenged with sunitinib, when a further median PFS of 7.2 months was achieved [26]. This suggests that initial resistance to sunitinib therapy can be reversible and adds support for the rationale for this study. Importantly, no additional or increased toxicities were observed upon re-challenge.

Another recent small retrospective analysis studied the effects of stopping sunitinib therapy in 11 patients who had either had a CR after sunitinib alone (n=5), or a surgical CR after sunitinib followed by a residual metastectomy (n=6) [27]. At median follow up of 8.5 months, 5 patients had recurrent disease, but in all those cases re-introduction of sunitinib was effective, providing additional support to the re-use of sunitinib after an initial response. A published case series also demonstrated a re-introduction of sunitinib sensitivity after changing from the standard dosing schedule (50 mg daily day 1-28 every 42 days) to a lower continuous daily dose (37.5mg) [28].

Finally, data from one other randomised phase II study presents further support to the hypothesis that a DFIS could be used for sunitinib. In this study, 202 patients with mRCC were treated with sorafenib (an alternative TKI). After 12 weeks of treatment, 73 patients had a PR and 65 patients had SD. The patients with SD were then randomly assigned to sorafenib (n =32) or placebo (n = 33). At 24 weeks 50% of patients continuing sorafenib were progression-free compared with 18% of placebo-treated patients (p=0.0077) and median PFS from randomisation was significantly longer in sorafenib-treated patients. When sorafenib was re-administered in 28 placebo-treated patients whose disease had progressed, further progression was delayed for a median of 24 weeks. The researchers concluded that the re-stabilisation of progressive disease in patients whose disease had progressed on placebo and were switched to sorafenib resulted in comparable median

summative PFS as for patients who had no gap in sorafenib treatment. This suggests that patients were not disadvantaged from a brief period of placebo treatment, providing further ethical support for this design [29].

There may be an additional benefit from a DFIS, as development of drug resistance may be delayed or reduced. This is supported by results from a small retrospective study from the USA [30] demonstrating that sensitivity to sunitinib therapy is restored (and therefore resistance reduced) by a treatment break. This provides additional confidence in the rationale underlying the trial.

4.7 Summary of Rationale for the STAR trial

This is a pragmatic randomised trial design of a sunitinib conventional continuation strategy (CCS) compared to a sunitinib drug-free interval strategy (DFIS).

In the UK, NICE approval for the use of sunitinib in the first line treatment for patients with locally advanced and/or metastatic RCC has been a major step forward in the management of renal cancer. There is increased interest in intermittent treatment strategies in many solid tumours due to associated reduced toxicity, improved QoL and cost-effectiveness, without compromised efficacy. It is also possible that the development of drug resistance may be delayed or reduced by using a DFIS rather than a CCS and evidence for this in relation to sunitinib is accumulating.

At present there is no clearly defined optimal treatment strategy for any targeted therapy, and research in this field is crucial both for patients and the NHS. Evidence for the cost effectiveness of sunitinib is currently poor and standard decision criteria did not support its implementation in the NHS, as it is likely it displaced more health than it produced at a population level. Our trial will address the need to gather robust evidence on the costs, QoL and clinical outcomes of sunitinib both in the dosing schedule used in routine clinical practice (CCS) and in the drug free interval strategy (DFIS). If successful, the design may be applicable to other drugs across a wide range of diseases.

5. Aims and Objectives

This is a randomised controlled, multi-stage, phase II/III trial in patients with inoperable locally advanced or metastatic clear cell renal cell cancer to evaluate the use of a drug-free interval strategy (DFIS) compared to the conventional continuation strategy (CCS) of sunitinib.

5.1 Overall Primary Objective

To determine whether a sunitinib DFIS is non-inferior in terms of 2-year overall survival (OS) and quality-adjusted life year (QALY) (averaged over trial recruitment and follow-up) compared to a sunitinib CCS in patients with locally advanced and/or metastatic clear cell renal cell carcinoma.

5.2 Stage-Specific Primary Objectives

The STAR trial is a multi-stage phase II/III study with stages A and B incorporated into the phase II trial component and Stage C incorporated into the phase III trial (which includes all 3 stages A/B/C). Should the trial not meet pre-determined intermediary endpoints in stages A and B, then recruitment will not continue. Achievement of stage-specific endpoints will be assessed by an Independent Data Monitoring and Ethics Committee (DMEC) (see section 19.1).

Stage A

- To establish the feasibility of performing the trial in terms of **average monthly recruitment between months 10-21 (inclusive) of recruitment.** This is to ensure that sufficient patients are being recruited to the trial to enable its completion in a timely manner, assuming continuation to stage C.

Stage B:

- To provide initial efficacy data by comparing time to strategy failure[4] (TSF) in both arms and test for non-inferiority between the approaches to assess comparability.

Stages A, B and C:

- 2 year OS and QALY averaged over trial recruitment and follow up (see section 17.3.3)

5.3 Secondary Objectives

The secondary objectives are to evaluate how utilisation of a DFIS compared to utilisation of a CCS impacts on:

- Summative Progression Free Interval (SPFI)[3]
- Time to Strategy Failure (TSF)[3]
- Toxicity (CTCAE v.4.0)
- Quality of Life (QoL) (FSKI-15, FACT-G, EQ-5D^{TM} and EQ-VAS)
- Cost-effectiveness
- Progression free survival (PFS)

5.4 Ancilliary Studies

5.4.1 Patient Preference and Understanding Study

There is a planned qualitative sub-study which will take place in two trial sites only and look at patients' reasons for entering or declining entry into the STAR trial. Details of this study are provided in a separate protocol.

5.4.2 Translational Studies

Translational research studies are planned which will investigate tissue biomarkers of sunitinib response and toxicity, and imaging biomarkers looking for improved and earlier markers of sunitinib response. Imaging sub-studies include an optional CT study (open to

[4] See section 16.4 for definition of term

patients at all sites) and an optional MRI study (open to patients at a limited number of sites). Further details regarding these studies are given in Appendices 4-6.

6. Trial Design

The STAR trial is a UK multi-centre, multi-stage, open-label phase II/III 2-arm randomised trial designed to compare treatment with sunitinib using either a conventional continuation strategy (CCS) or the experimental disease free interval strategy (DFIS) in the first-line setting in patients with advanced (inoperable loco-regional or metastatic) clear cell renal cell cancer.

Overall it is planned to recruit 1000 patients into the STAR trial (assuming continuation and completion of all 3 stages A-C). Patients will be randomised in a 1:1 ratio to receive either a DFIS or a CCS of sunitinib.

Due to the novelty of the DFIS approach, two initial intermediary stages have been integrated within the trial with stop/continuation rules. A total of 210 patients will be recruited in stages A and B which will ensure demonstration of adequate recruitment and efficacy to justify continuation to stage C. Patients recruited during stages A and B will be included in the overall sample size required (n=1000), i.e. an additional 790 patients will be required for stage C. All evaluable participants will be followed up until the end of the trial (see section 11.11 for end of trial definition). This approach will enable the primary trial objective to be attained in the timeliest manner.

The STAR trial will not be blinded to patients, medical staff, or clinical trial staff. Accurate radiological evaluations will be fundamental to the stage B endpoint, and for this reason all radiological evaluations in the initial two stages (A and B) will be performed centrally and by a radiologist blinded to the patient's treatment allocation. The central radiology report, not the local report, will be used to determine whether sunitinib is stopped, continued or recommenced (depending on individual patient arm and current situation). The local report will be used for this purpose in stage C.

7. Eligibility

The eligibility criteria are designed to include, as far as possible, any patient with renal cancer for whom sunitinib would be used as standard of care, in accordance with current NICE guidance and its marketing licence.

Patients meeting all of the inclusion criteria, and none of the exclusion criteria, will be considered for participation in the STAR trial.

7.1 Inclusion criteria

1. Male or female aged ≥ 18 years old
2. Histological confirmation of component clear cell renal cell cancer
3. Inoperable loco-regional or metastatic disease
4. No prior systemic therapy for advanced disease (inoperable loco-regional and/or metastatic disease)
    - *Allowed situation: previous treatment in the SORCE study providing on placebo arm and **not** active sorafenib arms (see section 7.4.1 for further details)*

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1
6. Uni-dimensionally measurable disease (RECIST criteria, see Appendix 3)
7. Full blood count:
   - Haemoglobin (Hb) ≥ 9 g/dl [5]
   - Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/l
   - Platelets ≥ 80 x 10^9/l
8. Renal biochemistry:
   - Measured or calculated GFR ≥ 30 ml/min (Cockcroft and Gault or Wright formula may be used according to local practice)
9. Hepatobiliary function
   - Aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x ULN
   - Bilirubin (BR) ≤ 1.5 x ULN, or in patients with Gilbert's syndrome BR ≤ 3 x ULN **and,** direct BR ≤ 35%
10. Provided written informed consent prior to any trial-specific procedures
11. Able and willing to comply with the terms of the protocol including:
    - commencement of sunitinib within 3 (actual not working) days of randomisation[6]
    - temporarily stopping sunitinib if randomised to the DFIS arm
    - capable of oral self-medication
    - capable of reporting toxicity and completing quality of life (QoL) and medical resource utilisation (MRU) questionnaires
12. If female and of child-bearing potential, must:
    - have a negative pregnancy test within 72 hours prior to randomisation, and not be breast-feeding
    - agree to use adequate, medically approved, contraceptive precautions (oral or barrier contraceptive under the supervision of a General Practitioner or Family Planning Clinic) during, and for 6 months after the last dose of sunitinib
13. If male with a partner of child bearing potential, must
    - agree to use adequate, medically approved, contraceptive precautions (oral or barrier contraceptive under the supervision of a General Practitioner or Family Planning Clinic) during, and for 6 months after the last dose of sunitinib

Allowed situations include:

- primary renal cancer in-situ or previous nephrectomy
- previous brain metastases treated with complete surgical resection or gamma knife with no subsequent evidence of progression (patients treated with whole brain radiotherapy are not eligible)
- previous radiotherapy and/or previous/ongoing bisphosphonates or bone anti-resorptive drugs for the treatment of symptomatic bony metastasis.

[5] Blood transfusions are acceptable

[6] Treatment may commence after more than 3 days post randomisation ONLY in exceptional circumstances and with case specific prior agreement from the CTRU.

7.2 Exclusion criteria

1. Pulmonary or mediastinal disease causing obstruction or bleeding/haemoptysis
2. Patients with an estimated life expectancy of <6 months
3. Known contraindications to sunitinib
4. Any previous treatment with sunitinib or other tyrosine kinase inhibitor (including in the adjuvant setting)
5. Untreated brain metastases [7]
6. Any concurrent or previous other invasive cancer that could confuse diagnosis

   Allowed situation: non-melanomatous skin cancer or superficial bladder cancer acceptable, for all other cases please discuss with Clinical Trials Research Unit (CTRU)
7. Hypersensitivity to sunitinib
8. Any concomitant medication or substances forming part of local ongoing care known to significantly affect, or have the potential to significantly affect, the activity or pharmacokinetics of sunitinib (see section 10.2 for further information on concomitant medications)
9. Poorly controlled hypertension despite maximal medical therapy [8]
10. Any other serious medical or psychiatric condition which in the opinion of the investigator could affect participation in the STAR trial, including gastro-intestinal abnormalities limiting effectiveness of orally administrated drugs, uncontrolled infections, current or recent history of clinically significant cardiovascular disease which, in the opinion of the local investigator, would render the patient unsuitable for standard sunitinib therapy

7.3 Eligibility Screening Assessments

Informed consent must be obtained prior to undertaking any trial-specific procedures, including non-routine screening investigations. With the exception of pregnancy tests, it is expected that all other screening investigations would fall within routine tests for this patient population. Informed consent must therefore be obtained prior to pregnancy testing and any other screening assessments if not part of routine pre-treatment investigations.

The following investigations and assessments must be carried out **prior to randomisation** in order to establish eligibility:

- Cross sectional imaging (chest abdomen pelvis, preferably within a calendar month prior to starting sunitinib but within 42 days as an absolute maximum) [9]

[7] Patients are eligible if previous brain metastases treated with complete surgical resection or gamma knife with no subsequent evidence of progression not eligible if brain metastases treated with whole brain radiotherapy.

[8] It is recommended that subjects should have a systolic blood pressure of less than 150 mmHg, and a diastolic blood pressure of less than 90 mmHg. Anti-hypertensive drugs may be used to achieve these values. Regular blood pressure assessments will be carried out in all subjects as stipulated in Table

[9] A contrast CT scan (chest abdomen pelvis) is the preferred modality of cross sectional imaging. If this is not possible (e.g. in the case of contrast allergy), then a non-contrast CT (chest abdomen pelvis) scan should be performed, assuming the disease is evaluable by this method. If the disease is

- Assessment of ECOG performance status and blood pressure (BP)
- Full blood count (Hb, ANC, platelets; within 16 days prior to randomisation)
- Measured or calculated GFR (within 16 days prior to randomisation)
- Liver function tests (ALT/AST, BR within 16 days prior to randomisation)
- Pregnancy test (if woman of child-bearing potential)

Although **NOT** mandated by the protocol, as per standard UK practice, it is recommended that a baseline 12-lead ECG should be performed in patients with pre-existing cardiac disease (e.g. hypertension, diabetes or significant other cardiac history). The ECG should be interpreted by the local investigator and if there are clinical concerns regarding reduced cardiac function then patients should be investigated as per local practice. This will usually involve performing an echocardiogram or Multiple Gated Acquisition (MUGA) scan. It is advised that patients treated with sunitinib have a baseline left ventricular ejection fraction (LVEF) of at least 50%. Repeat ECG and echocardiogram in patients with cardiac risk factors should be carried out at the discretion of the local investigator according to current best practice.

7.4 Prior and Concurrent Participation in Other Clinical Trials

7.4.1 SORCE Trial

The SORCE trial is investigating whether treatment of RCC with sorafenib (a different TKI) in the adjuvant setting is effective in reducing disease recurrence in high risk patients compared with placebo. By agreement with the Chief Investigator of the SORCE trial, patients who have previously participated in SORCE and have progressed and are no longer on the SORCE trial, will be eligible for STAR, subject to confirmation (through unblinding with reference to the SORCE protocol) that that they received placebo and not active drug (sorafenib).. SORCE trial patients randomised to either of the sorafenib containing arms are not eligible to participate in the STAR trial.

7.4.2 Other Clinical Trials

Eligibility for the STAR trial based on previous or concurrent participation in other trials will be determined on a case by case basis and must be discussed prior to randomisation with the CTRU.

8. Recruitment, Registration and Randomisation

8.1 Trial Site Participation

Participants will be recruited from multiple trial sites throughout the UK, with coordination and data collection via the Clinical Trials Research Unit (CTRU), University of Leeds.

The STAR trial will initially open in a limited number of UK sites (approximately 13) during stages A and B. It is planned that these sites will recruit 210 participants over a period of 21 months. Following this time, and assuming continuation to stage C, recruitment will be

not evaluable using a non-contrast CT scan, then a MRI scan of the abdomen and pelvis and a non-contrast CT scan of the chest should be performed.

extended to a wider number of UK sites (estimated 38 in total) in order to reach the overall recruitment target of 1000 participants over an additional recruitment period of 33 months.

To participate, each trial site must fulfil a basic set of criteria which will be pre-specified. Each site must complete a registration form which verifies that the trial site is willing and able to comply with the trial requirements. This will be signed by the proposed local Principal Investigator on behalf of all staff who will be affiliated with the trial. Trial sites will be required to have obtained local management approval and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

8.2 Patient Screening

All participating trial sites will be required to complete a log of all patients screened for eligibility for the main STAR trial. All screened patients should be included on the Screening Log, including those who go on to be randomised. Anonymised information will be collected including:

- Date screened
- Age
- Gender
- Approached/Not approached for main STAR trial
- Whether Patient Preference Questionnaire provided
- Ethnicity
- Randomised/Not randomised
- If not randomised, reason for non-randomisation:
    - not eligible for trial participation, or
    - eligible but declined and reason for this, or
    - other reason for non randomisation

This information will be collected from trial sites on a monthly basis during stages A and B of the trial, and at least 3-monthly during stage C.

8.3 Informed Consent

Patients will be approached during routine oncology appointments and will be provided with verbal and written details about the trial. The verbal explanation of the trial, and Participant Information Sheet (PIS) and Consent Form (CF) will be provided by the patient's clinical team (medical and nursing). This will include detailed information about the rationale, design and personal implications of the trial. In addition, the patient will be provided with a participant DVD which contains information about the trial and is theirs to keep should they wish.

An additional PIS and CF will be provided to study sites recruiting patients to the dynamic contrast enhanced (DCE) MRI sub-study (see Appendix 6). Verbal and written details regarding the DCE-MRI sub-study will be provided to patients at the same time as details about STAR.

Following information provision, patients will have as long as they need to consider participation (a minimum of 24 hours is advised) and will be given the opportunity to discuss

the trial with their family and other healthcare professionals before they are asked whether they would be willing to participate.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent. The Principal Investigator, or any other clinically qualified member of the trial team who has received Good Clinical Practice (GCP) training and is authorised on the STAR Authorised Personnel log, are permitted to take informed consent. Where the patient is able to provide fully informed consent but is unable to sign or otherwise mark the consent form, provision for completion of the consent form by a witness will be made. This should be a carer, friend/family member, or a local member of the clinical team who is independent of the research team. The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

A record of the consent process detailing the date of consent and all those present will be kept in the patient's notes. The original CF will be retained in the Investigator Site File, a copy of the CF will be given to the patient, a second copy filed in the hospital notes (as per local practice), and a third copy will be returned to the CTRU.

Where valid, informed consent is obtained from the patient and the patient subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid. Participants who lose capacity after informed consent has been obtained will continue with protocol treatment, assessments and follow-up subject to consultation with the Principal Investigator and participant's carer/ family with the participant's best interests foremost in the decision making process. Ongoing collection of safety and follow up data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the intention to treat analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

8.4 Registration - Optional DCE-MRI sub-study participants only

8.4.1 Timing of Registration

An optional DCE-MRI sub-study will be undertaken in approximately 5 sites (refer to Appendix 6 for full details). Patients participating in this sub-study are required to undergo a baseline DCE-MRI scan prior to commencement of sunitinib treatment on the STAR trial. Given the narrow window specified between randomisation and commencement of sunitinib (see below), it is anticipated that in many cases baseline DCE-MRI sub-study scans will need to be scheduled prior to randomisation. Patients agreeing to participate in this sub-study must therefore be registered with the CTRU prior to their baseline DCE-MRI scan in order to confirm their eligibility for the main trial, consent and participation in this sub-study. Participants will be allocated a unique trial identification number at registration which will be subsequently used at randomisation. The telephone number for registration is the same as for randomisation, please refer to Appendix 6 for full details on the process.

8.5 Randomisation – All participants

8.5.1 Timing of Randomisation

Randomisation should take place as soon as possible after consent is obtained and eligibility confirmed, and no more than 3 days[10] prior to the start date of sunitinib treatment. Randomisation is required to be as close as possible to starting sunitinib as the radiological assessments for the main trial are timed from the randomisation date but must still occur at appropriate timepoints during sunitinib treatment.

Note that patients must also complete their baseline quality of life questionnaires prior to randomisation (see section 11.6).

8.5.2 Treatment Allocation

Patients will be randomised on a 1:1 basis to receive sunitinib using either a CCS or a DFIS. A computer-generated minimisation programme that incorporates a random element will be used to ensure that treatment groups are well balanced by:

- Motzer/MSKCC (Memorial Sloan-Kettering Cancer Centre) prognostic group [31] (see Appendix 1)
    - Favourable risk (0 factors)
    - Intermediate risk (1-2 factors)
    - Poor risk (≥ 3 factors)
- Trial site
- Gender
- Age
    - < 60 years
    - ≥ 60 years
- Disease status at the time of randomisation
    - Metastatic
    - Locally advanced
- Previous nephrectomy
    - Yes
    - No

8.5.3 Randomisation process

Informed written consent for entry into the trial must be obtained prior to randomisation, subject to the patient meeting the eligibility criteria. Randomisation should take place as soon as possible after consent is obtained and must be performed by an authorised member of the clinical team at the site using the CTRU automated 24-hour telephone randomisation service. Authorisation codes and PINs, provided by the CTRU, will be required to access the randomisation system.

The following information is required in order for the patient to be randomised. The person making the randomisation telephone call should have all details to hand:

- Name and code (assigned by the CTRU) of trial site
- Name of person undertaking randomisation
- Name of the treating investigator
- Patient initials and date of birth
- Patient NHS number

[10] In exceptional circumstances this may be extended and is subject, in all cases, to prior approval from the CTRU

- If patient has participated in SORCE, confirmation they received placebo only
- Confirmation of eligibility
- Confirmation and date of written informed consent
- Minimisation factors (see section 8.5.2 above)
- Confirmation that baseline quality of life questionnaires have been completed

Direct line for 24 hour randomisation
0113 343 4849
Please ensure that you have completed the Initial Eligibility Checklist and Randomisation CRFs before telephoning

A unique STAR trial participant identifier will be assigned at randomisation and participants will be informed of their allocated treatment arm. Irrespective of their randomisation, all patients should commence sunitinib within 3 days of randomisation.

9. Trial Medicinal Product Management

Please refer to the STAR Pharmacy and Investigational Medicinal Product (IMP) Study Site Operating Procedure (SSOP) for full details of the trial IMP management requirements, including details of IMP destruction, accountability and disposal records

Within the STAR trial, only sunitinib is classed as an IMP.

9.1 Sunitinib

Sunitinib is commercially available in the UK as sunitinib malate. For further details of composition, refer to the current version of the manufacturer's Summary of Product Characteristics (SPC). A reference copy of the SPC can be found in the Investigator and Pharmacy Site Files or on the Electronic Medicines Compendium (eMC) website: http://www.medicines.org.uk/emc

9.1.1 Supply and handling

Use of sunitinib within the STAR trial is within its licensed indication and general 'off the shelf' pharmacy supplies of sunitinib will be used. There is no requirement to ring-fence 'off the shelf' supplies of sunitinib for the STAR trial. Sunitinib will be handled in line with manufacturer's recommendations. For further details, refer to the current version of the manufacturer's SPC.

9.1.2 Formulation, storage, and preparation

Sunitinib formulation, storage, and preparation is in line with the manufacturer's recommendations. For further details, refer to the current version of the manufacturer's SPC.

9.1.3 Labelling

Sunitinib will be used in accordance with the conditions set out in Regulation 46 (2) of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amended in 2006). As Sunitinib will be used within its licensed indication, no special trial labelling requirements apply and sunitinib may be labelled according to normal dispensing labelling requirements. Trial site pharmacy will be responsible for labelling sunitinib in accordance with the

requirements of the Medicines for Human Use (Marketing Authorisation etc.) Regulations 1994.

9.1.4 Use of 3rd Party Supply and Delivery of Sunitinib

Sunitinib supply and delivery to a participant's home by 3rd party home healthcare companies is permitted if this is in accordance with routine NHS practice at the participating trial site. Where this practice is adopted, prior CTRU approval must be sought and it will be the trial site's responsibility to ensure that the home healthcare company can fulfil all trial requirements i.e

- Prescribing - It will be the responsibility of the trial site to ensure the prescription identifies the patient as a trial participant and is approved by an authorised person (as listed on the Authorised Personnel Log).

- Dispensing – The home healthcare company must only dispense sunitinib upon receipt of a prescription directly from the participating trial site.

- Accountability and traceability – the home healthcare company must have a robust system in place for retracing sunitinib which is at least equivalent to that of the site pharmacy.

- MHRA inspection – Participating trial sites must ensure that the home healthcare company is aware of, and can comply with possible requirement to provide access to dispensing and distribution records in the event of inspection. Sites may also choose to collect copies in order to facilitate any required inspection of these documents.

- Trial appointments - It will be the responsibility of the participating trial site to liaise with the patient and co-ordinate trial appointments after scheduled medication deliveries.

Please refer to the STAR trial Pharmacy and IMP SSOP for full details of the trial IMP management requirements, including record keeping.

10. Treatment Details

10.1 Pre-Treatment Investigations and Tests Required

See section 11.2 for full details of baseline and pre-treatment assessments required following written informed consent, and ongoing clinical review to proceed with each cycle of sunitinib treatment.

10.2 Concomitant Medications

Normal practice for the use of sunitinib will apply in this trial. The following information may be helpful, but the investigator must refer to the current version of the sunitinib SPC for guidance on permitted concomitant medications and non-drug therapies. A history of all concomitant medications should be taken at the initial assessment and at all subsequent visits.

10.2.1 CYP3A4 inducers and inhibitors

Care should be taken with concomitant administration of potent CYP3A4 inducers (which may reduce the effective dose of sunitinib by increasing its metabolism and reducing plasma levels) or potent CYP3A4 inhibitors (which may increase the effective dose by reducing its metabolism and increasing plasma levels). See Table 1 for examples. These drugs should be stopped at least 14 days prior to commencing sunitinib.

Table 1: Common potent CYP3A4 inhibitors and inducers to avoid taking concomitantly with sunitinib (NB: these lists are not exhaustive)

CYP3A4 Inducers	CYP3A4 Inhibitors
Carbamazepine	Clarithromycin
Dexamethasone	Erythromycin
Echinacea	Grapefruit juice
Phenobarbitol	Itraconazole
Phenytoin	Ketoconazole
Rifampicin	Ritonavir
St John's Wort/ hypericumperforatum	

10.2.2 Warfarin

Participants on warfarin will require more frequent monitoring, or conversion to a low molecular weight heparin according to local practice.

10.2.3 Supportive care

Participants are permitted to receive supportive care throughout the trial including transfusion of blood and blood products, treatment with antibiotics, anti-diarrhoeals, anti-emetics, analgesics, bisphosphonates, localised radiotherapy etc., in accordance with local practice

10.2.4 Concomitant Anti-Cancer Therapies

Concomitant anti-cancer treatments for RCC or elective anti-cancer surgical procedures are not permitted.

10.3 Planned Surgery (non-cancer)

It is recommended that sunitinib treatment is stopped 2 weeks before the participant undergoes any planned surgery. The CTRU must therefore be notified prior to any planned surgery via the Surgery Notification CRF for a decision on whether the participant can continue on trial treatment.

10.4 Invasive dental procedures

Invasive dental procedures should be avoided, if possible, in patients treated with sunitinib who have recently received or are currently receiving bisphosphonates or denosumab (see section 12.2) due to the risk of osteonecrosis of the jaw.

10.5 Dosing and Frequency of Trial Treatment

10.5.1 All Patients (CCS and DFIS Arms)

Participants on both arms of the trial will receive sunitinib on a 42 day cycle. Sunitinib will be administered orally once daily at 50 mg/day on days 1 to 28 of each cycle, followed by no treatment on days 29 to 42.

Doses may be modified for toxicity to 37.5 mg and 25 mg per day, as per the dose modification guidelines (see section 10.7).

A sunitinib cycle will not be extended due to dose interruptions in the cycle; if the treatment is stopped due to toxicity then these doses are omitted and not replaced. However, the start of a cycle may be delayed due to toxicities; delays of up to 14 days are acceptable. Any delays greater than 14 days (excluding the standard 2 week drug-free period within each cycle on days 29 to 42) must be discussed with the CTRU.

Sunitinib can be taken with or without food. The time of administration of the sunitinib should be relatively constant. If a dose is missed, the patient should be instructed not to replace the dose, but to take the next dose of sunitinib as planned. Participants will be requested to return any unused sunitinib capsules in order to monitor compliance.

All trial participants will receive sunitinib for a minimum of 4 cycles **and** until achievement of maximum radiological response (whichever occurs later), except in cases of unacceptable toxicity, disease progression (RECIST)[11], or patient choice to withdraw from the trial. In all cases, these participants must be withdrawn from protocol treatment.

After completion of at least 4 cycles of sunitinib (dose reductions allowed in accordance with section 10.7) and maximal radiological response, participants will take up their allocated treatment arm (CCS or DFIS). During trial participation patients will be evaluated at a minimum every cycle (6 weekly) clinically and at alternate cycles (12 weekly) radiologically.

10.5.2 CCS Arm

After completion of at least 4 cycles of sunitinib and maximal radiological response, participants randomised to CCS will continue sunitinib. There is no change to scheduling or dose of sunitinib, excepting dose reductions for toxicity in accordance with section 10.7

10.5.3 DFIS Arm

After completion of at least 4 cycles of sunitinib and after attaining maximal radiological response, participants randomised to DFIS will temporarily stop sunitinib (planned treatment break).

[11] It is acknowledged that there will be rare circumstances when disease progression is determined clinically due to a global deterioration in clinical status attributable to disease progression in the view of the investigator. Treatment with sunitinib may be required to be stopped if clinically indicated, however please note that, if possible, an appropriate radiological assessment should be performed to document the disease status as per RECIST.

Participants will remain off treatment until evidence of disease progression (RECIST). At this time sunitinib will be restarted, and assuming further stable disease/response, continued for a minimum 4 cycles and following the same scheduling and dose as before. When considering restarting sunitinib after a planned treatment break, disease progression must be confirmed radiologically and not just clinically.

In participants who begin responding again, further planned treatment breaks will be implemented on completion of a minimum 4 cycles and maximal radiological response.

10.6 Duration of Treatment

All participants will continue with their allocated sunitinib treatment strategy as per protocol (with dose reductions as required) until disease progression (RECIST) [14] occurs whilst taking sunitinib[12], or until:

- unacceptable toxicity
- participant chooses to stop protocol treatment

10.7 Management of Toxicity: Delays and Dose Reductions

At each protocol-scheduled clinical assessment, participants should be evaluated for the occurrence of adverse events (see section 11.8) and laboratory abnormalities. Trial sites must take care to ensure that where laboratory tests are performed at more than one site, the correct reference ranges are used when considering the need for treatment modifications.

10.7.1 Toxicity

Treatment toxicity is an important endpoint for the STAR trial and therefore compliance with protocol guidelines for dose modifications and reductions is important for ensuring consistent management of participants across sites. The decision to delay or modify treatment should be based upon the treating investigator's assessment and judgement and by the individual participant's circumstances, taking into account the guidelines below. Information for participants regarding management of specific toxicities, such as hypertension and hand and foot syndrome is available in information packs provided with the drug and in patient booklets provided by the manufacturer; these should be given to participants as per local practice. Toxicity should be recorded on the appropriate clinical assessment CRF. Toxicities should be graded in accordance with normal practice using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0)[13]. In case of any uncertainties regarding dose delay or reduction then please contact the CTRU.

10.7.2 Dose delays

Dose delays should be made according to local practice. Treatment may be delayed for up to 2 weeks to allow for resolution of toxicity. In the case of any treatment delays greater than 2 weeks (excluding the standard 2 week drug-free period within each cycle on days 29

[12] For patients on the DFIS arm sunitinib should be continued for a minimum of 10 weeks before confirming disease progression, e.g. if cross-sectional imaging is initially performed after the patient has had < 10 weeks of sunitinib after re-commencing treatment, and the scan demonstrates PD (RECIST) then sunitinib should be continued and the decision regarding stopping sunitinib made with the results of the next imaging ≥ 10 weeks after re-commencing sunitinib

[13] http://evs.nci.nih.gov/ftp1/CTCAE/About.html

to 42), participants should stop trial treatment unless prior agreement is obtained from the STAR trial team at CTRU to resume treatment.

Except where specified in Table 3, for non-haematological toxicity which persists at ≥ grade 2 on day 1 of the subsequent treatment cycle, it is recommended that there is a delay in starting the next treatment cycle of one week and until resolution to grade ≤ 1.

10.7.3 Dose reductions

Dose modifications for toxicities, including hypertension and hand and foot syndrome, should be made according to local practice with reductions occurring in 12.5 mg stages (see Table 2: Sunitinib dose reduction levels), but it is recommended that the guidance in Table 3 is taken into consideration (as discussed previously, due to the importance of the toxicity and QoL endpoints in this trial). A maximum of two dose reductions are allowed. Participants requiring dose reduction to less than 25 mg/day sunitinib (i.e. more than two dose reductions) should permanently stop trial treatment. Participants must not be dose escalated after dose reduction.

Except where specified in Table 3, for non-haematological toxicity which reaches ≥ grade 3 a dose reduction of one level is recommended for all subsequent cycles.

Table 2: Sunitinib dose reduction levels

Dose Level	Daily Sunitinib Dose
0	50 mg
-1	37.5 mg
-2	25 mg

10.8 Withdrawal of Treatment

For participants in the STAR trial, treatment as per protocol is planned until radiologically-confirmed disease progression whilst on sunitinib, death, unacceptable toxicity or withdrawal of consent for other reasons.

In line with usual clinical care, withdrawal from protocol treatment and consequent cessation or alteration of regimens at any time will be at the discretion of the investigator on discussion with the participants. All participants withdrawn from protocol treatment or prescribed alternative treatment will still attend for follow-up assessments as per the STAR protocol, unless unwilling to do so, and relevant case report forms will continue to be completed and returned to the STAR trial team at the CTRU.

10.9 Further Systemic Therapy following Disease Progression

After disease progression on sunitinib in the STAR trial the option of further systemic therapy within or outside a clinical trial setting, or supportive care, may be considered. Participants withdrawn from STAR trial treatment in order to commence alternative anti-cancer therapy will continue to be followed-up for the purpose of the STAR trial in accordance with the protocol.

Table 3: Suggested dose modification algorithm for potential treatment-related adverse events (AE) at discretion of local investigator

AE	Grade	Guidance
Hypertension	Asymptomatic and persistent systolic BP of ≥150mmHg and/or ≤ 170mmHg or diastolic BP≥ 90mmHg and ≤110mmHg	Sunitinib: continue same dose Anti-hypertensive medication: adjust current dose or initiate new antihypertensive therapy as necessary
	Symptomatic or systolic BP of ≥ 170mm Hg or Diastolic BP of ≥110mm Hg	Interrupt sunitinib therapy, adjust or initiate new hypertensive therapy, titrate hypertensive medication until blood pressure well controlled, restart sunitinib at same dose or at lower dose once BP well controlled at discretion of the investigator. Dose adjustments of antihypertensive medication may be needed in periods when participants are not taking sunitinib (i.e. within treatment cycles in the 2 weeks off therapy d29-42, or in the DFIS arm during planned treatment breaks)
Haemorrhage/Bleeding/ Coagulopathy	Grade 1	Continue sunitinib at same dose. Monitor as clinically indicated.
	Grade 2	Withhold sunitinib until toxicity is Grade ≤ 1. Restart treatment with lower dose. Monitor as clinically indicated.
	Grade 3 or 4	Discontinue sunitinib therapy until the AE resolves to ≤ Grade 1 and restart if abnormality not associated with clear clinical consequences. If clear clinical consequences only consider restarting at a lower dose at the discretion of the investigator or advice from CTRU.
Venous Thrombosis	Grade 2	Continue sunitinib at same dose. Monitor.
	Grade 3 or asymptomatic grade 4	Withhold sunitinib. Treat with anti-coagulant. Restart treatment at same dose if no Grade 3 or 4 haemorrhagic events have occurred when on anticoagulant for at least 1 week.
	Symptomatic grade 4	Discontinue sunitinib.

Arterial thrombosis	Any grade	Discontinue sunitinib.
Neutropenia	Grade 1 or 2 or grade 3 lasting < 5 days	Continue sunitinib at same dose. Monitor.
	Grade 3 lasting ≥ 5 days	Withhold sunitinib until toxicity is Grade ≤ 2. Restart treatment at same dose.
	Grade 4	Withhold sunitinib until toxicity is Grade ≤ 2. Restart treatment at lower dose.
Thrombocytopenia	Grade 1 or 2 or grade 3 lasting < 5 days	Continue sunitinib at same dose. Monitor.
	Grade 3 lasting ≥ 5 days	Withhold sunitinib until toxicity is Grade ≤ 2. Restart treatment at lower dose.
	Grade 4	Withhold sunitinib until toxicity is Grade ≤ 2. Restart treatment at lower dose.
Fatigue	Grade 1 and 2	Continue sunitinib at same dose. Monitor.
	Grade 3 and 4	Withhold sunitinib until toxicity is Grade ≤ 2. Restart treatment at lower dose. In all cases reversible causes of fatigue such as hypothyroidism and anaemia should be considered and excluded.
Anaemia		No dose reduction unless due to haemorrhage
Hand-foot syndrome	Grade 1 and 2	Continue sunitinib at same dose. Monitor and supportive measures.
	Grade 3	Withhold sunitinib until toxicity is Grade ≤ 2. Restart treatment at same dose or lower dose as judged by investigator.
	Grade 4	Interrupt sunitinib until toxicity reduced until ≤ grade 2. Restart sunitinib at lower dose or discontinue at discretion of investigator.
Hepatotoxicity	ALT of ≤3.0 ULN	Continue sunitinib at current dose. Monitor.

	ALT ≥3.0 x ULN to ≤8.0 x ULN and total bilirubin ≤2.0 x ULN)	Continue sunitinib, but monitor subjects carefully for clinical signs of liver toxicity and perform full panel of LFTs, frequently as clinically indicated until ALT/AST is reduced to grade 1. Consider also more detailed liver assessment, depending on clinical features such as liver imaging and hepatitis screen
	ALT>8.0 x ULN any bilirubin or total BR > 2.0 x ULN[14]	Interrupt sunitinib therapy until toxicity resolves to ≤ grade1. Monitor subjects very closely for symptoms and signs of liver toxicity with frequent liver function tests. Consider liver imaging and hepatitis and other relevant viral screens. Once toxicity ≤ 1. Consider restarting sunitinib, at same dose if identifiable non drug cause found or with a dose reduction at discretion of local investigator
Other	SEE GENERAL ADVICE	BELOW

Although it is not required to measure uric acid or phosphate levels as part of this protocol, for participants who are found to have developed grade 4 hyperuricamia or grade ≥ 3 hypophosphateamia without clinical symptoms, then sunitinib can be continued without interruption at the discretion of the investigator.

To require a dose reduction, nausea, vomiting or diarrohea should persist at grade 3 or 4 despite maximal medical therapy.

Participants who develop grade 3 or 4 lymphopenia without other dose limiting events (e.g. opportunistic infection) may continue on trial treatment without interruption of the sunitinib dose. Thyroid function tests are recommended to be checked every 12 weeks, and if there is evidence of hypothyroidism then this should be treated with replacement thyroxine

[14] or BR in patients with Gilbert's syndrome BR ≤ x3 x ULN **and** direct BR ≤ 35%

11. Trial Assessments and Procedures

11.1 Schedule of Events

The timing of interventions and assessments required for the STAR trial are summarised in Table 4.

11.1.1 Visit schedule

Irrespective of their allocated treatment strategy (CCS or DFIS), participants will be seen for scheduled clinical assessment every 6 weeks at a minimum. For participants receiving sunitinib the start of the next cycle may be delayed by up to 2 weeks to allow resolution of toxicity, during this time participants should be seen weekly for assessment. In the event of delays greater than 2 weeks, participants should stop trial treatment unless prior agreement is obtained from the STAR trial team at CTRU to continue.

11.1.2 Radiological assessment schedule

All participants must have cross sectional imaging of the chest, abdomen and pelvis. This should be within 4 weeks before the start of protocol treatment. Radiological assessments will then be performed every 12 weeks (equivalent to 2 cycles of sunitinib treatment) whilst participants are receiving protocol treatment (CCS or DFIS).

A contrast CT scan (chest abdomen pelvis) is the preferred modality of cross sectional imaging. If this is not possible (e.g. in the case of contrast allergy), then a non-contrast CT (chest abdomen pelvis) scan should be performed, assuming the disease is evaluable by this method. If the disease is not evaluable using a non-contrast CT scan, then a MRI scan of the abdomen and pelvis and a non-contrast CT scan of the chest should be performed. All subsequent follow-up scans should be the same modality (CT or MRI) and performed using the same technique. Scans obtained from participants recruited during stages A and B of this trial will undergo central radiology review (see section 11.1.2).

Patients with known bony metastases are recommended to undergo a baseline whole body bone scan, as per local practice.

11.2 Baseline Assessments

Following written informed consent, the following baseline investigations and assessments will be carried out (existing assessments may be used if within the time specifications):

Within a calendar month (preferred, but within 42 days as an absolute maximum) before commencing sunitinib and prior to randomisation:

- Cross-sectional imaging (CT scan preferred)

Within 16 days before commencing sunitinib and prior to randomisation (* indicates required for trial eligibility):

- *Medical history and physical examination (including height, weight, vital signs, heart rate (HR) and /BP)
- Laboratory tests
    - *Full blood count (FBC)
    - *Biochemistry (UE) (including urea, creatinine, sodium, potassium)
    - *Liver function tests (LFT) (including alkaline phosphatase (ALP), ALT/AST, total BR and albumin)
    - Lactate dehydrogenase (LDH) (baseline only)
    - Thyroid function tests (TFT)
    - Bone profile (calcium and phosphate) if bony metastases
- *Baseline QoL (FACT-G and FSKI-15, EQ-5D^{TM}/EQ-VAS) and medical resource utilisation (MRU) questionnaires[15]
- *(Where site is participating in sub-studies)* Consider approaching for participation in the associated qualitative study exploring patients' reasons for accepting or declining participation in a clinical trial and/or translational sub-studies

Within 72 hours prior to randomisation:

- *Pregnancy test (if woman of child-bearing potential)

In addition if a bone scan would be carried out in standard local practice, this should be performed in accordance with routine timeframes but is not mandated by the protocol.

11.3 Treatment Assessments

Irrespective of allocated treatment arm (DFIS or CCS) participants will be assessed clinically for symptoms and toxicity at the start of each sunitinib treatment cycle (i.e. every 6 weeks). The CRF completed will include specific questions about expected side effects associated with sunitinib (CTCAE v.4.0), plus any other toxicity experienced during the preceding cycle.

The following assessments should be conducted within 5 (actual not working) days prior to each treatment cycle and/or clinical review (while on planned treatment break for DFIS arm participants):

- Clinical assessment including weight and ECOG PS
- AE reporting/toxicity assessment (CTCAE v.4.0)
- Treatment details of preceding cycles include any dose reductions, dose delays and/or omitted doses (and reason)
- Laboratory investigations
    - FBC
    - UE

[15] Should be completed prior to randomisation but as close as possible to commencing treatment.

  - LFT
  - TFT (q 12 weeks)
- Radiological assessment (12 weeks post randomisation then q 12 weeks)
  - If there is clinical evidence of disease progression at a time other than that when radiological reassessment is due, then radiological assessments should be performed to confirm progression, unless there is a compelling reason not to.
  - The timing of the radiological assessments should be the same in both the CCS and DFIS arm. If during a planned treatment break in the DFIS arm, an extra radiological assessment has been performed due to clinical suspicion of disease progression, then assuming treatment with sunitinib is restarted, subsequent scans should revert to planned timings **but** if the next radiological assessment would be within 10 weeks of restarting sunitinib, then this scan should be omitted (as it will be too early to assess the effect of re-challenge by sunitinib)
  - Please note in stages A and B electronic images on CD-ROM of the baseline scan are required for external central review and the central results (**not** local results) will be used to determine continuation/cessation/recommencement of sunitinib (depending on allocated treatment arm (CCS or DFIS) and situation within the trial; see section 11.1.2 for further details).
- Review of appropriateness to continue sunitinib and review of sunitinib dosage in view of toxicities.

11.3.1 Treatment compliance

At each visit participants should return unused sunitinib capsules and non-compliance assessed by counting of remaining capsules, should be recorded in the CRF.

Table 4: Schedule of Events
(Further guidance on acceptable time limits/ windows can be found under the relevant protocol sections)

Week:		**0**	**4**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**		
Timepoint:	Pre-Rand	C1 d1	C1 d28	C2 d1	C3 d1	C4 d1	C5 d1[2]	C6 d1[2]	C7 d1[2]	C8 d1[2]	C9 d1[2]	C10 d1[2]	C*n* d1[2]	PD[3]
IC	X													
Patient baseline information	X													
Clinical assessment	X	X		X	X	X	X	X	X	X	X	X	X	X[11]
BP	X	X		X	X	X	X	X	X	X	X	X	X	
Lab tests [4]	X	X		X	X	X	X	X	X	X	X	X	X	N/S
TFT	X				X		X		X		X		q3m	N/S
ECG [5]	X													
Routine CT/MRI scan [6]	X				X		X		X		X		q3m	N/S
WBBS [7]	X													
EQ-5D/EQ-VAS [8]	X			X	X	X	q2w [9]				X	X	X	N/S
FSKI-15 [8]	X			X	X	X	X	X	X	X	X	X	X	N/S
FACT-G [8]	X			X	X	X	X	X	X	X	X	X	X	N/S
MRU	X			X	X	X	X	X	X	X	X	X	X	
Toxicity review	X	X		X	X	X	X	X	X	X	X	X	X	
AE reporting		X	X	X	X	X	X	X	X	X	X	X	X	
SAE reporting		Expedited reporting (<24 h) up to 30 days following **permanent** cessation of sunitinib (strategy failure) whilst on-trial [10]												
Survival/PD		X	X	X	X	X	X	X	X	X	X	X	X	X
Registration for DCE-MRI sub-study [1]	X													
DCE-MRI sub-study scan [1]	X		X		X									

Abbreviations: IC informed consent; C cycle; d day; w week; m month; C*n* ongoing cycles of sunitinib, n=cycle number; BP: blood pressure; TFT thyroid function tests; ECG: electrocardiogram; WBBS: whole body bone scan: MRU medical resource utilisation questionnaire; AE: adverse events; SAE: serious adverse event; PD: progressive disease; q2w every 2 weeks; q6w every 6 weeks; q3m every 3 months; N/S not specified

[1] Only participants taking part in DCE-MRI sub-study (see Appendix 6). Participants must be registered with CTRU prior to baseline DCE-MRI scan. Follow-up DCE-MRI scans: C1 d28 (±4 days); day 72 (±4 days)

[2] Variable treatment at this point for participants on DFIS arm; some participants will be on a planned treatment break (DFI) and others will continue/recommence sunitinib treatment. If the participant recommences sunitinib after a planned treatment break then clinical assessments will

coincide with their new treatment schedule. However, the participant should continue to undergo CT/MRI scans according to their original schedule, i.e. every 12 weeks based on date of randomisation.

[3] Only relevant if PD occurs whilst taking sunitinib (not PD in the DFIS arm during a planned treatment break[16])

[4] Full blood count (FBC), urea and electrolytes (UE), liver function tests (LFT) (calcium and phosphate only if known bone metastases)

[5] If any cardiac disease, other investigations should occur as per local practice

[6] Radiological reassessment: A contrast CT scan (chest abdomen pelvis) is the preferred modality of cross sectional imaging. If this is not possible (e.g. in the case of contrast allergy), then a non-contrast CT (chest abdomen pelvis) scan should be performed, assuming the disease is evaluable by this method. If the disease is not evaluable using a non-contrast CT scan, then a MRI scan of the abdomen and pelvis and a non-contrast CT scan of the chest should be performed. All subsequent follow-up scans should be the same modality (CT or MRI) and performed using the same technique. Radiological assessments will be centrally reported in real time for the stages A and B.

[7] Participants with metastatic bone disease are recommended to undergo a baseline whole body bone scan (WBBS) as per local practice, this is not mandated by the protocol.

[8] To be completed at clinic visits unless otherwise specified.

[9] EQ-5D/EQ-VAS completed by participants at home every 2 weeks during this period (sufficient questionnaire to be provided to participants to take home with them).

[10] Note that participants on a planned treatment break in the DFIS arm are still on-trial.

[11] Clinical assessment as per local practice. Details of subsequent treatment received for renal cancer and the participants status will be collected at 6 months after treatment strategy failure, then annually thereafter.

[16] For patients on the DFIS arm sunitinib should be continued for a minimum of 10 weeks before confirming disease progression, e.g. if cross-sectional imaging is initially performed after the patient has had < 10 weeks of sunitinib after re-commencing treatment, and the scan demonstrates PD (RECIST) then sunitinib should be continued and the decision regarding stopping sunitinib made with the results of the next imaging ≥ 10 weeks after re-commencing sunitinib

11.4 Follow-up Assessments

The planned duration of follow-up, for all evaluable trial participants is until the end of the trial (see section 11.11 for definition). During this time, 6 weekly clinical assessment data will be collected for all participants prior to treatment strategy failure (CCS or DFIS). After treatment strategy failure (see section 16.4 for definition), details of any subsequent treatment received for renal cancer and the participant's status will be collected at 6 months after treatment strategy failure, and then annually thereafter.

As OS is an endpoint, all randomised participants, including any who have permanently stopped trial treatment, must be followed up for survival. The only exceptions to this are those who withdraw consent for the trial and collection of follow up data.

Any participants still responding to their protocol-defined treatment strategy after the end of the trial, will continue to receive sunitinib treatment at their treating clinician's discretion (it is assumed this would be to their randomised strategy). However, only data relating to serious adverse events will continue to be collected until 30 days after the last dose of trial treatment.

11.5 End of Trial Treatment

If the patient discontinues STAR protocol treatment for any reason other than death, an end of trial treatment CRF must be faxed to the CTRU within 7 days of the trial site team becoming aware of this.

11.6 Quality of Life

Due to the importance of QoL in this trial, frequent measures are necessary to accurately capture the information required. This drives the timings of QoL data collection as seen in Table 4: Schedule of Events.

Information from all questionnaires (FACT-G, FSKI-15 and EQ-5D^{TM}/EQ-VAS) will be collected at clinic visits at baseline (before the participant is informed of their randomisation allocation) and at day 1 of cycles 2, 3 and 4 during which time participants on both arms will receive sunitinib, assuming clinical appropriateness to continue. Administration in clinic will enable participants to be supported in their completion, if required, prior to initiation of postal questionnaires.

After this timepoint EQ-5D^{TM}/EQ-VAS information will be collected every 2 weeks (a simple 2 page assessment) for 24 weeks and then return to every 6 weeks. During 2 weekly collection questionnaires will be completed by participants at home (sufficient questionnaires to be provided to participants to take home with them). During this time at clinical assessment visits the FSKI-15 and FACT-G will continue to be completed 6 weekly. Clinic staff will remind participants of the importance of the quality of life assessments at each clinic visit.

After the intensive completion has finished (24 weeks) QoL information will revert to all being collected in clinic every 6 weeks at clinical assessment visits (FACT-G, FSKI-15 and EQ-5D™/EQ-VAS).

11.7 Health Economics

Data on primary, secondary, tertiary and community health care utilization will be collected through MRU and standard case report forms (CRF) at baseline and then at each clinical assessment visit.

11.8 Adverse and Serious Adverse Events

All AEs occurring in the trial will be collected on the 6-weekly trial treatment CRFs. They should be reported via the standard data management routes and not expedited.

For all SAEs occurring in the trial, a Serious Adverse Event (SAE) CRF must be completed and faxed to the CTRU within 24 hours of becoming aware of the event (see section 12.3.3).

For all Suspected Unexpected Serious Adverse Reactions (SUSARs), a SUSAR CRF should be completed and faxed to the CTRU **within 24 hours** of becoming aware of the event (see section 12.3.3).

11.9 Pregnancies

All pregnancies and suspected pregnancies occurring from the date of randomisation to 30 days following **permanent** cessation of sunitinib must be reported to the CTRU **within 7 days** of the site becoming aware. All protocol treatment must be stopped immediately if a pregnancy in a female patient or patient's female partner occurs or is suspected.

The CTRU will report all pregnancies occurring during treatment to the Sponsor along with any follow-up information.

11.10 Deaths

All deaths occurring from the date of randomisation to 2 years after the last patient has been randomised must be recorded on the Notification of Death CRF and sent to the CTRU **within 7 days** of the trial site team becoming aware of the death.

11.10.1 Treatment-related deaths

In addition to completing a Notification of Death CRF, suspected treatment-related deaths must be notified **immediately** to the CTRU in accordance with section 12 Pharmacovigilance.

11.11 End of Trial

The end of the trial is defined as 2 years after the last patient was randomised. All evaluable trial participants will be followed up until this timepoint.

11.12 Submission of Trial Data

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU. Participating sites will also be expected to keep copies of all completed Case Report Forms (CRFs).

11.12.1 Case report forms (CRFs)

Data will be recorded by trial site research staff on trial-specific paper CRFs and then submitted by post to the STAR trial team at the CTRU, University of Leeds. Only the participant's trial number plus date of birth and initials will be added to the CRFs. **Trial sites are responsible for obliterating all other personal identifiable data prior to sending CRFs and any other reports to the CTRU.** Following receipt, the CTRU will contact trial sites to resolve any missing or discrepant data.

A participant may withdraw consent for further follow-up information to be collected from their medical record (the only exception being any applicable adverse events experienced within the 30 days after suntitinib treatment has stopped which are needed to comply with regulatory requirements). However, any outstanding data applicable to time points prior to withdrawal will continue to be requested from the trial site until it is received by CTRU, and all information collected prior to the date of withdrawal will be included in the trial analyses.

It is the responsibility of each trial site to retain copies of all completed CRFs and to maintain their file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, on site during the trial and then at their designated archive facility.

11.12.2 CT scans (stage A and B trial participants only)

Participants in stages A and B of the trial will have their radiological assessments centrally reported, with minimal delay, by radiologists approved by the STAR Trial Management Group (TMG). Central reporters will be blinded to participants' allocated trial treatment strategy.

Management of STAR trial treatment will be based on central radiological reports in stages A and B of the trial, **not** the local radiological reports. **Sites must ensure that scans are anonymised prior to transfer such that only the following identifiers are included: unique trial number, participant initials, participant date of birth**. Further details can be found in the STAR Central Radiology Reporting (stages A & B) SSOP.

Type of scan: A contrast CT scan (chest abdomen pelvis) is the preferred modality of cross sectional imaging. If this is not possible (e.g. in the case of contrast allergy), then a

non-contrast CT (chest abdomen pelvis) scan should be performed, assuming the disease is evaluable by this method. If the disease is not evaluable using a non-contrast CT scan, then a MRI scan of the abdomen and pelvis and a non-contrast CT scan of the chest should be performed. All subsequent follow-up scans should be the same modality (CT or MRI) and performed using the same technique. Scans obtained from participants recruited during stages A and B of this trial will undergo central radiology review (see below).

Timing of scans

- Baseline (within 4 weeks prior to randomisation)
- 72 days (± 4 days) post-randomisation and prior to commencement of cycle 3 sunitinib
- Subsequent scans every 12 weeks from day 72 (± 4 days) post-randomisation (scans must be scheduled to allow a minimum of 3 full working days for central reporting of scans in Leeds and reporting back to site).
- The timing of the radiological assessments should be the same for the CCS and DFIS arm. If during a planned treatment break in the DFIS arm, an extra radiological assessment has been performed due to clinical suspicion of disease progression, then assuming treatment with sunitinib is restarted, subsequent scans should revert to planned timings BUT if the next radiological assessment would be within 10 weeks of restarting sunitinib, then this scan should be omitted (as it will be too early to assess the effect of re-challenge sunitinib)

Transfer of scans

Scans must be anonymised and downloaded as soon as possible onto CD prior to transfer by courier to

Radiology Department
Bexley Wing,
St James's University Hospital
Beckett Street
Leeds
LS9 7TF

Participant consent for the main STAR study must be obtained before any scans are sent. Note that scans can only be accepted at St James's University Hospital during standard office hours: 9.00 – 17.00, Mon-Fri, excl. Bank Holidays in England). Sites must notify the radiology team at St James's University Hospital to confirm dispatch of scans and expected delivery:

Fax: 0113 206 4640 Email: STARradiology@leedsth.nhs.uk

Central reporting of scans

Scans will be reported centrally according to Response Evaluation Criteria of Solid Tumours (RECIST) guidelines V1.1 (see Appendix 3). The completed CRFs and the

radiology reports will be emailed to sites within 3 full working days of receipt, and a hard copy sent by post.

12. Pharmacovigilance

12.1 General Definitions

12.1.1 Adverse events

An adverse event is any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with this treatment and can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests

In addition the following criteria may be used in order to collect protocol-defined reportable adverse events which do not meet the criteria for serious (below):

- requires medical or surgical intervention to prevent permanent impairment of function or permanent damage to body structure.

12.1.2 Serious Adverse Events (SAE) and Reactions (SAR)

A Serious Adverse Event (SAE) is defined in general as “any untoward medical occurrence or effect that:

- results in death
- is life-threatening [17]
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Medical judgement should be exercised in deciding whether an SAE is serious in other situations. Important SAE/SARs 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 or the other outcomes listed in the definition above, should also be considered serious.

[17] The term life-threatening 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 was more severe.

Where an SAE is deemed to have been related to an IMP used within the trial, the event is termed as a Serious Adverse Reaction (SAR).

Medical judgement should be exercised in deciding whether an AE or 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 participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

12.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Reaction which also demonstrates the characteristic of being unexpected, the nature and severity of which is not consistent with the information about the medicinal product in question set out, in the case of a product with a marketing authorisation (e.g. sunitinib), in the summary of product characteristics (SPC) for that product supplied in the Investigator Site File (or the latest version as instructed by CTRU).

12.2 Reporting Requirements for Adverse Events (AE)

Adverse events (AEs) will be recorded in the appropriate CRFs from the commencement of sunitinib until 30 days after sunitinib is **permanently** ceased (strategy failure has occurred), or up to the end of the trial, whichever is sooner.

Information about adverse events, whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the CRF.

All AEs, both related and unrelated to advanced renal cell cancer and its treatment with sunitinib, will be collected for all participants and will be evaluated for duration and intensity according to the National Cancer Terminology Criteria for Adverse Events (NCI CTCAE) v4 [18].

All AEs must be recorded in the 6 weekly clinical assessment CRF.

12.3 Reporting Requirements for Serious Adverse Events (SAE)

12.3.1 Events not to be classed as SAEs

The following events will **not** be recorded as SAEs within the trial:

Hospitalisation for:

- Routine treatment or monitoring of renal cancer not associated with any deterioration in condition

[18] http://evs.nci.nig.gov/fpt1/CTCAE/About.html

- Treatment which was elective and pre-planned, for a pre-existing condition not associated with any deterioration in condition
- Admission to hospital or other institution for general care, not associated with any deterioration in condition
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions for serious as given above, and not resulting in hospital admission

Diagnosis of progression of disease and death due to progression of disease **do not** require reporting as SAE, as these are the results of the disease under study and are incorporated into the endpoints of the trial.

12.3.2 Events classed as expected SAEs

Example of events which will be classed as expected SAEs within this trial and therefore will **not** be reportable as SUSARs are given below. This is not intended to be an exhaustive list, therefore when determining whether an SAE is expected or not, please always refer to the sunitinib SPC supplied in the Investigator Site File (or the latest version as instructed by the CTRU).

Examples of expected SAEs related to metastatic renal cancer:

- Anaemia
- Fatigue
- Abdominal Pain
- Shortness of breath
- Weight loss

Examples of expected SAEs related to sunitinib:

- Skin discolouration (yellowish tinge)
- Thyroid dysfunction
- Hand Foot Syndrome
- Pancreatitis (increased lipase and amylase)
- Bleeding
- Liver failure
- Nausea/ vomiting
- Anaemia
- Neutropenia
- Thrombocytopenia
- Reduced cardiac function
- Increased QTc
- Proteinuria/nephrotic syndrome
- Diarrhoea
- Hypersensitivity
- Stomatitis
- Taste change
- Dyspepsia
- Seizure
- Hypertension
- Venous thrombosis

Expected SAEs related to sunitinib in association with bisphosphonates or other bone anti-resorptive drugs (e.g. denosumab) which require expedited reporting:

- Osteonecrosis of the jaw (see section 12.3.5)

All events should be reviewed and classed by the Principal Investigator, or another clinically qualified member of the medical team authorised in the STAR Authorised Personnel Log.

12.3.3 SUSARs

All SAEs assigned by the local investigator (or following central review) as both suspected to be related to IMP-treatment (sunitinib) and unexpected will be classified as SUSARs and will be subject to expedited reporting to the MHRA. The CTRU will inform the MHRA, the main REC and the Sponsor of SUSARs within the required expedited reporting timescales.

12.3.4 Recording & Reporting SAEs and SUSARs

All SAEs and SUSARs occurring from the date of randomisation to 30 days following **permanent** cessation (i.e. not a planned treatment break) of sunitinib (strategy failure) must be recorded on the SAE and SUSAR Form and faxed to the CTRU **within 24 hours** of the trial site team becoming aware of the event (this includes participants who have withdrawn consent for data collection, see section 11.12.1).

For each SAE and SUSAR the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates if applicable)
- action taken
- outcome
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected

Any follow up information should be faxed to the CTRU as it is available. Events will be followed up until the event has resolved or a final outcome has been reached.

Assessment of causality and expectedness for trials involving IMPs must be made by an authorised medically qualified person. If such a person is unavailable, initial reports without causality and expectedness assessment should be submitted to the CTRU by a healthcare professional **within 24 hours**, but must be followed up by medical assessment as soon as possible thereafter.

Please ensure that only one event is reported on each SAE and SUSAR CRF (details of multiple symptoms should be listed if they relate to the same event). Once all resulting queries have been resolved, the CTRU will request the original form, and this should also be posted to the CTRU and a copy retained on site.

12.3.5 Recording & Reporting Osteonecrosis of the Jaw (ONJ)

In January 2011, the MHRA Drug Safety Update discussed osteonecrosis of the jaw (ONJ) which has been reported in patients with cancer in association with the use of bevacizumab or sunitinib. The following advice was provided:

- *Treatment with bevacizumab or sunitinib may be a risk factor for the development of ONJ*
- *Patients treated who have previously received, or are treated concurrently with, bisphosphonates may be particularly at risk*
- *Dental examination and appropriate preventive dentistry should be considered before treatment with bevacizumab or sunitinib. Invasive dental procedures should be avoided, if possible, in patients treated with bevacizumab or sunitinib who have previously received bisphosphonates.*

MHRA Drug Safety Update: Vol 4, Issue 6, Jan 2011
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/DrugSafetyUpdatePDFarchive/index.htm

Approximately one third of patients with RCC will develop bone metastases and may therefore receive bishosphonates or newer anti-resorptive drugs such as denosumab, which has also been associated with ONJ. Although the incidence of ONJ is low, the STAR trial is one of the largest planned trials in RCC and is therefore an excellent opportunity to collect further data in this important area.

The trial CRF will therefore specify the symptoms which may lead an investigator to suspect possible ONJ and the investigator should give participants guidance regarding specialist dental advice which will include confirmation or otherwise of ONJ. This must be listed as a SAE which will require expedited reporting (within 24 hrs on the research staff becoming aware of event) to the CTRU. Investigators may contact the CTRU if they have any queries.

12.4 Responsibilities

Principal Investigator:

- Checking for SAEs when participants attend for treatment / follow up
- Medical judgement in assigning:
  - Seriousness
  - Causality
  - Expectedness
- To ensure all SAEs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further follow up information as soon as available.
- To report SAEs to local committees in line with local arrangements.

Chief Investigator (or nominated individual in CI's absence):

- Assign causality and expected nature of SAEs where it has not been possible to obtain local assessment.
- Undertake SAE review
- Review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and the Chief Investigator, local assessment will not be downgraded but the Chief Investigator may add comments prior to reporting to MHRA and Main REC.

CTRU:

- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK), main REC and Sponsor (dependent on Sponsor processes) within required timelines.
- Preparing annual safety reports in collaboration with appropriate members of the TMG to Competent Authority and main REC, periodic safety reports to TSC and DMEC as appropriate.
- Notifying Investigators of SUSARs that occur within the trial.

TSC:
In accordance with the trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

DMEC:
In accordance with the trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

13. Serious Breaches of Good Clinical Practice (GCP)

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP of the trial protocol are picked up and reported. Investigators are required to notify the CTRU **immediately** of a serious breach as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928 that they become aware of. A "serious breach" is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the participants of the trial; or
- The scientific value of the trial.

In the event of doubt, or for further information or guidance, the investigator should contact the CTRU.

14. Quality of Life

Quality of life is a major consideration in care of people with RCC and is a key component of this proposal. This aims to explore the impact on QoL of a DFIS strategy compared to CCS. The selection of averaged QALY as a co-primary endpoint of the trial underlines the importance of this.

Quality of life will be assessed with the following questionnaires: FACT-G (28 items in four domains) [32], the FKSI-15 (15 items) [33] and the EuroQol instrument (including EQ-5D Index and EQ VAS) (all validated in cancer patients to assess health-related quality of life) [34].

Due to the importance of QoL in this trial, frequent measures are necessary to accurately capture the information required. This drives the timings of QoL data collection as seen in Table 4. However, during the period when participants are being measured two-weekly, only the EQ-5D and EQ-VAS (a simple two page assessment) will be used.

Initial information (FACT-G, FSKI and EQ-5D/EQ-VAS) will be collected at clinic visits at baseline, day 1 cycle 2, 3 and 4, during which time participants on both arms will receive sunitinib.

During more frequent information collection the EQ-5D and EQ-VAS (2 page questionnaire) will be completed by participants at home. It is the period when CCS arm participants continue treatment and most participants on the DFIS arm stop treatment (i.e. after 6 months), when QoL differences are predicted to be greatest and hence this is when QoL data collection is most frequent. This difference between arms will also vary within cycles as, for participants on sunitinib, QoL is expected to be lowest when toxicity of treatment is greatest i.e. at day 28 of the cycle, and expected to be highest after their 14 days off treatment, i.e. at day 1 of the next cycle. This variation necessitates the frequent QoL data collection. This will continue for 24 weeks, and during this time participants will continue to complete the FACT-G and FSKI questionnaires every 6 weeks i.e. at each clinical assessment, After 48 weeks all information (FACT-G, FSKI and EQ-5D and EQ-VAS) will continue to be collected every 6 weeks, at each clinical assessment visit.

Quality of life questionnaires during the first 6 months will be administered in clinic in order to support patient use before postal questionnaires are instituted after 6 months for the EQ-5D/EQ-VAS (FACT-G and FSKI will continued to be collected at clinic visits). Clinic staff will remind participants of the importance of the quality of life assessments at each clinic visit.

15. Economic Evaluation

The star trial will also collect data which will contribute to a cost-effectiveness analysis of a drug-free interval (DFIS) strategy, assuming non-inferiority in terms of OS is demonstrated. The economic evaluation analysis is of interest even if the non-inferiority OS criterion is not met. A cost-effectiveness analysis in this latter context would permit establishing the value of information of further research on the question.

Extensive QoL data were collected as part of the pivotal sunitinib trial programme [35, 36], including both generic measures (FACT-G, EQ-5D and EQ-VAS) and disease-specific measures (FKSI-15 and FKSI-DRS subscale), but the reporting of the EQ-5D and EQ-VAS data in the subsequent publications was restricted to baseline mean and standard deviations (SD) and modelled average for all follow-up. In addition, QoL data from participants who stopped treatment were not included in the analysis.

As a result these data are of limited use for estimating the QALY gains from a sunitinib DFIS strategy in the NHS. A small Japanese trial [37] reported baseline EQ-VAS and follow-up EQ-VAS data for day 1 and day 28 of each treatment cycle. These data, plotted graphically, show the 'sawtooth' pattern of QoL whilst on sunitinib treatment (higher measures on day 1 and lower measures on day 28) consistent with clinical experience. The authors report that the same pattern was seen in the EQ-5D data, providing reassurance that both these instruments will be sensitive to the hypothesised benefit.

The QoL data collected in this trial represents a unique source of information valuing health at every point of time. Using each follow-up collection point, the distribution of QALY gains will be precisely plotted over time and compared between the two arms. If clinical measures allow, QoL curves over time will be drawn for different sub-groups of participants. It should be noted that the limitations of the reported trial data [35, 36] means uncertainty remains about the profile, timing and magnitude of the QoL impact of sunitinib treatment and so we have chosen to retain OS as a co-primary endpoint. There is also uncertainty regarding the utilities of different health states in advanced RCC; i.e. the value of Q used to measure Quality Adjusted Life Years (QALYs); for example NICE report a range for utility values 0.6 to 0.8 for stable/progression free disease states [38]. In addition, the small sample size increases in previous studies facilitated the likelihood of error, because inter-arm differences may not be apparent in short term data, even if they exist. However, results of a longer trial answer questions about the risks and benefits of structured treatment interruption and may allow robust conclusions to be drawn. The uncertainty around the appropriate utilities for specific health states will be examined within the probabilistic sensitivity analysis and using scenario analyses where alternative EQ-5D algorithms are used to attach utilities to specific health states. We will also examine the relationship between EQ-5D and condition specific measures of QoL to examine whether all important domains of health related QoL (HrQol) are captured by the EQ-5D and the relative importance of any domains that are missed.

Data on primary, secondary, tertiary and community health care utilization will be collected through MRU and standard case report forms (CRF) at each clinical assessment visit. Striking a balance between minimising respondent burden and comprehensiveness of data collection, the resource use questions will relate to a 6 weeks recall period as recall over longer periods has been found inaccurate [39]. We will also ask whether there have been any significant out-of-pocket expenses associated with their care (costs of over-the-counter medications, transportation and other out-of-pocket expenses) and whether patients and/or their carers have taken time away from work directly related to their care.

Our economic evaluation will consider both the NHS and Personal Social Services (PSS) perspective and a societal perspective. The latter will include the out-of-pocket expenses, and the productivity costs to the participants and carers. Wherever possible

unit costs for resources will be obtained from national sources such as the British National Formulary and the PSSRU Costs of Health and Social Care [19]. Costs and benefits will be discounted at 3.5% p.a. Furthermore, other quality of life instruments will be used for further subgroups analyses and cost consequences analyses.

Drug free intervals may be viewed by some stakeholders as primarily a cost containment strategy. Therefore it is important to provide a demonstrably unbiased cost effectiveness analysis. For the within-trial analysis, the researcher undertaking the cost-effectiveness analysis will be blinded to the treatment allocation. The costing work and construction of the QoL profile will be undertaken by a different research fellow to maintain the blinding of the analyst to the treatment allocation. To reduce missing data an automated system for co-ordinating site reminders for missing data will be set up and managed by the CTRU trial coordinators. Parameter uncertainty will be explored using probabilistic sensitivity analysis. The within-trial analysis will use the non-parametric bootstrap method to generate simulations of the mean costs and effects for each arm of the trial [40]. The analysis will estimate the expected incremental cost per QALYs. We will also present the cost effectiveness acceptability curves and the cost effectiveness acceptability frontier. The expected net benefit will also be calculated for a range of values of lambda [41-43], including lambda=20,000 per QALY. In the NHS the manufacturer (Pfizer™) estimated the incremental cost-effectiveness ratio (ICER) for sunitinib to be £29,440 per QALY. An independent analysis, undertaken using ITT estimates of effectiveness, reported an ICER of £62,365. A NICE Decision Support Unit re-analysis of the manufacturer's model reported an ICER of £54,366 for sunitinib, with the price discount (first cycle provided free) taken into account, demonstrating that the price of sunitinib is a key determinant of its cost-effectiveness. Treatment strategies that reduce the total quantity of sunitinib administered whilst maintaining total health gain are likely to be significantly more cost-effective than the current treatment regimen [44], thus supporting the DFIS model.

Towards the end of the trial, a precise review of the recent literature and the structures of the models used for the NICE appraisals will be performed. A second set of economic analyses will adopt a lifetime horizon and involve constructing a decision analytic cost effectiveness model. As far as possible parameters in the model will be specified using data collected within the trial. The long term clinical pathway will be constructed through a clinical expert consensus process following the recommendations of Murphy et al. [45]. The agreed clinical pathway will be used to specify the evidence required to specify the model. Focused literature searches will be undertaken to identify literature following the work of Paisley [46]. Where additional evidence is in the public domain we will update the parameter values using the trial data. The outcome measure for these analyses will be the QALY. The utility weights will be calculated using the quality of life data collected within the trial and parameter uncertainty will be explored using probabilistic sensitivity analysis and Monte Carlo simulation. The decision analytic cost effectiveness model will also be used to estimate a value of information analysis (VoI) [47]. VoI provides a methodological framework that explicitly considers the uncertainty surrounding the decision of a health care system to adopt a new technology. The expected cost of uncertainty can be interpreted as the Expected Value of Perfect Information (EVPI), given that if there was perfect information there would not be any wrong decision. The cost-effectiveness threshold places an upper bound on the value of conducting further

[19] Unit Costs of Health and Social Care 2009, http://www.pssru.ac.uk/uc/uc2009contents.htm

research. Therefore, this method allows a comparison of the potential benefits of further research with the costs of further investigation.

16. Endpoints

16.1 Primary Endpoints (co-primary)

- 2 year Overall Survival
- Quality Adjusted Life Years averaged over trial recruitment and follow up

This trial of sunitinib in renal cancer will determine whether, by utilising a DFIS, survival benefits can be maintained, whilst other important outcomes, such as QoL and cost effectiveness, can be improved, compared to utilising a CCS. Oncological treatments for patients with incurable disease require assessment using standard measures of efficacy, such as survival. It is however recognized that other measures must also be taken into consideration including QoL and cost, particularly in the context of the economic constraints of the NHS. When seeking approval from NICE for a new treatment, all of these outcomes are considered.

16.2 Stage-Specific Primary Endpoints

Stage A

- Recruitment rate between months 10-21 (inclusive) of the trial

Stage B

- Time to Strategy Failure (TSF)

Stages A, B and C

- 2 year Overall Survival
- Quality Adjusted Life Years averaged over trial recruitment and follow up

16.3 Secondary Endpoints

- Overall Summative Progression Free Interval (SPFI)
- Time to Strategy Failure (TSF)
- Toxicity (CTCAE v4.0)
- Quality of Life (FSKI-15, FACT-G, EQ-5D^{TM} and EQ-VAS)
- Cost effectiveness
- Progression free survival (PFS)

16.4 Trial Definitions

1. Overall survival is defined as the time from randomisation to the trial to death from any cause or date last known to be alive. Analyses are targeted to look at differences in 2 year survival, but all follow-up will be incorporated.
2. Recruitment rate between months 10-21 of the trial is defined as the average recruitment rate per trial site open per month between months 10 -21 inclusive.
3. Time to Strategy Failure is defined as time from randomisation until:

   a) death;

   b) disease progression[20] on sunitinib in the CCS arm;

   c) disease progression assuming no further disease response or stabilisation on subsequent sunitinib occurs, in DFIS arm, or

   d) patient requires use of a new systemic anti-cancer agent for RCC (end point measured at the first of either time of disease progression or time of initiation of new agent), or

   e) disease progression during a planned treatment break where the participant's performance status is clearly clinically deteriorating and the participant is, from a clinical point of view, no longer suitable to continue sunitinib treatment. Under these conditions, the stopping of treatment is classed as strategy failure.

4. The date of disease progression is the date of the radiological investigation which confirms disease progression. At stage B, analyses are targeted to look at differences in 15-month strategy failure rates between arms, but all follow-up will be incorporated. At stage C, analyses are for the whole trial duration.
5. Overall Summative Progression Free Interval is defined as the sum of the intervals from the start of each treatment block with sunitinib until radiological evidence of progressive disease[21] provided there has been some evidence of disease control (SD, PR or CR) before evidence of ongoing progression. Analyses are for the whole trial duration.
6. Toxicity will be reported based on adverse events from the start of treatment, as graded by CTCAE v4.0 and determined by routine clinical assessments at each trial site.
7. FSKI-15, FACT-G, EQ-5D and EQ-VAS will be used to measure patient-assessed QoL in detail.
8. Progression free survival is defined as time from randomisation to the date of the radiological investigation which confirms disease progression or death from any cause. Participants who do not progress will be censored at the last date they were known to be alive and progression free.

[20] For the purposes of the trial disease progression will usually be defined radiologically (RECIST), however it is acknowledged that there will be rare circumstances when disease progression is determined clinically due to a global deterioration in clinical status attributable to disease progression in the view of the investigator. Treatment with sunitinib may be required to be stopped if clinically indicated, however please note that if possible an appropriate radiological assessment should be performed to document the disease status as per RECIST.

[21] In the rare circumstances that disease progression is determined clinically and it is not appropriate to confirm it radiologically, then the date of progression is defined as the date of stopping sunitinib due to clinical suspicion of disease progression

17. Statistical Considerations

17.1 Design

Detailed and careful consideration was given to the optimal timing for randomisation, either prior to receiving any treatment (baseline), or just prior to taking up the DFIS or CCS treatment arms. Detailed discussions were held with the National Renal Cancer Clinical Studies Group and the NIHR HTA during the funding application process. Several pieces of evidence led to the decision to randomise at baseline. A major factor was evidence from a colorectal trial that this might lead to a higher patient take up of randomisation [48]. There is also further evidence supporting this from a previous lung cancer trial comparing differing durations of chemotherapy [49]. Evidence showed that patients are more compliant if uncertainty is removed and they know what to expect in terms of stopping or continuing treatment, and this was reinforced after a number of consultations with participants taking sunitinib regarding their preferences. Patients' feelings about this will be further explored in a patient preference and understanding study in the initial stages of the trial (see separate protocol).

17.2 Sample Size

Assuming recruitment continues through all 3 stages a total of 1000 participants will be required (allowing for a 10% drop-out, i.e. 900 participants for final primary analysis).

17.3 Primary Endpoints

17.3.1 Stage A

An essential part of any trial is ensuring that recruitment targets are met. This will be formalised in STAR to ensure that the results can be delivered to time and target, To do this the recruitment per month during months 10-21 (inclusive) of recruitment (not utilising the initial 9 months to enable site set up and familiarity with the trial) will be determined and, in order to continue the trial, a specific recruitment rate must be attained.

An initial required recruitment rate of approximately 1 patient per trial site per month has been estimated. With the 13 sites (already approached and agreed to participate) expected to begin recruitment in a staggered way over the first 9 months a target recruitment of approximately 60 participants has been assumed over this period, plus approximately another 150 per year subsequently; this provides the 210 participants required over 21 months for stages A-B. Assuming continuation to Stage C, a further 25 UK sites will be recruited. Based on the assumption that sites will recruit at about 60 to 65% of the rate that they recruited in stage A and B, this would increase recruitment up to 24 per month and would fulfill the 288 per year required over the subsequent 33 months to produce the total sample size requirement of 1,000 participants. Based on informed discussions in the National Renal Clinical Studies Group (CSG) and 2005-2006

data from the Yorkshire Cancer Network covering a population of 2.6 million, assuming 30-40% recruitment of eligible patients and extrapolating to the 13 million population of the anticipated initial stage trial sites, an annual accrual rate of 288 participants per year should be readily achievable. To coincide interim stage analyses we will look at recruitment between months 10 and 21 (inclusive).

Average recruitment will be calculated between months 10 – 21(inclusive) of recruitment. The 95% CI for a recruitment rate of 1 patient per trial site per month, with 13 trial sites for 12 months, is 0.85-1.15. Therefore a minimum of 0.85 participants per trial site open per month is required, i.e. a minimum of 133 participants recruited over the 12 month period, assuming all 13 trial sites open and commence recruitment in a timely manner.

17.3.2 Stage B

An interim efficacy endpoint has been included to further ensure the appropriateness of extending recruitment and continuing the trial to stage C. PFS is not an appropriate comparator endpoint in the trial as due to planned treatment breaks the initial PFS could be shorter in the DFIS arm. TSF will be analysed (targeted to look at differences in 15 months strategy failure rates) in both arms and non-inferiority will be required to be demonstrated between the arms for the trial to continue.

The primary outcome measure is the TSF. For the decision to progress to stage C, preliminary evidence of efficacy is required, therefore the TSF in the DFIS arm must be less than 15% worse than in the CCS arm (strategy failure is assumed to be 80% at 15 months [4]). Assuming 21 months of accrual and immediate analysis, 80% power, and assuming proportional hazards, this would require 67 events and a population of 111 participants (approximately 56 in each arm; approximately 53% of the 210 in total that will be randomised) who reach/take up their randomisation at 6 months[22]. Note the implication that this will therefore be a per-protocol analysis since an intention-to-treat analysis on these participants would be likely to dilute any effect as there is no difference in treatment strategy between the CCS and DFIS arms up to 6-months. This sample size calculation uses a 1-sided 97.5% confidence interval, as described by Kay [50]. These estimates were derived from simulations to allow for the relatively small sample size. Note that at the end of stages A and B (at 21 months after start of recruitment) a formal interim analysis of the utility data so far obtained will be performed to revise the estimates of the power to detect the composite QALY endpoint and to evaluate possible refinements in the trial design as a result.

17.3.3 Stage C

There are two primary outcome measures: overall survival (OS) and quality adjusted life years (QALYs). The two null hypotheses are that DFIS is not inferior to CCS in terms of OS and QALYs. To calculate a sample size for the primary OS end point a difference of ≤7.5% in OS at two years between the two arms has been assumed to be an acceptable non-inferiority margin (equivalent to a hazard ratio of 0.806). To demonstrate this non-inferiority with 80% power will require the recruitment of approximately 1000 participants (allowing for 10% of participants being lost to follow-up). To calculate a sample size for the primary QALY end point a difference of ≤10% in mean QALYs between the two arms has been assumed to be an acceptable non-inferiority margin. While it is hoped that

[22] Assuming 60% take up randomisation, allowing for cessation of treatment due to disease progression or toxicity or withdrawal from study

survival will be equivalent between the two arms, a slightly poorer survival in the DFIS arm would be acceptable if offset by a quality of life gain in these participants, such a gain to be captured through the QALY measure. With a hazard ratio of 0.9 in favour of CCS and 1000 participants recruited, simulations give a power of 84% to show non-inferiority in the QALY endpoint. Both non-inferiority sample sizes are calculated assuming a 1-sided 97.5% confidence interval, as described by Kay [50] and assuming participants are recruited in total over 4.5 years, with a further follow-up of 2 years before evaluating the data.

There are a number of additional assumptions involved in the QALY endpoint simulations. QALYs were analysed using utilities derived from the EQ-5D. Despite strenuous efforts it was not possible to obtain the individual patient data for participants on the registration sunitinib trial [35]. Utility estimates were therefore derived from the EQ-VAS data reported in the Japanese sunitinib trial [37] of approximately 0.57 for periods on-treatment (SD 0.21) and 0.68 for periods off-treatment (SD 0.19). In the CCS arm an initial median PFS of 11 months [5] was used and subsequent PFS durations with medians of 7.2 months [30], with reductions in the DFIS arm commensurate with the assumed hazard ratio (so for a hazard ratio of 0.9 this gave medians of 9.9 and 6.5 months respectively in the DFIS arm). It was also assumed that re-treatment with sunitinib at progression in the DFIS arm is for 6 months unless progression intervenes. An additional assumption that approximately a third of participants die at or just after progression produced the anticipated median survival of 2.2 years [4]. Note that 100,000 such trials were simulated to produce each of these power estimates.

For the QALY endpoint, the average QALYs per patient was estimated from the simulations at 1.34. With a hazard ratio of 0.9 (equivalent to a survival difference of 3.6% at 2 years) the survival loss (about 0.064 QALYs per patient if there was no off-treatment QALY gain) is more than offset by the QALY gain (about 0.14 QALYs per patient), so on average the QALYs will be better for DFIS with this approach under these assumptions, but not sufficiently better to give good power to show a benefit, with power for the superiority comparison of only 13%. However, as stated above, this approach does gives 84% power for the non-inferiority endpoint. With a hazard ratio of 1 there is no survival loss and the QALY gain (about 0.14 QALYs per patient) is big enough to give 98% power to show DFIS is non-inferior (with about 56% power to show DFIS superior). We have therefore powered the trial on non-inferiority, rather than superiority, in the QALY.

17.4 Quality of Life

For sample size and power calculations a simple comparison of means for the FKSI and FACT-G scales and subscales is assumed. The more comprehensive planned analyses of the FKSI-15 and FACT-G scores are detailed in section 18.3. From the published Cella analysis [36] the main differences between sunitinib as compared with IFNα were observed in the FKSI-15 score, and, encouragingly, in the physical well-being and functional well-being subscales of the FACT-G score. With 1000 participants, and assuming 90% power, significance level of 0.05, the trial is powered to detect small effect differences in both physical and functional wellbeing.

18. Statistical Analysis

Statistical analysis is the responsibility of the CTRU STAR Trial Statistician. A full statistical analysis plan will be written before any analyses are undertaken. The analysis plan will be written in accordance with current CTRU standard operating procedures and will be finalised and agreed by the following people: the trial statistician and supervising statistician, the Chief Investigator, the CTRU principal investigator and the senior trial coordinator. Any changes to the finalised analysis plan, and reasons for changes, will be documented.

All analyses will be conducted on the intention-to-treat (ITT) population, unless otherwise stated, where participants will be included according to the treatment they were randomised to receive regardless of whether they prematurely discontinued the treatment or did not comply with the regimen with the exception of those who had been misdiagnosed. A per-protocol analysis, where participants will be included according to the treatment they received, will also be conducted. Participants defined as major protocol violators will be excluded from the per-protocol analysis. Major protocol violators will be defined prior to the start of recruitment and any subsequent changes, and reasons for changes, will be documented. For the superiority endpoints the ITT analysis will be given primacy, however for the non-inferiority endpoints equal weighting will be given to both the ITT analysis and the per-protocol analysis, as the ITT is likely to be the least conservative approach when testing for non-inferiority. The safety population will consist of all participants who receive at least one dose of the relevant trial treatment.

An overall two-sided 5% significance level will be used for all superiority endpoint comparisons, and a one-sided 2.5% significance level will be used for all non-inferiority endpoints.

18.1 Formal Interim Analysis

Interim analyses will be presented to the Data Monitoring and Ethics Committee (DMEC) in strict confidence at approximately yearly intervals. This committee, in the light of the interim data, and of any advice or evidence they wish to request, will advise the Trial Steering Committee if there is proof beyond reasonable doubt that one treatment is better.

The trial will have a formal interim analysis after the end of stages A and B (at 21 months after start of recruitment). The primary analysis will comprise Kaplan-Meier curves including those adjusted for the minimisation factors (except trial site) and other relevant patient characteristics [51] giving 95% CIs for the TSF difference, plus a Cox proportional hazards model analysis adjusting for the minimisation factors (except trial site) and other relevant patient characteristics with associated hazard ratios plus 95% CIs for the DFIS vs. CCS comparisons, as appropriate for the non-inferiority analysis. The analysis of primacy is the Cox model. A formal interim analysis of the utility data so far obtained will also be performed at the end of stages A and B (at 21 months after start of recruitment) to revise the estimates of the power to detect the composite QALY co-primary endpoint and to evaluate possible refinements in the trial design as a result. The DMEC, in the light of the interim data, and of any advice or evidence they wish to

request, will make their recommendations to the Trial Steering Committee who will in turn decide whether the trial can continue to Stage C .

No formal interim analysis is planned for stage C.

Apart from the interim analysis to the DMEC, no other formal analyses are planned until after the trial is closed to accrual. Final analysis is planned when a median follow-up of 2 years is observed.

18.2 Primary Endpoint Analyses

The primary analysis will comprise Kaplan-Meier curves including those adjusted for the minimisation factors (except trial site) and other relevant patient characteristics [51], giving 95% CIs for the 2-year survival difference, plus a Cox proportional hazards model analysis adjusting for the minimisation factors (except trial site) and other relevant patient characteristics with associated hazard ratios plus 95% CIs for the DFIS vs. CCS comparisons, as appropriate for the non-inferiority analysis. The analysis of primacy is the Cox model.

For the QALY-based co-primary non-inferiority endpoint mean differences in QALYs, calculated via the EQ-5D, between the arms, with 95% confidence limits, will be calculated. Multivariate linear regression will be used to adjust for the minimisation factors (except trial site) and other relevant patient characteristics. If the data are not normally distributed, transformations to normality will be investigated. If no such transformations can be found we will analyse the difference between median QALYs and we will calculate confidence intervals for the differences between these medians as described by Campbell and Gardner [52].

18.3 Secondary Endpoint Analyses

Analysis of Overall Summative Progression Free Interval and time to strategy failure will comprise Kaplan-Meier curves including those adjusted for the minimisation factors (except trial site) and other relevant patient characteristics [51], plus a Cox proportional hazards model analysis adjusting for the minimisation factors (except trial site) and other relevant patient characteristics with associated hazard ratios plus 95% CIs for the DFIS vs. CCS comparisons. The analysis of primacy is the Cox models.

Analysis of CTCAE v4 data will use an approach similar to ‘area under the curve’ measures and thus takes account of intermittent toxicities by comparing sums of toxicity scores after randomisation between the two arms (this can be adjusted for any differences in the toxicity profile between the two arms at the time of randomisation). Analyses will employ t-tests, if appropriate, or Mann-Whitney tests if the data are not normally distributed. Both these analyses are likely to be extremely sensitive to differences in toxicity profile between the arms as a number of different scores will be summed, all of which could be expected to be affected by stopping sunitinib treatment.

QoL measures (Total FKSI, FKSI Disease Related Subscale, FACT-G total and FACT-G subscales) will be compared using multi-level repeated measures modelling (allowing for time, treatment, treatment by time interaction, adjusting for baseline QoL, all fixed effects), patient and patient by time (random effects) and pattern mixture multi-level models. To ease clinical interpretation, treatment estimates from a logistic regression model investigating proportion of participants improving for each of the primary and highlighted endpoints, adjusted by baseline score, will also be presented.

The analysis of progression free survival will comprise Kaplan-Meier curves including those adjusted for the minimisation factors (except trial site) and other relevant patient characteristics [51], plus a Cox proportional hazards model analysis adjusting for the minimisation factors (except trial site) and other relevant patient characteristics with associated hazard ratios plus 95% CIs for the DFIS vs. CCS comparisons. The analysis of primacy is the Cox model.

19. Data Monitoring

19.1 Data Monitoring and Ethics Committee

An independent DMEC will review the safety and ethics of the trial. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at approximately yearly intervals which will include toxicity and survival data by treatment group. The formal interim analysis will be reported to the DMEC after the end of stages A and B (at 21 months after start of recruitment). Although the trial will have a formal interim analysis after the end of stages A and B (at 21 months after start of recruitment), the DMEC can request these stages reported separately and to suspend recruitment if they deem it necessary while awaiting the results from either.

The DMEC will be provided with detailed unblinded reports containing the following information:

- Rates of occurrence of SAEs, SARs and SUSARs

19.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be pursued until it is received, confirmed as not available or the trial is at analysis. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports. A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule including primary endpoint and safety data will be defined and agreed by the Trial Management Group (TMG) if necessary.

19.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

20. Quality Assurance and Ethical Considerations

20.1 Quality Assurance

The trial will be conducted in accordance with the principles of Good Clinical Practice in clinical trials, as applicable under UK regulations, and the NHS Research Governance Framework (and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland).

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are identified and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) that they become aware of. A “serious breach” is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial.

In the event of doubt, or for further information or guidance, the investigator should contact the CTRU.

20.2 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000*. Informed written consent will be obtained from the participants prior to randomisation/registration into the trial. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment. The trial will be submitted to and approved by a main Research Ethics Committee (main REC) and the appropriate Site Specific Assessor for each participating trial site prior to entering participants into the trial. The CTRU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant trial documentation.

20.3 Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name (via consent form), date of birth, email address and telephone number, NHS number, hospital number, GP name and address.
- appropriate storage, restricted access and disposal arrangements for patient personal and clinical details
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- patient name (via consent form), email address and telephone number will be collected when a patient is randomised into the trial but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two patient identifiers, usually the patient's initials and date of birth.
- where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the patient's name must be obliterated by site before sending
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU

If a participant withdraws consent from further trial treatment and / or further collection of data their samples will remain on file and will be included in the final trial analysis.

21. Archiving

At the end of this trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at the participating sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

22. Statement of Indemnity

This trial is sponsored by the University of Leeds and the University of Leeds will be liable, in certain circumstances, for harm caused by participation in the trial.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and the NHS remains liable for harm to patients due to clinical negligence under this duty of care.

23. Trial Organisational Structure

23.1 Responsibilities

Sponsor: In accordance with the NHS Research Governance Framework, the Sponsor will take responsibility for confirming there are proper arrangements to initiate, manage, monitor and finance the study.

Chief Investigator: The Chief Investigator will have responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial. In this trial a Co-Chief Investigator will assist in this role.

Clinical Trials Research Unit: The CTRU will have responsibility for conduct of the trial in accordance with relevant GCP standards and CTRU SOPs.

The Leeds Teaching Hospitals Trust: During stages A and B of the trial, the Radiology Department at St James's University Hospital will have responsibility for reporting all participant CT scans (or MRI scans in cases where these are performed in the place of CT), This reporting will be blind to participant's randomisation allocation but will take place in real time and the central report generated used by the participating trial sites to inform participant treatment decisions.

23.2 Operational Structure

23.2.1 Trial Management Group (TMG)

The TMG, comprising the Chief Investigator, the Co-Chief Investigator, the CTRU team and other key external members of staff involved in the trial, will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

23.2.2 Clinical Trials Research Unit (CTRU)

The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data

verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support main REC, Site Specific Assessment and R&D submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will provide the first point of contact for trial site queries relating to the protocol and conduct of the trial and will direct these for resolution as appropriate to the relevant member(s) of the TMG.

23.2.3 Trial Steering Committee (TSC)

The TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, patient safety and consideration of new information. It will include an Independent Chair, not less than two other independent members and a consumer representative. The Chief Investigator and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

23.2.4 Data Monitoring and Ethics Committee (DMEC)

The DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet annually as a minimum.

24. Publication Policy

The trial will be registered with an authorised registry, according to the ICMJE Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, the Co-Chief Investigator, relevant senior CTRU staff and other significant contributors who meet the above criteria will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral

presentation purposes, without the permission of the Trial Steering Committee. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

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Appendix 1: Motzer Score

Definition of risk factors

Score 1 point for each risk factor that applies:

- Karnofsky performance status: <80% (see table below)
- Lactate dehydrogenase: >1.5 times Upper Limit of Normal (ULN)*
- Low serum haemoglobin: <Lower Limit of Normal (LLN)*
- Corrected serum calcium: >10 mg/dL
- Prior nephrectomy: No

***** LLN and ULN relate to reference ranges of the laboratory where blood tests are performed

Calculation of risk

Number of risk factor points scored	Risk category
None	Favourable
Fewer than three	Intermediate
Three or more	Poor

Karnofsky Performance Status [23]

100% normal, no complaints, no signs of disease
90% capable of normal activity, few symptoms or signs of disease
80% normal activity with some difficulty, some symptoms or signs
70% caring for self, not capable of normal activity or work
60% requiring some help, can take care of most personal requirements
50% requires help often, requires frequent medical care
40% disabled, requires special care and help
30% severely disabled, hospital admission indicated but no risk of death
20% very ill, urgently requiring admission, requires supportive measures or treatment
10% moribund, rapidly progressive fatal disease processes
0% death

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Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance 24

Grade	ECOG Performance
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

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Appendix 3: Response Evaluation Criteria In Solid Tumours (RECIST)

Response to treatment will be assessed based on RECIST V1.1. a copy of the revised RECIST guideline is provided in the Investigator Site File and may also be obtained at:

http://www.eortc.be/recist/

Published date: January 2009

Appendix 4: Tissue studies

The STAR trial is especially timely in the context of the need to collect renal cancer tissue samples from patients receiving TKIs for validation of tissue biomarkers, particularly to develop markers which will predict response to the new generation of treatments which are being developed and toxicity. Diagnostic pathology samples are routinely taken from all patients with suspected renal cancer, either at the time of nephrectomy, or from a diagnostic biopsy. Such samples will therefore already exist for patients entering the STAR trial. Informed consent will be sought from all patients participating in the STAR trial for the collection and use of surplus tissue from these pathology samples for biomarker studies in the future.

The proposed tissue studies involve processing retrieved formalin-fixed paraffin-embedded tissue blocks to prepare tissue micro-arrays (TMAs) for use in future research studies. Separate ethical approval will be sought for the specific use of the TMAs for future research studies.

Examples of future studies that may be performed (pending ethical approval) include the following (this list is not exhaustive):

- **Type 1 insulin-like growth factor receptor (IGF-1R).** High IGF-1R expression has been shown to be associated with poor prognosis in RCC [1, 2], but the correlation between IGF-1R and response to anti-angiogenic therapy has not yet been investigated. Access to TMAs generated in the STAR trial provides an ideal opportunity to study such correlations and evaluation of the potential use of IGF-1R as a biomarker for prediction of response.
- **The CAGEKID study.** This is a renal cancer, whole genomic re-sequencing study. The STAR TMA will play an important role in validating biomarkers discovered in the CAGEKID study.
- **The PREDICT study.** PREDICT is a European consortium focusing on the identification of reliable predictive biomarkers to approved agents with anti-angiogenic activity for which no reliable predictive biomarkers currently exist, for example, sunitinib. The STAR TMA are also expected to play an important role in validating biomarkers discovered in the PREDICT study.

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Appendix 5: Computerised Tomography Imaging Sub-study

Background and Sub-study Rationale

There is an urgent clinical need to identify biomarkers predictive of response early in sunitinib treatment to allow early cessation of ineffective treatment, thus reducing toxicity and cost, and allowing non-responders to be offered alternative therapy. The STAR trial provides a unique opportunity to address this unmet clinical need and pilot studies using computerised tomography (CT)(see below) give us encouragement that it will be possible to identify such biomarkers in the course of the STAR trial. Whilst the data obtained will refer specifically to sunitinib treatment in mRCC, it is likely to have more general application to anti-angiogenic therapy in cancer. To maximise utility of the resources available, we have planned a CT substudy to map directly onto the phase II part of the STAR trial (210 patients) and to utilise the STAR clinical database and trial infrastructure already established in the Leeds Clinical Trials Research Unit (CTRU). STAR phase II sites have already been identified and all 12 have expressed interest in participating in the CT substudy. It should be noted that if the STAR trial proceeds to phase III, an additional 790 patients will be available for further prospective validation of any exploratory imaging biomarkers showing promise in the initial substudy.

Since 2000, Response Evaluation Criteria of Solid Tumours (RECIST) has been the standard method of imaging-based evaluation of treatment response to cytotoxic chemotherapy in solid tumours, including RCC [1]. RECIST response depends on the proportional change in the sum of uni-dimensional measurements of the tumour target lesions. Although there is some evidence that RECIST may not accurately reflect response to anti-angiogenic therapy as well as to chemotherapy, it remains the current 'gold' standard which applies to all RCC studies including STAR [2-4].

Alternative CT-based criteria to RECIST based on tumour size and density have been proposed by Choi et al for response assessment of gastrointestinal stromal tumours treated with imatinib [5]. However, a pilot study in 30 patients treated with sunitinib or cediranib showed that at 3 months after administration of TKI, mChoi criteria, in which a PR required a reduction of **both** size by >10% **and** enhancement by >15% (compared to **either/or** with standard Choi criteria), was superior to either RECIST or Choi for prediction of time to progression [6]. Tumour enhancement was measured in the arterial phase following contrast administration. A similar study also proposed new criteria for CT response assessment in RCC accounting for changes in tumour size, attenuation and morphology [7]. Evaluation using the new criteria for assessment of initial post-therapy contrast-enhanced CT (CE-CT) was more sensitive for predicting prolonged PFS than by initial RECIST response. These pilot data suggest that response assessment using mChoi criteria could identify patients who would and who would not derive significant clinical benefit from treatment with sunitinib at an earlier stage than currently occurs with RECIST. This important hypothesis now requires validation in a larger prospective study. The cohort of STAR patients are ideal for this as the clinical trial infrastructure and database already in place can be utilised, and patients will already be having CT assessments at baseline and around 10 weeks, and 12 weekly thereafter. This approach provides high resolution anatomical information and tumour

density information from the standard routine clinical practice CT with no additional patient burden.

Aims of the CT Translational Studies

- To define the inter-operator variability (reliability) and hence the robustness of CE-CT as a potential biomarker in this setting by performing a test-retest comparison (dual reporting)

- To prospectively evaluate the utility of CE-CT modified Choi criteria (mChoi) assessed at 3 months (primary objective) after initiation of sunitinib to predict for progressive disease (PD) within 6 months.

- Exploratory studies will also be performed to: a) examine the relative sensitivity of arterial and porto-venous phase contrast CT imaging on the ability to predict response, b) the ability of the 3 month scans to predict time to strategy failure and c) the ability of a novel textural analysis methodology to predict response of mRCC to sunitinib.

Recruitment and Informed Consent

This study will be performed at all phase II trial sites participating in the STAR trial using CE-CT as standard of care. No additional scans are required over those performed routinely as part of the clinical STAR trial. The study is explained in the main STAR trial PIS and patients will then be asked, if they agree to participate, to complete an optional box on the consent form which will permit their anonymised images to be sent to the Division of Imaging Sciences, Kings College London to be reviewed and reported for the purposes of the substudy. All participants will have been required to have consented for transfer for their anonymised images to the Department of Radiology, St James's Institute of Oncology, Leeds for the purposes of the central reporting of the phase II part of the clinical trial.

Imaging

In the sub-study, CE-CT will be performed as per STAR clinical trial requirements at baseline and at day 72+/-4 days. CE-CT will provide the standard CT scan report information (RECIST) as well additional data on the arterial venous phase comparison. CT substudy participants will therefore not need to have any additional scans compared with STAR trial participants not participating in the CT substudy. For any phase II trial sites performing routine scans at other times (e.g. 1 month), participant consent will also enable these additional scans to be reviewed, although no clinical decisions will be made on scans performed outwith those required as per protocol in the STAR clinical trial.

Scans will be reported using RECIST, mChoi and Choi criteria. CE-CT images will be obtained of the thorax, abdomen and pelvis and will be performed with arterial phase imaging of the thorax/upper abdomen to include the kidneys, and porto-venous phase imaging of the abdomen/ pelvis.

Transfer of Scans

The CT scans will be reported centrally in Leeds and then dual reported by a second experienced consultant radiologist within the Division of Imaging Sciences, Kings College London .

Sites must ensure that scans are anonymised prior to transfer such that only the following identifiers are included: unique trial number, participant initials, participant date of birth. Anonymisation of scans will be checked on receipt at St James's University Hospital prior to central review and dual reporting. Scans will be stored securely in the radiology department, St James's Hospital, Leeds prior to transfer for dual reporting at the Division of Imaging Sciences, Kings College London.

Endpoints

Primary: Two co-primary endpoints will be evaluated at the end of phase II. The first will describe the inter-operator variability within the assay, thus evaluating the reliability of CT-defined size and enhancement reporting. This will be novel data and will be essential if this imaging approach is to be used as a future predictive biomarker with confidence. The second primary endpoint is the ability of mChoi at 10 weeks months to predict patients who have RECIST-defined PD within 6 months of commencing treatment.

Secondary endpoints include the ability of mChoi criteria at 10 week scan to predict time to strategy failure, assessment of the effect of arterial phase and porto-venous phase of contrast CT scans upon response criteria, and the use of CT textural analysis (CTTA) as a predictive tool. The latter is a novel technique that can quantify tumour heterogeneity to provide a biomarker in oncology. CTTA uses software (texRAD) that selectively extract features of different sizes and intensity variations (fine to coarse textures) from the standard CT images to measure heterogeneity, and has been associated with advanced disease and poor survival. A pilot study on 55 lesions in 25 RCC patients following 2 cycles of TKI therapy has demonstrated the potential of baseline and post therapy CTTA to provide a predictive imaging biomarker of response of advanced renal cancer to targeted therapy independent to tumour enhancement change.

Statistical Analysis

Both primary endpoints can be met by using the whole (13 site) patient population in the phase II part of STAR, assuming 150/210 patients participate in the CE-CT sub-study (allows for 30% non participation e.g. due to inability to have contrast-enhanced scans due to co-morbidity, dropout etc). The reproducibility of size and attenuation measurements (test versus retest), will be analysed by the Bland-Altman approach [8] using the inter-operator variability. The intra-operator variability is also of interest but is assumed to be smaller and would, hence, have less impact on the true observed reduction in attenuation and size over time. Assuming that each scan will on average have 2.5 measurable lesions, with 150 scans, the upper 95% confidence interval of the reliability coefficient would be 10.0% denoting that changes greater than 10.0% can be attributed with 95% certainty to the underlying biological process rather than physiological or hardware variability. As the smallest change we are looking for is a 10% change in lesion size, this would demonstrate a high degree of confidence that patients were being assigned to response groups due to real tumour changes.

If the 10 week mChoi assessment is able to predict RECIST progression at 6 months, a high degree of concordance will be required to change practice, ie for clinicians to change therapy early before RECIST defined progression is attained. The ability of mChoi defined PD at 10 weeks to predict RECIST defined PD at 6 months will be analysed by kappa measurements in 2x2 contingency tables [9], where kappa is a measure of agreement between two ratings or measurements. In kappa, the observed agreement proportion is adjusted to correct for the agreement expected by chance with the observed proportion of successes. With 150 patients and assuming a "by chance" agreement of 50% an agreement of more than 95% can be demonstrated with at least 99% power at a 5% significance level.

Archiving

At the end of this sub-study, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by both CTRU (CRFs) and St James's Hospital, Leeds (scans) will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at the participating sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

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Appendix 6: Functional Imaging Sub-Study: Dynamic Contrast Enhanced-MRI (DCE-MRI) Evaluation

Background and Sub-study Rationale

The STAR trial represents a unique opportunity to carry out key associated translational studies, particularly in the early prediction of those patients who will respond to sunitinib and those who will not. In this translational sub-study, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) will be used to see if it is possible to obtain a prediction of those patients who will responding to sunitinib and those who will not, much earlier than with the current CT scanning approach. If this can be done then, in future, instead of continuing to give sunitinib to patients who are not responding and exposing them to unnecessary toxicity for longer, alternative treatments could be offered earlier.

Magnetic Resonance Imaging (MRI) has a number of advantages for functional imaging due to its high spatial and contrast resolutions. The STAR radiology team already have wide experience of assessment of tumour perfusion and vascularity with DCE-MRI, in relation to treatment planning of, and monitoring local response to, tumour radiofrequency ablation (RFA) in Leeds.

Our hypothesis for this sub-study is that, for patients with advanced RCC treated with sunitinib, early DCE-MRI will be predictive of patients who progress within 6 months and rhis is supported by very recent data [1]. A recent pilot study in Leeds has optimised DCE-MRI techniques to enable quantification of vascularity and perfusion [2]. An optimised volume acquisition DCE-MRI technique has allowed quantitative assessment of the treated RCC (i.e. zone of ablation) at one month post RFA and confirmed diminished perfusion. This proven DCE-MRI technique will be used in the proposed study to assess the change in vascularity and perfusion of the target lesions, at baseline, 1 month and 3 months after treatment of advanced RCC with sunitinib.

Aims and Objectives

The utility of tumour vascularity measured by DCE-MRI post randomisation around 10 weeks i.e. day 72 ± 4 days to coincide with the initial assessment CT scan (primary endpoint) and at 4 weeks i.e. day 28 ± 4 days (secondary endpoint) after initiation of sunitinib to predict patients who have Response Evaluation Criteria of Solid Tumours (RECIST) defined progressive disease within 6 months of commencing treatment, will be assessed.

Other secondary endpoints will determine the ability of other DCE-MRI-based parameters (perfusion, Ktrans, endothelial permeability) at 4 and 10 weeks predict for progressive disease (PD) within 6 months and also overall survival (OS). DCE-MRI scans will be obtained for up to 5 target lesions at baseline, 4 weeks and 10 weeks following initiation of sunitinib and will be analysed using compartmental analysis.

Recruitment and Informed Consent

This is an optional part of the STAR trial and will involve a sub-set of approximately 55 participants from the main trial. It is anticipated that these functional imaging sub-study participants will be recruited from 5 of the trial sites participating in the STAR trial. These sites have already provisionally agreed to participate. A separate patient information sheet and consent form will be provided to potential sub-study participants.

Participant Registration

Participants taking part in this sub-study are required to undergo a baseline DCE-MRI scan prior to commencement of sunitinib treatment on the STAR trial. Given the narrow window specified between randomisation and commencement sunitinib (3 days; see section 8.5.1), it is anticipated that in many cases baseline DCE-MRI sub-study scans will need to be scheduled prior to randomisation. Participants agreeing to participate in this sub-study must therefore be registered with the CTRU prior to their baseline DCE-MRI scan in order to confirm their consent and participation in this sub-study. Participants will be allocated a unique trial identification number at registration.

Direct line for 24 hour registration
0113 343 4849

Please ensure that you have completed the Registration CRF before telephoning

Schedule of Imaging

Consenting participants will undergo a body DCE-MRI scan at baseline and around 4 and 10 weeks post-randomisation i.e. day 28 ± 4 days and day 72 ± 4 days. Each of the DCE-MRI scans will involve 30 minutes of scanning time for the participant.

After the patient has consented to the trial, the baseline DCE-MRI scan of the body must be performed after the patient has been registered and before starting trial treatment. The follow-up DCE-MRI scans must take place day 28 (± 4 days) and day 72 ± 4 days.

Imaging Details

DCE-MRI will be acquired in the coronal plane using a 3D T1 weighted sequence on a 1.5 T MRI scanner i.e. pre- and post-contrast. Dynamic contrast-enhanced imaging is performed following injection of 0.1 mmol/kg Gd-based contrast agent (e.g. Dotarem). Quantitative measurement of perfusion will use the software PMI 0.4. The DCE-MRI will be scanned to include all target lesions within the field of view.

Transfer and Storage of Scans

Scans for the DCE-MRI sub-study do not require expedited courier transfer. Once the DCE-MRI scan is available, a copy of the body DCE-MRI scan will be transferred on a CD or DVD by standard Royal Mail post to the radiology department, St. James University Hospital along with a scan transfer proforma completed at site. **Sites must ensure that scans are anonymised prior to transfer such that only the following identifiers are included: unique trial number, participant initials, participant date of birth**. Anonymisation of scans will be checked on receipt at St James's University Hospital prior to central review. Scans will be stored securely in the radiology department, St James's Hospital, Leeds.

Data Analysis

All DCE-MRI scans will be reported centrally and measurement of perfusion using the software PMI 0.4.

Data Collection

Trial data required for the DCE-MRI imaging sub-study will be recorded on the DCE-MRI sub-study specific Case Report Forms (CRFs) by the central reviewer at St James's University Hospital and submitted to the CTRU at the University of Leeds.

Endpoints

Primary Endpoint

The correlation of tumour vascularity measured by DCE-MRI at 10 weeks i.e. day 72 ± 4 days after initiation of sunitinib to predict participants who have Response Evaluation Criteria of Solid Tumours (RECIST) defined progressive disease within 6 months of commencing treatment.

Secondary Endpoints

1. The correlation of tumour vascularity measured by DCE-MRI at 4 weeks i.e. day 28 ± 4 days after initiation of sunitinib to predict participants who have Response Evaluation Criteria of Solid Tumours (RECIST) defined progressive disease within 6 months of commencing treatment.
2. To determine the ability of other DCE-MRI-based parameters (perfusion, Ktrans, endothelial permeability) at 10 weeks i.e. day 72 ± 4 days and at 4 weeks i.e. day 28 ± 4 days to predict for progressive disease (PD) within 6 months and overall survival (OS).
3. DCE-MRI scans will be obtained for up to 5 target lesions at baseline, 4 weeks and 10 weeks following randomisation and will be analysed using compartmental analysis.

Statistical Analysis

Assuming DCE-MRI has a coefficient of variation of 25%, and the mean baseline vascularity is 16 mls/100mg and is 8 mls/100mg at 3 months (responders) then 42 participants (55 allowing for 25% attrition) will enable demonstration of a significant difference in mean vascularity at 10 weeks of 1.6 mls/100mg between participants demonstrating RECIST-defined PD and those with RECIST-defined CR+PR+SD at 6 months, using a 2-sided t-test, with significance level 5% and 95% power. However, this would only identify about 15% of the participants still identified as responders (CR/PR or SD) at 10 weeks who would progress by 6 months (4 cycles of treatment) using the DCE-MRI vascularity information. We would anticipate a much larger difference in means: a realistic difference of 4 mls/100mg rather than 1.6 mls/100mg would enable us to identify, by DCE-MRI at 10 weeks, half of the participants who will progress (assessed by RECIST) by 6 months. Detection at 4 weeks would be even more beneficial, enabling us to stop an ineffective treatment and switch to an alternative.

Archiving

At the end of this sub-study, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by both CTRU (CRFs) and St James's Hospital, Leeds (scans) will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at the participating sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made

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