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STAR:
Standard vs Modified Drug Therapy in Renal Cancer

A Randomised Multi-Stage Phase II/III Trial of Standard first-line therapy (sunitinib or pazopanib) Comparing Temporary Cessation with Allowing Continuation, in the 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 Standard first-line therapy (sunitinib or pazopanib) Comparing Temporary Cessation with Allowing Continuation, in the treatment of locally advanced and/or metastatic Renal Cancer
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 had been demonstrated with sunitinib over previous therapies and sunitinib (which is a tyrosine kinase inhibitor (TKI)) became the standard therapy. It is however associated with significant toxicities and is expensive. The objectives of the initial trial design were to determine in the first-line treatment of locally advanced/metastatic RCC with sunitinib, whether the utilisation of a drug-free interval strategy (DFIS) was non-inferior to the 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 National Health Service (NHS), with a potential saving of approximately £16 million annually. It was proposed that a DFIS may also prolong response by reducing development of resistance. *Protocol v4.0 amendment* STAR had originally mandated that sunitinib was the only drug permitted for use in the Phase II trial with a pre-planned reconsideration of pazopanib (another TKI drug under consideration by NICE and the subject of a comparative study against sunitinib – COMPARZ) prior to opening the Phase III part of the STAR trial, based on the available data at that time. However, the COMPARZ trial reported data early (October 2012) which showed pazopanib to be non-inferior to sunitinib (Progression-Free Survival (PFS)) and no significant difference in OS. Also NICE approved pazopanib for first-line treatment in 2011. Based on these data, it appeared likely that some clinicians would wish to offer pazopanib in standard practice, as an alternative to sunitinib, which would potentially reduce the number of participants taking sunitinib for this trial. Following discussion with the funder (National Institute for Health Research Health Technology Assessment (NIHR HTA)), Trial Steering Committee (TSC), Data Monitoring & Ethics Committee (DMEC), key investigators and patient representatives, the protocol had been amended (v4.0) to include the option of using pazopanib, with the type of TKI as a stratification factor.

	Interim Analysis (end of Phase II) The trial oversight committees reviewed the results of the interim analysis (end of Phase II) in July 2014 and concluded that the trial had demonstrated recruitment feasibility (stage A) and that there was no evidence that the DFIS was inferior to the CCS arm for Time to Strategy Failure (TSF)[1] (stage B). As both the stage A and B endpoints of the Phase II trial had been met the DMEC advised continuation of the trial to Phase III (with both sunitinib and pazopanib). The TSC also gave their approval for trial continuation. It was also decided in consultation with the clinical advisors to remove the requirement for participants to meet the maximal radiological response threshold prior to commencing a treatment break in the DFIS arm. This change was made as only around 5% of participants had not reached the maximal radiological response threshold at 6 months and without central radiological review of all scans (not planned or possible for phase III) maximal radiological response would not be feasible to routinely assess at individual sites. This was approved by the TSC and DMEC. *Final Analysis (end of Phase III)* The trial was designed to demonstrate non-inferiority of the DFIS arm compared to the CCS arm in terms of overall survival with 80% power. This required the recruitment of 920 participants in order to observe 720 survival events (allowing for 5% of participants being lost to follow-up). 920 participants were recruited. However, due to multifactorial reasons the survival event rate was lower than predicted, and therefore the study follow-up period was extended by 15 months (until 31st December 2020). This was based on event rate modelling by Renfro et al[1] aiming to still observe 720 survival events. Ongoing event rate monitoring over the last year has demonstrated that the event rate has reduced further. As we are currently in the tails of any applied distribution we cannot therefore accurately predict when 720 events will be observed, however it is clear that it would not be until a significant additional time after the planned end of follow up. As such it is not feasible to extend the trial for a further fixed duration and after careful consideration the recommendation from the TMG was to complete follow up on 31st December 2020 as planned. This decision was supported by both the DMEC and the TSC and final analysis will proceed at the end of December 2020.
Trial design	A Phase II/III randomised (1:1) controlled, multicentre (UK) 3-stage trial. Participants from all 3 stages will contribute to the final Phase III analysis.

[1] Renfro, L.A., Grothey, A.M., Paul, J., Floriani, I., Bonnetain, F., Niedzwiecki, D., Yamanaka, T., Souglakos, I., Yothers, G. and Sargent, D.J., 2014, December. Projecting event-based analysis dates in clinical trials: An illustration based on the international duration evaluation of adjuvant chemotherapy (IDEA) collaboration. Projecting analysis dates for the IDEA collaboration. In Forum of clinical oncology (Vol. 5, No. 2, pp. 1-7). De Gruyter Open

	Stages A and B (Phase II) were conducted in 16 UK renal cancer trial sites (equivalent to 13.5 whole sites) and were designed to confirm an adequate recruitment rate and early indication of non-inferiority in terms of efficacy (TSF), with pre-defined objectives determining continuation to stage C (which will be expanded to around 38 trial sites).
Trial Objectives	The overall primary objective is to determine whether a sunitinib or pazopanib DFIS is non-inferior to a CCS in terms of OS and QALYs averaged over trial recruitment and follow-up in patients with advanced clear cell renal cell carcinoma.
Trial Endpoints	Primary endpoints: • Stage A: Recruitment rate • Stage B: TSF[2] • Stage C/Overall: OS[1] and averaged QALY (over recruitment and follow-up) Secondary endpoints: • TSF[1] • Time to Treatment Failure (TTF)[1] • Summative Progression Free Interval (SPFI)[1] • Cost-effectiveness (health economic endpoints) • Toxicity • Quality of Life (FACT-G, FSKI-15, EQ-5D™ and EQ-VAS™) • PFS[1] *Ancillary studies*: • Translational: Tissue and imaging[3] • Patient Preference and Understanding Study
Trial Population:	Phase II (stages A/B): A minimum of 210 participants. Overall Phase II+III (stages A/B/C): 920 participants 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 or pazopanib.
Trial Treatment:	Sunitinib - One cycle of treatment refers to 50mg (starting dose) on days 1-28, repeated every 42 days.

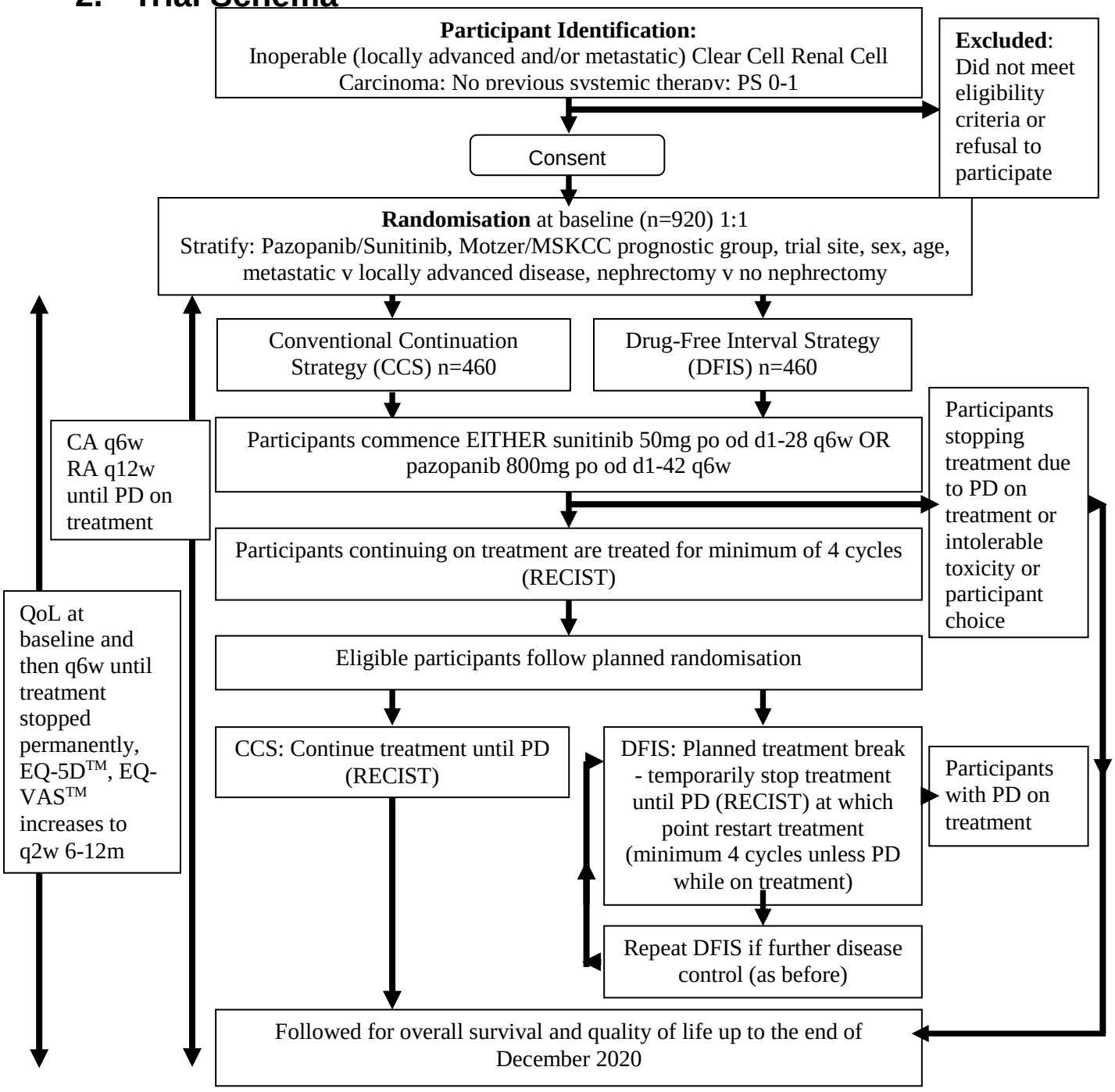
[2] See section 16.4 16.4 for definitions.
[3] Pending successful funding applications.

	Pazopanib - One cycle of treatment refers to 800mg (starting dose) on days 1-42, repeated every 42 days. All participants are planned to receive at least 24 weeks (4 cycles) of sunitinib or pazopanib treatment, assuming clinically appropriate to continue. After 4 cycles of treatment participants will take up their allocated treatment arm (randomised at baseline). *Control arm: Conventional continuation strategy (CCS)* All participants should continue sunitinib or pazopanib with regular radiological assessments every 12 weeks until protocol-defined Progressive Disease (PD) (RECIST), unacceptable cumulative toxicity or participant decision to stop treatment or withdraw from the study. *Research arm: Drug-free interval strategy (DFIS)* Participants stop treatment and continue 6-weekly active surveillance (clinical assessment) and 12-weekly radiological assessment, with planned recommencement of sunitinib or pazopanib at the time of PD (RECIST)[4]. On restarting sunitinib or pazopanib, assuming further disease control is achieved, sunitinib or pazopanib is then planned to be continued for a minimum of 4 cycles. At this point, assuming ongoing disease control, consideration should be given to a further planned treatment break from sunitinib or pazopanib until evidence of PD (RECIST) when again sunitinib or pazopanib is restarted. This DFIS (planned treatment break strategy) is continued until PD occurs during sunitinib or pazopanib treatment, cumulative toxicity or participant decision to stop treatment or withdraw from the study. Second and subsequent planned treatment breaks are at the treating clinician's discretion and need not be discussed in advance with CTRU.
Duration:	Stage A/B: There were 29 months of recruitment in stages A/B, including the formal monitored period for 12 months up until 31st May 2014. Stage C: There were a further 39 months of recruitment (following Stage A/B) until recruitment closed on the 12th September 2017. The planned follow-up period was 2 years after the last patient was randomised. This was extended to allow for collection of 720 overall

[4] After 4 cycles of treatment, when participants take up their allocated treatment arm, all DFIS participants should stop treatment. However, in the exceptional circumstance that the treating physician wishes the participant to continue sunitinib or pazopanib, and only if this is based on clear radiological evidence that the participant is continuing to respond (i.e. significant further tumour shrinkage between the 12-week and 24-week scans according to RECIST), continuation may be possible for a further 12 weeks before starting the treatment break, but this must be discussed with CTRU and with the Chief Investigator/Co-Chief Investigator before a decision is taken.

	survival events. The final analysis will be carried out when at least 2 years of follow-up and 720 events have been observed or the end of December 2020, whichever is sooner.
Evaluation of outcome measures	Participants 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™ 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
- Stage C: 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, Progression Free Survival
- Patient Preference and Understanding study (qualitative and quantitative)
- Bolt on translational studies

CA clinical assessment; CCS conventional continuation strategy; DFIS drug free interval strategy; MSKCC Memorial Sloan-Kettering Cancer Centre; 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; od once daily; po *per os* (by mouth)

3. Abbreviations

ACRONYM	DEFINITION
AE	Adverse Events
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate transaminase
BP	Blood Pressure
BR	Bilirubin
CCS	Conventional Continuation Strategy
CE-CT	Contrast Enhanced - Computerised Topography
CF	Consent Form
CI	Confidence Interval
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CSG	Clinical Studies Group
CT	Computerised Topography
CTA	Clinical Trial Authorisation
CTCAE v4.0	Common Terminology Criteria for Adverse Events version 4.0
CTRU	Clinical Trials Research Unit
CTTA	Computerised Topography Textural Analysis
CYP3A4	Cytochrome P450 3A4
DCE-MRI	Dynamic Contrast Enhanced - Magnetic Resonance Imaging
DFI	Drug Free Interval
DFIS	Drug Free Interval Strategy
DMEC	Data Monitoring and Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eMC	Electronic Medicines Compendium
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
FA	Folinic Acid
FACT-G	Functional Assessment of Cancer Therapy - General
FBC	Full Blood Count
FKSI-15	Functional Assessment of Cancer Therapy–Kidney Symptom Index-15 item
GFR	Glomerular Filtration Rate
GIST	Gastrointestinal Stromal Tumours
GP	General Practitioner
GCP	Good Clinical Practice
Hb	Haemoglobin
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICMJE	International Committee of Medical Journal Editors
IFNα	Interferon-α
IGF	Insulin-like Growth Factor
IMP	Investigational Medicinal Product
ITT	Intention to Treat
KPS	Karnofsky Performance Status

LDH	Lactate dehydrogenase
LFT	Liver Function Tests
LVEF	Left Ventricular Ejection Fraction
MHRA	Medicines and Healthcare Products Regulatory Agency
mRCC	Metastatic Renal Cell Carcinoma
MRU	Medical Resource Utilisation
MSKCC	Memorial Sloan-Kettering Cancer Centre
mTOR	mammalian Target Of Rapamycin
MUGA	Multiple Gated Acquisition
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NIHR	National Institute for Health Research
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
ONJ	Osteonecrosis of the Jaw
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PIS	Participant Information Sheet
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PR	Partial Response
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QTc	corrected QT
RCC	Renal Cell Carcinoma
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RFA	Radiofrequency Ablation
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBRT	Stereotactic Brain Radiation Therapy
SD	Stable Disease
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
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
TMA	Tissue Micro-Array
TMG	Trial Management Group
TSF	Time to Strategy Failure
TSC	Trial Steering Group
UE	Urea and Electrolytes
WBBS	Whole Body Bone Scan

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.

Prior to the routine use of tyrosine kinase inhibitors (TKIs), Interferon-α (IFNα) was the UK standard of care for treatment of mRCC, but has only an 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. 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 (Eastern Cooperative Oncology Group (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% vs 1% complete response (CR), 44% vs 11% partial response (PR) and 40% vs 54% stable disease (SD) as the best responses seen.

Early in 2009, sunitinib was approved in the UK by National Institute for Health and Clinical Excellence (NICE) for use in the first-line treatment of advanced and/or metastatic RCC in patients with a good performance status (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 impacts 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].

Taking sunitinib as the example, the average cost per cycle is £3,700 per 6-week cycle with average cost per patient £47,000 and total National Health Service (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 Drug Free Interval Strategy (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 also been recommended by NICE as a first-line treatment option for patients with advanced RCC (based on the pivotal Phase III study VEG105192 comparing pazopanib to placebo[16]), conditional on pricing and further data from GSK, including the results from the COMPARZ [17] trial. At the time of commencing the STAR trial, the introduction of pazopanib was already anticipated for the Phase III part of the trial. There was no evidence as to the relative clinical effectiveness of the two TKI drugs, but a clinical trial was ongoing (COMPARZ) which was directly comparing the two drugs. The initial data from this study were presented at ESMO October 2012 [17]. The trial was designed with the primary endpoint being non-inferiority of PFS at a margin of 1.25 (upper 95% CI), however the EMA-defined primary endpoint was non-inferiority in PFS at a margin of 1.22 (upper 95% CI). Patients with locally advanced/metastatic clear cell RCC requiring first-line therapy and with measureable disease, KPS >70 and adequate organ function were eligible, and stratified based on KPS, whether they had had a prior nephrectomy and baseline LDH. Patients were randomised 1:1 to sunitinib or pazopanib (50mg OD 4wk on/2wk off v 800mg OD continuous dosing). Analysis of the primary endpoint (with independent review), with 557 patients on the pazopanib arm and 553 patients on the sunitinib arm demonstrated a PFS HR of 1.047 (0.898-1.220), hence achievement of the primary endpoint demonstrating non-inferiority of pazopanib to sunitinib. There was no significant difference in OS between the arms with HR 0.908 (0.762-1.082), p=0.275. Clinical benefit rate (CR + PR + SD) was similar between the arms, 79% pazopanib and 69% sunitinib, although there was a slight increase in the rate of objective responses (CR + PR) seen with pazopanib (31% vs 25%, p=0.032). Although the two drugs had many toxicities in common (all grades including grade 3/4), there was significantly more fatigue (63% vs 55%), hand-foot syndrome

(50% vs 29%), taste changes (36% vs 26%) and thrombocytopenia (34% vs 10%) with sunitinib, but more hair changes (30% vs 10%) and increases in ALT (31% vs 18%) with pazopanib. The median duration of treatment was similar in both arms (8.0 months pazopanib and 7.6 months sunitinib), and importantly the number of dose reductions (44% pazopanib and 51% sunitinib) and discontinuations due to AEs (24% pazopanib and 19% sunitinib) were substantial in both arms. These dose reduction and discontinuation data confirm the relevance of the STAR study, i.e. investigating a DFIS, whether with sunitinib or pazopanib, due to the potential benefits to patients in terms of reduced toxicity and improved Quality of Life (QoL) and cost benefits to the NHS. In the COMPARZ study, the QoL data presented (FACIT-fatigue) demonstrated reduced QoL in the sunitinib arm compared to pazopanib, however the time-points used for comparison were day 28 of each cycle which is the time when the difference will be maximised as sunitinib toxicity peaks at this point [18]. The differences seen in COMPARZ between sunitinib and pazopanib appear less marked than those from the previously reported patient preference PISCES study, possibly as within PISCES each treatment was only taken for 10 weeks [19] and this study was based on significantly fewer patients.

STAR had originally mandated that sunitinib was the only drug permitted for use in the Phase II part with planned reconsideration prior to opening the Phase III part based on available data. However after consideration of the data available in October 2012, and discussions with investigators, it appeared likely that some sites may wish to offer pazopanib in standard practice, as an alternative to sunitinib. Following discussion with the funder (National Institute for Health Research Health Technology Assessment (NIHR HTA)), Trial Steering Committee (TSC) and Data Monitoring & Ethics Committee (DMEC), from protocol version 4.0 the Trial Management Group (TMG) introduced the option of using pazopanib into the Phase II part of the study (and to include the TKI used as a stratification factor).The STAR trial was designed to be a pragmatic trial testing the strategy of introducing planned treatment breaks, and this approach is justified and has significant potential patient benefits whether sunitinib or pazopanib is used. There are implications of introducing the use of pazopanib into the STAR trial (for example on the proposed co-primary averaged Quality Adjusted Life Year (QALY) endpoint) and these issues are discussed in the appropriate sections of the protocol.

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. Although, there is no current evidence that these will replace sunitinib or pazopanib as first-line therapy in the foreseeable future, the ability of STAR to demonstrate the feasibility of treatment breaks will have more general application as future therapies develop.

4.5 Intermittent treatment strategies in other cancer types

There is increased interest in 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 [20-23]. 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% [20]. 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 [21] 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 [24].

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 [25]. 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 [26].

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 [27] 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 [28]. 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 Drug Free Interval (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 [29]. 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 and pazopanib however are associated with a significant side-effect burden and currently are recommended only for fitter patients. The initial first-line trial for sunitinib reported 8% of patients discontinued treatment due to AEs and in the reported sunitinib open access program 8% of patients discontinued drug due to SAEs and a further 33% had at least one dose reduction (13% had 2 dose reductions) [14]. The previously mentioned Phase III study (VEG105192) of pazopanib to placebo, reported a discontinuation rate due to AEs of 14% and dose reductions due to an AE in 24% of patients. The COMPARZ study suggested that pazopanib was associated with similar substantial patterns of dose reductions and discontinuations as sunitinib. A treatment strategy incorporating a DFI, assuming no survival disadvantage, would potentially give patients periods of time when symptoms attributable to sunitinib or pazopanib 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 or pazopanib. 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 [30]. 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 metastasectomy (n=6) [31]. 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) [32].

Finally, data from one other randomised Phase II study presents further support to the hypothesis that a DFIS could be used for sunitinib or pazopanib. 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 [33].

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 [34] 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 or pazopanib CCS compared to a sunitinib or pazopanib DFIS.

In the UK, NICE approval for the use of sunitinib or pazopanib 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 and pazopanib 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 and pazopanib 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 DFIS compared to the CCS of sunitinib or pazopanib.

5.1 Overall Primary Objective

To determine whether a sunitinib or pazopanib DFIS is non-inferior in terms of OS and QALY (averaged over trial recruitment and follow-up) compared to a sunitinib or pazopanib 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 three stages A/B/C).

Stage A

- To establish the feasibility of performing the trial in terms of **average monthly recruitment.** This is to ensure that sufficient participants 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[5] (TSF) in both arms and test for non-inferiority between the approaches to assess comparability.

Update: The independent DMEC reviewed the stage A and B data in July 2014 and concluded that the Phase II endpoints had been met.

Stages A, B and C:

- OS and QALYs 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)[4]
- Time to Strategy Failure (TSF)[4]
- Time to Treatment Failure (TTF)[4]
- Toxicity (Common Terminology Criteria for Adverse Events (CTCAE) v.4.0)
- Quality of Life (QoL) (FSKI-15, FACT-G, EQ-5D™ and EQ-VAS™)
- Cost-effectiveness
- Progression Free Survival (PFS)

5.4 Ancillary Studies

5.4.1 Patient Preference and Understanding Study

Exploration of participants' feelings regarding the study and planned treatment breaks will be performed through a qualitative sub-study. This will take place in approximately three trial sites only and use semi-structured interviews to investigate participants' feelings in detail in a cohort of participants on the DFIS arm during or after a planned treatment break. Details of this study are provided in a separate protocol (MREC reference: 11/YH/0261).

5.4.2 Translational Studies

Future translational research studies are planned which will include investigation of potential tissue biomarkers of sunitinib and pazopanib response and toxicity, and imaging biomarkers looking for improved and earlier markers of sunitinib and pazopanib response. Imaging sub-studies include an optional Computerised Tomography (CT) study (open to participants at all sites if appropriate imaging is performed routinely) and an optional dynamic contrast enhanced magnetic resonance imagery (DCE-MRI) study (open to participants at a limited number of sites). Further details regarding these studies are given in Appendices 4-6.

[5] See section 16.4 16.4 for definitions.

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 or pazopanib using either a CCS or the experimental DFIS in the first-line setting in patients with advanced (inoperable loco-regional or metastatic) clear cell renal cell cancer. The study is to compare the conventional continuation strategy with a drug-free interval strategy; it is NOT to compare sunitinib with pazopanib.

A total of 920 participants were recruited into the STAR trial (stages A-C). Participants were randomised in a 1:1 ratio to receive either a DFIS or a CCS of sunitinib or pazopanib.

Due to the novelty of the DFIS approach, two initial intermediary stages have been integrated within the trial with stop/continuation rules. A minimum of 210 participants are planned to be recruited during stages A and B which will ensure demonstration of adequate recruitment. To enable evaluation of the stage B efficacy endpoint and to justify continuation to stage C, we require a minimum of 80 pazopanib participants to be recruited into the trial (see Section 17.3 for further details). Should the number of participants receiving pazopanib on the trial be less than 80 by the time of the interim analysis (at the end of stages A/B), recruitment will continue until this minimum number has been achieved. Participants recruited during stages A and B will be included in the overall sample size required (i.e. n=920). All evaluable participants will be followed up until the end of December 2020 (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 participants, 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. Consideration was given to blinding of the central radiologist, however due to the nature of RECIST reporting this was not possible as the radiologist is required to know which is the baseline scan for comparison at the start of each treatment block (relevant in DFIS arm).

Update (Protocol Version 7.0): 249 participants were recruited during the Phase II trial (up until 31st May 2014) from 16 UK renal cancer centres, including 100 pazopanib participants. The trial oversight committees reviewed the results of the interim analysis (end of Phase II) in July 2014 and concluded that both the stage A and B endpoints had been met. As such it was agreed that the trial could continue to Phase III.

Update: Recruitment closed on the 12th September 2017 following the recruitment of 920 participants. The trial is now in follow-up until 720 overall survival events have been observed and when all participants have been followed up for at least 2 years or the end of December 2020, whichever is sooner.

7. Eligibility

The eligibility criteria are designed to include, as far as possible, any patient with renal cancer for whom sunitinib or pazopanib 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.

Eligibility waivers to inclusion and exclusion criteria are not permitted.

7.1 Inclusion criteria

1. Male or female aged ≥ 18 years old
2. Histological confirmation of a component of 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 (see Appendix 2)[6]
6. Uni-dimensionally measurable disease (RECIST criteria, see Appendix 3)
7. Full blood count:[7]
   - Haemoglobin (Hb) ≥ 9 g/dL[8]
   - Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L
   - Platelets ≥ 80 x 10^9/L
8. Renal biochemistry:[9]
   - Measured or calculated Glomerular Filtration Rate (GFR) ≥ 30 ml/min (Cockcroft and Gault or Wright formula may be used according to local practice)
9. Hepatobiliary function:[10]
   - Aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x ULN
   - Bilirubin (BR) ≤ 1.5 x Upper Limit of Normal (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 or pazopanib within 5 (actual not working) days of randomisation
    - temporarily stopping sunitinib or pazopanib if randomised to the DFIS arm
    - capable of oral self-medication
    - commencement of sunitinib or pazopanib within 42 days of the baseline CT scan
    - capable of reporting toxicity and completing Quality of Life (QoL) and Medical Resource Utilisation (MRU)/Health Economics 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 (GP) or

[6] ECOG performance status must be assessed prior to randomisation and within 16 days of starting treatment with either sunitinib or pazopanib.
[7] Blood tests must be performed prior to randomisation and within 16 days of starting treatment with either sunitinib or pazopanib.
[8] Blood transfusions are acceptable.
[9] Renal tests must be performed prior to randomisation and within 16 days of starting treatment with either sunitinib or pazopanib.
[10] Liver tests must be performed prior to randomisation and within 16 days of starting treatment with either sunitinib or pazopanib.

Family Planning Clinic) during, and for 30 days after the last dose of sunitinib or pazopanib

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 GP or Family Planning Clinic) during, and for 30 days after the last dose of sunitinib or pazopanib
14. Requirement to start first-line therapy with either sunitinib or pazopanib and decision already made as to which TKI to be used according to local standard practice.

Allowed situations include:

- primary renal cancer in-situ or previous nephrectomy
- previous brain metastases treated with complete surgical resection. Stereotactic Brain Radiation Therapy (SBRT) or gamma knife with no subsequent evidence of progression (patients treated only 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. Care should be taken to follow dental guidelines for the anti-bone resorptive drug.

7.2 Exclusion criteria

1. Pulmonary or mediastinal disease causing obstruction or clinically significant bleeding/haemoptysis
2. Patients with an estimated life expectancy of <6 months
3. Known contraindications to the particular TKI to be used (i.e. sunitinib or pazopanib)
4. Any previous treatment with sunitinib, pazopanib or other TKI (including in the adjuvant setting)
5. Untreated brain metastases[11]
6. Any concurrent or previous other invasive cancer that could confuse diagnosis or endpoints
    - *Allowed situations include (but not limited to): non-melanomatous skin cancer or superficial bladder cancer; for all other cases please discuss with CTRU*
7. Hypersensitivity to the particular TKI to be used (i.e. sunitinib or pazopanib)
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 the particular TKI to be used (i.e. sunitinib or pazopanib) (see section 10.2 for further information on concomitant medications)
9. Poorly controlled hypertension despite maximal medical therapy.[12]

[11] Patients are eligible if previous brain metastases treated with complete surgical resection, Stereotactic Brain Radiation Therapy (SBRT), or gamma knife with no subsequent evidence of progression. Patients are not eligible if brain metastases treated only with whole brain radiotherapy.

[12] It is recommended that subjects should have a systolic blood pressure of either less than 150 mmHg, and/or 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 3a and 3b.

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, significant haemorrhage or gastrointestinal perforation or fistula which, in the opinion of the local investigator, would render the patient unsuitable for standard sunitinib or pazopanib therapy.

7.3 Eligibility Screening Assessments (Sunitinib and Pazopanib participants)

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 is recommended), preferably within a calendar month prior to starting sunitinib or pazopanib but within 42 days as an absolute maximum[13]
- Assessment of ECOG performance status and blood pressure (BP) prior to randomisation and within 16 days before commencing sunitinib or pazopanib
- Full blood count (Hb, ANC, platelets; prior to randomisation and within 16 days before commencing sunitinib or pazopanib)
- Measured or calculated GFR (prior to randomisation and within 16 days before commencing sunitinib or pazopanib)
- Liver function tests (ALT/AST, BR prior to randomisation and within 16 days before commencing sunitinib or pazopanib)
- Pregnancy test (if woman of child-bearing potential) within 72 hours prior to randomisation

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 or risk factors (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.

[13] 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 or renal insufficiency), 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.

Proteinuria has been reported with pazopanib treatment; as per the Summary of Product Characteristics (SPC) baseline and periodic urinalysis is recommended as per standard UK practice, however this is **NOT** mandated by the protocol.

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 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 CTRU, University of Leeds.

The STAR trial was initially opened in a limited number of UK sites (16) during stages A and B. In Stage C, recruitment will be extended to a wider number of UK sites (approximately 38 in total) in order to reach the overall recruitment target of 920 participants.

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, excluding those who go on to be randomised. Anonymised information will be collected including:

- Date screened
- Approached/Not approached for main STAR trial
- Which TKI or other type of treatment planned outwith STAR

- 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.

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 the version of the Participant Information Sheet (PIS) and Consent Form (CF) appropriate for the TKI recommended for use (sunitinib or pazopanib) 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, sunitinib patients will be provided with a participant DVD which contains information about the trial and is theirs to keep should they wish. A pazopanib-specific video-recording is being considered currently.

An additional PIS and CF will be provided to trial sites recruiting patients to the 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 the main STAR trial.

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 participant will remain free to withdraw consent for 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 participant's notes. The original CF will be retained in the Investigator Site File, a copy of the CF will be given to the participant, 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 participant and the participant 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 at St James University Hospital, Leeds (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 or pazopanib treatment on the STAR trial. Given the narrow window specified between randomisation and commencement of sunitinib or pazopanib (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 5 days prior to the start date of sunitinib or pazopanib treatment. Randomisation is required to be as close as possible to starting sunitinib or pazopanib as the radiological assessments for the main trial are timed from the randomisation date but must still occur at appropriate time-points during sunitinib or pazopanib treatment.

Note that participants must also complete their baseline QoL questionnaires prior to randomisation (see section 11.6).

8.5.2 Treatment Allocation

The randomised treatment allocation within STAR is the treatment strategy (DFIS vs CCS) and **not** the type of TKI. Participants will be randomised on a 1:1 basis to either a CCS or a DFIS and receive treatment with either sunitinib or pazopanib.

The decision regarding whether sunitinib or pazopanib is used will be at the discretion of the treating clinician and **MUST be decided before randomisation**.

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 [35] (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
- TKI:
    - Sunitinib
    - Pazopanib

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 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 participant 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
- 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 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 (F02) and Randomisation (F04) 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 participants should commence sunitinib or pazopanib within 5 days of randomisation.

9. Trial Medicinal Product Management

Within the STAR trial, only sunitinib and pazopanib are classed as Investigational Medicinal Products (IMPs).

9.1 Sunitinib and Pazopanib

Sunitinib is commercially available in the UK as sunitinib malate.

Pazopanib is commercially available in the UK as pazopanib hydrochloride.

For further details of composition of either IMP, refer to the current version of the manufacturer's Summary of Product Characteristics (SPC), which can be accessed via the Electronic Medicines Compendium (eMC) website: http://www.medicines.org.uk/emc. A reference copy of both SPCs can be found in the Investigator and Pharmacy Site Files; please note however that these may not necessarily be the most up-to-date versions.

9.1.1 Supply and handling

Both sunitinib and pazopanib are used within their licensed indication and general 'off the shelf' supplies will be used. There is no requirement to ring-fence 'off the shelf' supplies of sunitinib or pazopanib for the STAR trial. Both IMPs 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 and pazopanib formulation, storage, and preparation are in line with the manufacturers' recommendations. For further details, refer to the current version of the relevant manufacturer's SPC (via http://www.medicines.org.uk/emc).

9.1.3 Labelling

Sunitinib and pazopanib 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 both IMPs will be used within their licensed indication, no special trial labelling requirements apply and both sunitinib and pazopanib may be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisation etc.) Regulations 1994.

9.1.4 Use of 3rd Party Supply and Delivery of IMP

IMP 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. The trial does not require any additional actions beyond existing standard care practices. CTRU should be informed during the site set-up process, or if this is adopted during the life of the study.

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 or pazopanib treatment.

10.2 Concomitant Medications

Normal practice for the use of sunitinib or pazopanib will apply in this trial to reflect standard care as much as possible. The general guiding principle is that if outwith the trial the participant would be prescribed sunitinib or pazopanib alongside another medication as standard care then it is acceptable to continue the other medication within the STAR trial. As explained in the relevant, updated SPCs, there are known drug interactions between sunitinib or pazopanib and other medications and the investigator should refer to the current version of the relevant SPC for guidance on permitted concomitant medications and non-drug therapies (accessible via the eMC website: http://www.medicines.org.uk/emc).

10.2.1 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.

10.2.2 Concomitant Anti-Cancer Therapies

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

10.3 Planned Surgery (non-cancer)

It is recommended that sunitinib or pazopanib 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 (F14) CRF for a decision on whether the participant can continue on trial treatment.

10.4 Invasive dental procedures

Oral hygeine should be optimised before starting a TKI. Invasive dental procedures should be avoided, if possible, in patients treated with sunitinib or pazopanib 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

> **NOTE:** For the purpose of STAR and the timing of clinical review, both sunitinib and pazopanib are considered to be given on 6-week cycles.

It is not permitted to change from sunitinib to pazopanib or vice versa after randomisation. If this is required then the participant will not be able to continue on trial treatment. Please contact the CTRU for advice.

10.5.1 All Sunitinib Participants (CCS and DFIS Arms)

Sunitinib participants 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.

NOTE: 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 (or other medical reason) then these doses are omitted and not replaced. However, the start of a cycle may be delayed due to toxicities; delays of up to 28 days are acceptable. Thus, if a cycle is completed or stopped, the next cycle must begin within 28 days from the date of completion or stopping. Any proposed delays greater than 28 days must be discussed with the CTRU.

Sunitinib can be taken with or without food. The time of administration of sunitinib should be relatively constant. If a dose is missed, the participant should be instructed not to replace the dose, but to take the next dose of sunitinib as planned.

All trial participants will receive sunitinib for 4 cycles except in cases of unacceptable toxicity, disease progression (RECIST)[14], or participant choice to stop treatment or withdraw consent for the trial. In all cases, these participants must permanently stop protocol treatment.

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

10.5.2 CCS Arm (Sunitinib Participants)

After completion of 4 cycles of sunitinib, 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 (Sunitinib Participants)

After completion of 4 cycles of sunitinib[15] participants randomised to DFIS will temporarily stop sunitinib (planned treatment break).

Participants will remain off treatment until evidence of disease progression (RECIST)[16]. At this time sunitinib will be restarted, and assuming further stable disease/response, continued for 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[14]

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[14] 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.

[15] After 4 cycles of treatment, when participants take up their allocated treatment arm, all DFIS participants should stop treatment. However, in the exceptional circumstance that the treating physician wishes the participant to continue sunitinib, and only if this is based on clear radiological evidence that the participant is continuing to respond (i.e. significant further tumour shrinkage between the 12-week and 24-week scans according to RECIST), continuation may be possible for a further 12 weeks before starting the treatment break, but this must be discussed with CTRU and with the Chief Investigator/Co-Chief Investigator before a decision is taken.

[16] In the very rare circumstance where there is substantial ongoing response during the treatment break in DFIS arm, the latest best response scan (minimal SLD) may be used to define progression rather than the usual new baseline scan (the scan performed immediately prior to commencing a treatment break), if this is clinically appropriate. Please contact CTRU for guidance if you plan to use the latest best response scan.

All scans performed during the treatment break must be compared to the scan immediately before the treatment break started as per the standard RECIST reporting guidelines.[15]

When participants on the DFIS arm restart sunitinib treatment following a planned treatment break, the new baseline scan that is used to determine response/ progression should be the scan performed immediately prior to restarting treatment, NOT the baseline scan performed prior to randomisation or the best response scan during the previous course of treatment.

Please contact CTRU if uncertain as to which scan to use as the new baseline scan following a planned treatment break.

On restarting sunitinib or pazopanib, assuming further disease control is achieved, sunitinib or pazopanib is then planned to be continued for a minimum of 4 cycles. At this point, assuming ongoing disease control, consideration should be given to a further planned treatment break from sunitinib until evidence of PD (RECIST) when again sunitinib or pazopanib is restarted.

This DFIS (planned treatment break strategy) is continued until PD occurs during sunitinib or pazopanib treatment, cumulative toxicity or participant decision to stop treatment or withdraw from the study. Second and subsequent planned treatment breaks are at the treating clinician's discretion and need not be discussed in advance with CTRU.

10.5.4 All Pazopanib Participants (CCS and DFIS Arms)

Pazopanib participants will receive pazopanib on a 42-day cycle. Pazopanib will be administered orally once daily at 800 mg/day on every day of the cycle.

NOTE: Doses may be modified for toxicity to 600mg and 400mg per day, as per the dose modification guidelines (see section 10.7).

A pazopanib cycle will not be extended due to dose interruptions in the cycle; if the treatment is stopped due to toxicity (or other medical reason) then these doses are omitted and not replaced. However, the start of a cycle may be delayed due to toxicities; delays of up to 28 days are acceptable. Thus, if a cycle is completed or stopped, the next cycle must begin within 28 days from the date of completion or stopping. Any proposed delays greater than 28 days must be discussed with the CTRU.

Pazopanib should be taken without food, at least one hour before and two hours after a meal and tablets should be taken whole with water and not broken or crushed. If a dose is missed, the participant should be instructed not to replace the dose, but to take the next dose of pazopanib as planned.

All trial participants will receive pazopanib for 4 cycles, except in cases of unacceptable toxicity, disease progression (RECIST)[17], or patient choice to stop treatment or withdraw consent for the trial. In all cases, these participants must permanently stop protocol treatment.

[17] 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 pazopanib may be required to be stopped if clinically indicated, however

After completion 4 cycles of pazopanib (dose reductions allowed in accordance with section 10.7), 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 every second cycle (12-weekly) radiologically.

Liver Toxicity: Cases of hepatic failure in a small minority of patients have been reported during use of pazopanib, which therefore requires careful liver function monitoring (whether as part of a trial or as standard treatment), especially at the beginning of treatment. Assessment of liver function will therefore be carried out, at scheduled study visits at screening and before every 6-week cycle. Additional assessments of liver function tests should be performed at timings recommended as per the current pazopanib SPC (available via the eMC website: http://www.medicines.org.uk/emc). These additional blood tests may be performed by the participant's GP with the results reviewed by the treating physician / Principal Investigator. More frequent monitoring may be required for individual participants, according to investigator discretion and local practice. Administration of pazopanib to participants with mild or moderate hepatic impairment should be undertaken with caution and close monitoring, following local guidelines and information in the SPC.

10.5.5 CCS Arm (Pazopanib Participants)

After completion of 4 cycles of pazopanib participants randomised to CCS will continue pazopanib. There is no change to scheduling or dose of pazopanib, excepting dose reductions for toxicity in accordance with section 10.7.

10.5.6 DFIS Arm (Pazopanib Participants)

After completion of 4 cycles of pazopanib[18], participants randomised to DFIS will temporarily stop pazopanib (planned treatment break) .

Participants will remain off treatment until evidence of disease progression (RECIST)[19]. At this time pazopanib will be restarted, and assuming further stable disease/response, continued for 4 cycles and following the same scheduling and dose as before. When considering restarting pazopanib after a planned treatment break, disease progression must be confirmed radiologically and not just clinically.[20]

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please note that, if possible, an appropriate radiological assessment should be performed to document the disease status as per RECIST.

[18] After 4 cycles of treatment, when participants take up their allocated treatment arm, all DFIS participants should stop treatment. However, in the exceptional circumstance that the treating physician wishes the participant to continue pazopanib, and only if this is based on clear radiological evidence that the participant is continuing to respond (i.e. significant further tumour shrinkage between the 12-week and 24-week scans according to RECIST), continuation may be possible for a further 12 weeks before starting the treatment break, but this must be discussed with CTRU and with the Chief Investigator/Co-Chief Investigator before a decision is taken.

[19] In the very rare circumstance where there is substantial ongoing response during the treatment break in DFIS arm, the latest best response scan (minimal SLD) may be to used define progression rather than the usual new baseline scan (the scan performed immediately prior to the commencing a treatment break), if this is clinically appropriate. Please contact CTRU for guidance if you plan to use the best response scan.

[20] 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 pazopanib 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.

All scans performed during the treatment break must be compared to the scan immediately before the treatment break started as per the standard RECIST reporting guidelines. [20]

When participants on the DFIS arm restart pazopanib treatment following a planned treatment break, the new baseline scan that is used to determine response/ progression should be the scan performed immediately prior to restarting treatment, NOT the baseline scan performed prior to randomization or the best response scan during the previous course of treatment.

Please contact CTRU if uncertain as to which scan to use as the new baseline scan following a planned treatment break.

On restarting sunitinib or pazopanib, assuming further disease control is achieved, sunitinib or pazopanib is then planned to be continued for a minimum of 4 cycles. At this point, assuming ongoing disease control, consideration should be given to a further planned treatment break from sunitinib until evidence of PD (RECIST) when again sunitinib or pazopanib is restarted.

This DFIS (planned treatment break strategy) is continued until PD occurs during sunitinib or pazopanib treatment, cumulative toxicity, participant decision to stop treatment or withdraw from the study or the end of study follow-up (see Section 11.11). Second and subsequent planned treatment breaks are at the treating clinician's discretion and need not be discussed in advance with CTRU.

Participants who have restarted pazopanib after a treatment break will already have had several months of pazopanib treatment. However, there is little information on the risks of liver toxicity in such participants following re-commencement of pazopanib. Liver function should therefore continue to be assessed before commencement of each cycle of pazopanib and investigators should exercise caution and are recommended to follow the guidelines for assessment of liver function at timings recommended as per the current pazopanib SPC (available via the eMC website: http://www.medicines.org.uk/emc).

10.5.7 Imaging

Imaging should occur every 12 weeks. Unlike the case for Phase II, central reporting of scans will not be carried out in Phase III of the STAR trial. It is therefore important that local reporting of scans should occur according to RECIST (see Appendix 3).

If the scan scheduling becomes out of sync with the cycles of treatment (for example a delay due to toxicity or other medical reason) scans can be delayed by up to four weeks to allow the scan to coincide with the usual treatment cycles and schedule of events. If an extra scan has been performed due to a clinical indication then optimally a further scan should be performed so that there is a time period of at least 10 weeks between the two trial scans (as per protocol-defined imaging timings) unless the treating clinician deems that this is clinically inappropriate due to specific time periods involved. Scans should continue at the specified time-intervals from randomisation.

All scans performed during the treatment break must be compared to the scan immediately before the treatment break started as per the standard RECIST reporting guidelines.[21]

[21] In the very rare circumstance where there is substantial ongoing response during the treatment break in DFIS arm, the latest best response scan (minimal SLD) may be used to define progression rather than the usual new baseline scan (the scan performed immediately prior to commencing a

When participants on the DFIS arm restart sunitinib or pazopanib treatment following a planned treatment break, the baseline scan that is used to determine response/ progression should be the scan performed immediately prior to restarting treatment, NOT the baseline scan performed prior to randomization or the best response scan during the previous course of treatment.

Please contact CTRU if uncertain as to which scan to use as the new baseline scan following a planned treatment break.

10.6 Duration of Treatment

All participants will continue with their allocated sunitinib or pazopanib treatment strategy as per protocol (with dose reductions as required):

- until disease progression (RECIST) occurs whilst taking sunitinib or pazopanib[22], or until:
- unacceptable toxicity
- participant chooses to stop protocol treatment
- end of study follow-up (see section 11.1).

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 is important for ensuring consistent management of participants across sites. However, 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, wherever possible 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 Case Report Form (CRF).

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treatment break), if this is clinically appropriate. Please contact CTRU for guidance if you plan to use the best response scan.

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

Toxicities should be graded in accordance with normal practice using the CTCAE v4.0[23]. 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 28 days to allow for resolution of toxicity (or other medical reason). Thus, if a cycle is completed or stopped, the next cycle must begin within 28 days from the date of completion or stopping. Any proposed delays greater than 28 days must be discussed with the CTRU.

Except where specified in Table 2, 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 12.5mg stages for sunitinib and in 200mg stages for pazopanib (Table 1), but it is recommended that the guidance in Table 2 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 on the trial. Participants requiring dose reduction to less than 25 mg/day sunitinib or to less than 400mg/day pazopanib (i.e. more than two dose reductions) should permanently stop trial treatment. Except where specified in Table 2, for non-haematological toxicity which reaches ≥ grade 3 a dose reduction of one level is recommended for all subsequent cycles.

Table 1: Recommended sunitinib and pazopanib dose reduction levels

Dose Level	Daily Sunitinib Dose	Daily Pazopanib Dose
0	50 mg	800mg
-1	37.5 mg	600mg
-2	25 mg	400mg

10.7.4 Dose re-escalation

In many situations following dose reduction, dose re-escalation will be judged not to be appropriate by the local investigator. However, occasionally, this may be justified and the following guidance should then be followed. For participants who have received dose reduction on sunitinib, if the toxicity does not recur or worsen, the dose can then be increased step-wise back to the next dose level (37.5mg or 50mg as appropriate) at the start of the next treatment cycle. For participants who have received dose reduction on pazopanib, if the toxicity does not recur or worsen, the dose can then be increased step-wise back to 600mg and 800mg at the start of the next treatment cycle. Increases to the next dose level should only be initiated at the start of the next treatment cycle, not during a treatment cycle.

10.8 Permanently Stopping Protocol-Defined Treatment

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

For participants in the STAR trial, treatment as per protocol is planned until radiologically-confirmed disease progression[24] whilst on sunitinib or pazopanib, death, unacceptable toxicity, withdrawal of consent for other reasons or end of study follow up (see Section 11.11).

The protocol-defined follow-up period ends on the 31st December 2020. There may be patients who are still receiving trial treatment at that time. Treatment given after the end of trial treatment period is at the discretion of the treating clinician, and is **not considered to be trial treatment** (even if given as per protocol).

In line with usual clinical care, permanently stopping protocol-defined treatment and consequent cessation or alteration of regimens at any time will be at the discretion of the investigator on discussion with the participant. All participants permanently stopping protocol-defined treatment or prescribed alternative treatment will still attend for follow-up assessments as per the STAR protocol, unless unwilling to do so, and relevant CRFs will continue to be completed and returned to CTRU.

10.9 Further Systemic Therapy following Disease Progression

After disease progression on sunitinib or pazopanib in the STAR trial (i.e. not on a treatment break), participants will permanently stop protocol-defined treatment but the option of further systemic therapy within or outside a different clinical trial setting, or supportive care, may be considered. At this point, participants will be recorded as having reached their strategy failure endpoint but will continue to be followed-up for QoL and survival, in accordance with the protocol. If participants wish to receive the alternate study drug once having progressed, this will only be considered outside of the trial setting (i.e. strategy failure is recorded at the time of progression on the original study drug, after which participants will only be followed-up for survival and QoL data).

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

Table 2: Suggested dose modification guidance for potential treatment-related adverse events (AE). This may be used at discretion of local investigator, but the current SPC (available via http://www.medicines.org.uk/emc) must always take precedence.

AE	Grade	Guidance
Hypertension	Asymptomatic and persistent systolic BP of ≥150mmHg and/or ≤ 170mmHg or diastolic BP≥ 90mmHg and ≤110mmHg	Sunitinib or pazopanib: 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 or pazopanib therapy. Adjust or initiate new hypertensive therapy, titrate hypertensive medication until blood pressure well controlled, restart sunitinib or pazopanib at same dose or at lower dose once BP well controlled at discretion of the investigator. Consider restarting sunitinib or pazopanib at lower dose. For sunitinib and pazopanib dose adjustments of antihypertensive medication may be needed in periods when participants are not taking drug (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 or pazopanib at same dose. Monitor as clinically indicated.
	Grade 2	Withhold sunitinib or pazopanib until toxicity is Grade ≤ 1. Restart treatment with lower dose. Monitor as clinically indicated.
	Grade 3 or 4	Discontinue sunitinib or pazopanib 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 or pazopanib at same dose. Monitor.
	Grade 3 or asymptomatic grade 4	Withhold sunitinib or pazopanib. 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. Monitor. See section 10.2.2.
	Symptomatic grade 4	Discontinue sunitinib or pazopanib.

Arterial thrombosis	Any grade	Discontinue sunitinib or pazopanib.
Neutropenia	Grade 1 or 2 or grade 3 lasting < 5 days	Continue sunitinib or pazopanib at same dose. Monitor.
	Grade 3 lasting ≥ 5 days	Withhold sunitinib or pazopanib until toxicity is Grade ≤ 2. Restart treatment at same dose.
	Grade 4	Withhold sunitinib or pazopanib until toxicity is Grade ≤ 2. Restart treatment at lower dose.
Thrombocytopenia	Grade 1 or 2 or grade 3 lasting < 5 days	Continue sunitinib or pazopanib at same dose. Monitor.
	Grade 3 lasting ≥ 5 days or Grade 4	Withhold sunitinib or pazopanib until toxicity is Grade ≤ 2. Restart treatment at lower dose.
Fatigue	Grade 1 and 2	Continue sunitinib or pazopanib at same dose. Monitor.
	Grade 3 and 4	Withhold sunitinib or pazopanib 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 or pazopanib at same dose. Monitor and supportive measures.
	Grade 3	Withhold sunitinib or pazopanib until toxicity is Grade ≤ 2. Restart treatment at same dose or lower dose as judged by investigator.
	Grade 4	Interrupt sunitinib or pazopanib until toxicity reduced until Grade ≤ 2. Restart sunitinib at lower dose or discontinue at discretion of investigator.
Hepatotoxicity (Pazopanib)	Bilirubin < 1.5 x ULN (with any ALT/AST)	Continue pazopanib at current dose. Monitor LFTs in accordance with the current SPC (available via e-MC website: http://www.medicines.org.uk/emc/).
	Bilirubin >1.5 to 3 x ULN (with any ALT/AST)	Dose reduce to 200mg – participants must therefore come off STAR trial (see section 10.7.3 above).

	Bilirubin >3 x ULN (with any ALT/AST)	Permanently stop pazopanib.
	ALT/AST ≥3.0 x ULN to ≤8.0 x ULN and total bilirubin ≤2.0 x ULN)	Continue on pazopanib with weekly monitoring of liver function until transaminases return to Grade 1 or baseline.
	AST/ALT>8.0 x ULN and any bilirubin	Interrupt pazopanib until transaminases return to Grade 1 or baseline. If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then reintroduce pazopanib at a reduced dose of 400 mg daily and measure serum liver tests weekly for 8 weeks. Following reintroduction of pazopanib, if transaminase elevations > 3 x ULN recur, then pazopanib should be permanently discontinued.
	AST/ALT elevations >3 x ULN concurrently with bilirubin elevations >2 x ULN	Permanently discontinue pazopanib. Participants should be monitored until return to Grade 1 or baseline. Pazopanib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in participants with Gilbert's syndrome. Participants with only a mild indirect hyperbilirubinaemia, known or suspected Gilbert's syndrome, and elevation in ALT > 3 x ULN should be managed as per the recommendations outlined for isolated ALT elevations

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 hypophosphatemia without clinical symptoms, then sunitinib or pazopanib can be continued without interruption at the discretion of the investigator.

To require a dose reduction, nausea, vomiting or diarrhoea 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 or pazopanib 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.

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 3a (sunitinib) and 3b (pazopanib).

11.1.1 Visit schedule (Sunitinib Participants)

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 28 days to allow resolution of toxicity (or other medical reason), during this time participants should, if possible, be seen weekly for assessment. Thus, if a cycle is completed or stopped, the next cycle must begin within 28 days from the date of completion or stopping. Any proposed delays greater than 28 days must be discussed with the CTRU.

11.1.2 Visit schedule (Pazopanib Participants)

Irrespective of their allocated treatment strategy (CCS or DFIS), participants will be seen for scheduled clinical assessment (including liver function assessment) every 6 weeks at a minimum. LFTs will need to be monitored more frequently as per local guidelines and the SPC.

For participants receiving pazopanib treatment delays up to 28 days may be required to allow resolution of toxicity (or other medical reason). During this time participants should, if possible, be seen weekly for assessment. In the event of delays greater than 4 weeks, participants should stop trial treatment unless prior agreement is obtained from CTRU to continue.

11.1.3 Radiological assessment schedule

All participants must have cross sectional imaging (chest, abdomen and pelvis is strongly recommended) within 42 days before the start of protocol treatment. Radiological assessments will then be performed every 12 weeks (equivalent to 2 cycles of sunitinib or pazopanib treatment) whilst participants are receiving protocol treatment (CCS or DFIS). If the scan scheduling becomes out of sync with the cycles of treatment (for example a delay due to toxicity or other medical reason) scans can be delayed by up to four weeks to allow the scan to coincide with the usual treatment cycles and schedule of events.

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 or renal insufficiency), 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 underwent central radiology review; this has now ceased as the STAR trial has entered its stage C.

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

11.2 Baseline Assessments (All Participants)

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 or pazopanib and prior to randomisation:

- Cross-sectional imaging (CT contrast chest abdomen pelvis scan preferred, see 11.1 above for guidance where contrast may not be possible)

Prior to randomisation and within 16 days before commencing sunitinib or pazopanib (* indicates required for trial eligibility):

- *Medical history and physical examination (including height, weight, ECOG PS and vital signs, heart rate (HR) and BP)
- Laboratory tests:
    - *Full blood count (FBC)
    - *Biochemistry (urea and electrolytes (UE)) (including urea, creatinine, sodium, potassium)
    - * LFTs (including alkaline phosphatase (ALP), ALT/AST, total BR and albumin)
    - Lactate dehydrogenase (LDH) (baseline only)
    - Thyroid function tests (TFT)
    - Bone profile (calcium) – allows calculation of Motzer score
- *Baseline QoL (booklet A) (FACT-G and FSKI-15, EQ-5D™/EQ-VAS™ and MRU/Health Economics questionnaires)[25]
- *(Where site is participating in sub-studies)* Consider approaching for participation in the associated 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.

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

11.3 Treatment Assessments (All Participants)

Irrespective of allocated treatment arm (DFIS or CCS) participants will be assessed clinically for symptoms and toxicity at the start of each treatment cycle (i.e. every 6 weeks for sunitinib and for pazopanib participants).

The Case Report Form (CRF) completed will include specific questions about expected side effects associated with sunitinib or pazopanib (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 (6-week cycles for both sunitinib and pazopanib for the purpose of STAR) and/or clinical review (while on planned treatment break for DFIS arm participants):

- Clinical assessment including weight, ECOG PS and vital signs (HR and BP)
- 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[26]:
    - FBC
    - UE
    - LFT (Note requirement also for more frequent monitoring of liver function for participants receiving pazopanib at timings recommended as per the current pazopanib SPC (available via the eMC website: http://www.medicines.org.uk/emc/)
    - TFT (q 12 weeks)
- Radiological assessment (72 days (± 4 days) post-randomisation and prior to commencement of cycle 3 of sunitinib or pazopanib and 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 ideally be the same in both the CCS and DFIS arm, but if the scan scheduling becomes out of sync with the cycles of treatment (for example a delay due to toxicity or other medical reason) this can be delayed by up to four weeks to allow the scan to coincide with the usual treatment cycles and schedule of events.
- Review of appropriateness to continue sunitinib or pazopanib and review of sunitinib or pazopanib dosage in view of toxicities.

[26] Apart from cycle 1 where baseline bloods can be used, provided they were taken prior to randomisation and within 16 days before commencing sunitinib or pazopanib.

Table 3a: Schedule of Events (Sunitinib Participants) (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**		
6 Weekly On-Study Review	n/a	1st	n/a	2nd	3rd	4th	5th	6th	7th	8th	9th	10th		
Time-point:	Pre-Rand	C1 d1	C1 d28	C2 d1	C3 d1	C4 d1	C5 d1[1]	C6 d1[1]	C7 d1[1]	C8 d1[1]	C9 d1[1]	C10 d1[1]	C*n* d1[1]	PD[2]
Informed Consent	X													
Baseline information	X													
Clinical assessment[3]	X	X[4]		X	X	X	X	X	X	X	X	X	X	X[5]
Lab tests (FBC, UE & LFT)[6]	X	X		X	X	X	X	X	X	X	X	X	X	N/S
Calcium[7]	X													
LDH	X													
TFT	X				X		X		X		X		q12w	N/S
ECG [8]	X													
Routine CT/MRI scan [9]	X				X		X		X		X		q12w	N/S
WBBS [10]	X													
EQ-5D™/EQ-VAS™ [11]	X			X	X	X	q2w [12]				X	X	X	X
FSKI-15 [11]	X			X	X	X	X	X	X	X	X	X	X	N/S
FACT-G [11]	X			X	X	X	X	X	X	X	X	X	X	N/S
MRU/Health Economics	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	
SAE / SAR / SUSAR reporting		Expedited reporting (<24h) For SAEs: up to 30 days following **permanent** cessation of sunitinib (strategy failure) whilst on-trial[13]. For SARs and SUSARs up to the end of trial[12]												
Survival/PD		X		X	X	X	X	X	X	X	X	X	X	X
Registration for DCE-MRI sub-study [14]	X													
DCE-MRI sub-study scan [14]	X		X		X									

Abbreviations: C cycle; d day; w week; C*n* ongoing cycles of sunitinib, n=cycle number; BP blood pressure; TFT thyroid function tests; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ECG electrocardiogram; WBBS whole body bone scan;MRU medical resource utilisation questionnaire; AE: adverse event; SAE: serious adverse event; PD progressive disease; q2w every 2 weeks; q6w every 6 weeks; q12w every 12weeks; N/S not specified.

Table 3b: Schedule of Events (Pazopanib Participants) (Further guidance on acceptable time limits/ windows can be found under the relevant protocol sections)

Week:		**0**	**2**	**4**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**		
6 Weekly On-Study Review	n/a	1st	n/a	n/a	2nd	3rd	4th	5th	6th	7th	8th	9th	10th		
Time-point:	Pre-Rand	C1 d1	C1 D14	C1 D28	C2 d1	C3 d1	C4 d1	C5 d1[1]	C6 d1[1]	C7 d1[1]	C8 d1[1]	C9 d1[1]	C10 d1[1]	C*n* d1[1]	PD[2]
Informed Consent	X														
Baseline information	X														
Clinical assessment[3]	X	X[4]			X	X	X	X	X	X	X	X	X	X	X[5]
Lab tests (FBC, UE & LFT)[6]	X	X			X	X	X	X	X	X	X	X	X	X	N/S
Calcium[7]		X													
Additional LFTs			In line with recommendations in the current pazopanib SPC (see 10.5.4)												
LDH	X														
TFT	X					X		X		X		X		q12w	N/S
ECG [8]	X														
Routine CT/MRI scan [9]	X					X		X		X		X		q12w	N/S
WBBS [10]	X														
EQ-5D™/EQ-VAS™ [11]	X				X	X	X	q2w [12]				X	X	X	X
FSKI-15 [11]	X				X	X	X	X	X	X	X	X	X	X	N/S
FACT-G [11]	X				X	X	X	X	X	X	X	X	X	X	N/S
MRU/Health Economics	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	
SAE /SAR / SUSAR reporting		Expedited reporting (<24 h) For SAEs: up to 30 days following **permanent** cessation of pazopanib (strategy failure) whilst on-trial. For SARs and SUSARs up to the end oftrial [13]													
Survival/PD		X			X	X	X	X	X	X	X	X	X	X	X
Registration for DCE-MRI sub-study [14]	X														
DCE-MRI sub-study scan [14]	X			X		X									

[1] Variable treatment at this point for participants on DFIS arm; some participants will be on a planned treatment break (DFIS) and others will continue/recommence sunitinib or pazopanib treatment. If the participant recommences sunitinib or pazopanib 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.

[2] Only relevant if PD occurs whilst taking sunitinib or pazopanib (not PD in the DFIS arm during a planned treatment break[27]).

[3] Clinical assessments include weight, height, ECOG PS and vital signs (heart rate and blood pressure).

[4] If the baseline clinical assessment is performed within 16 days of starting treatment with either sunitinib or pazopanib, the cycle 1 clinical assessment can be omitted and findings from the baseline assessment used.

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

[6] Full blood count (FBC), urea and electrolytes (UE), liver function tests (LFT).

[7] Calcium required for randomisation (as part of the Motzer score).

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

[9] Radiological re-assessment: 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.

[10] 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.

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

[10] EQ-5D™/EQ-VAS™ completed by participants at home every 2 weeks from week 24 to week 46 inclusive (sufficient questionnaires should be provided to participants to take home with them). At week 48 completion returns to 6-weekly completion.

[13] Note that participants on a planned treatment break in the DFIS arm are still on-trial. Expedited (<24 hours) reporting of SAEs is required up to 30-days post the **permanent** cessation of sunitnib/pazopanib for that participant; expedited (<24 hours) reporting of SARs and SUSARs is required up to the end of trial . See section 12.3.4 for further information.

[14] Only participants taking part in the 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).

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[27] For participants on the DFIS arm who have recommenced treatment following a treatment break, treatment should be continued for a minimum of 10 weeks before disease progression on treatment can be confirmed, e.g. if cross-sectional imaging is initially performed after the participant has had a treatment period of <10 weeks after recommencing treatment, and the scan demonstrates PD (RECIST) then sunitinib or pazopanib should be continued and the decision regarding stopping sunitinib or pazopanib made with the results of the next imaging ≥10 weeks after recommencing sunitinib or pazopanib. Please contact the CTRU for further advice in this situation.

11.4 End of Trial Treatment

If the participant discontinues STAR protocol treatment for any reason during the trial follow-up period (see Section 10.8) a Permanent End of treatment (F07) CRF must be faxed to the CTRU **within 7 days** of the trial site team becoming aware of this.

The protocol defined trial follow-up period ends on 31st December 2020. There may be patients who are still receiving trial treatment at that time. Treatment given after the end of trial treatment period is at the discretion of the treating clinician and **is not considered to be trial treatment (even if given as per protocol)**.

A Permanent End of Treatment (F07) CRF is not required for those participants who stop trial treatment due to the end of the trial treatment period on 31st December 2020.

11.5 Follow-up Assessments

After a participant permanently discontinues STAR protocol treatment, they will be followed up until the end of the trial follow-up period. SAEs, SARs and SUSARs will be collected for 30 days following the end of the trial follow-up period and will be included in the final analysis. SARs and SUSARs will be collected until the end of trial (in line with regulatory requirements), but will not be included in the final analysis (see Section 12.3.4).

During a participant's follow-up, they will be seen in clinic 6 months after permanently discontinuing STAR protocol treatment, and then annually thereafter; details of any subsequent treatment received for renal cancer and the participant's status will be collected at these follow-up clinic visits.

As OS is a co-primary 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.

After a participant has permanently discontinued trial treatment, all AEs should be collected up to 30 days post-treatment or up to the end of the trial follow-up period, whichever is sooner. If it is not possible for the patient to attend clinic, these may be collected by telephone call if considered to be appropriate by the treating clinician.

After a participant has permanently discontinued trial treatment, if the trial site team become aware of any Serious Adverse Reactions (SARs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) these must be reported to CTRU up until the end of the trial (see section 11.11 for definition) but these will not be included in the the final analysis. Further guidance is provided in section 12.3.4.

Any participants still responding to their protocol-defined treatment strategy after the end of the trial will continue to receive sunitinib or pazopanib treatment (or not) at their treating clinician's discretion. Post-trial arrangements for participants on the intermittent arm will be established with NHS England, and details of these will be confirmed to sites once

agreed. Breaks in anti-cancer treatment are currently permitted under NICE COVID-19 rapid guidance (COVID-19 rapid guideline: delivery of systemic anticancer treatments NICE guideline [NG161] Published date: 20 March 2020 Last updated: 09 November 2020).

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 Tables 3a and 3b (Schedule of Events).

Information from all questionnaires (FACT-G, FSKI-15 and EQ-5D™/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 or pazopanib, assuming clinical appropriateness to continue.

After this time-point EQ-5D™/EQ-VAS™ information will be collected every 2 weeks (a simple 2 page assessment) for 24 weeks, and then the frequency will return to every 6 weeks. During 2-weekly collection questionnaires will be completed by participants at home (sufficient questionnaires must 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 should remind participants of the importance of the quality of life assessments at each clinic visit. It is appreciated that 2-weekly questionnaire completion may be considered a significant burden for participants, however it is key to informing the QALY co-primary endpoint and because any differences between the treatment strategies are likely to be greatest from the 24-week point (as this is when most DFIS participants stop treatment). For participants on sunitinib, 2-weekly collection is also important due to differences in QoL at different time-points within the 6-week cycle, given that sunitinib is given over 28 days followed by 14 days off treatment.

Post the analysis of stage A/B primary endpoints we assessed the importance of continuing at this frequency. Compliance rates were higher than expected and the data showed up very interesting patterns relating to this two-weekly collection, therefore the decision was made to keep this two-weekly frequency.

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™).

In order to capture any differences in QALYs between the arms after treatment strategy failure, EQ-5D™/EQ-VAS™ information will continue to be collected for all participants (where possible) until the end of follow-up. After participants have permanently stopped protocol-defined treatment, EQ-5D™/EQ-VAS™ data will still be collected at all subsequent follow-up clinic visits, i.e. 6 months and annually thereafter.

Due to the importance of QoL data in this trial, measures will be taken to ensure maximum compliance of questionnaire completion. For the two-weekly questionnaires which

participants complete at home from the 24-week time-point, where the participant consents to this, reminders for completion are sent by email or text message to the participant by the research team at CTRU: this is an optional part of the STAR Informed Consent Form. Where a QoL questionnaire would be completed at a hospital clinic visit, but the local research team forget to give this to the participant, of the participant no longer attends clinic visits at hospital during their follow-up period, a questionnaire for the local research team will send this out by post to the participant's home after checking the participant's status and establishing it is appropriate to do so.

11.7 Health Economics

Data on primary, secondary, tertiary and community health care utilisation will be collected through MRU/Health Economics and standard CRFs at baseline and then at each clinical assessment visit.

11.8 Adverse and Serious Adverse Events

All Adverse Events (AEs) occurring in the trial will be collected on the 6 Weekly On-Study Review (F05) CRFs. They should be reported via the standard data management routes and not expedited.

For all Serious Adverse Events (SAEs) occurring in the trial, a SAE Report (F09) CRF must be completed and faxed to the CTRU **within 24 hours** of becoming aware of the event (see sections 12.3.3 and 12.3.4).

For all Suspected Unexpected Serious Adverse Reactions (SUSARs), a SUSAR Report (F10) CRF should be completed and faxed to the CTRU **within 24 hours** of becoming aware of the event (see sections 12.3.3 and 12.3.4).

11.9 Pregnancies

All pregnancies and suspected pregnancies occurring from the date of randomisation to 30 days following **permanent** cessation of sunitinib or pazopanib 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 participant 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 the end of trial must be recorded on the Notification of Death (F17) CRF and sent to the CTRU **within 7 days** of the trial

site team becoming aware of the death. It is key that F17 is sent promptly so that any questionnaire reminders sent by CTRU are ceased promptly.

11.10.1 Treatment-related deaths

In addition to completing a Notification of Death (F17) CRF, suspected treatment-related deaths must be notified **immediately** to the CTRU via F09 (SAE) or F10 (SUSAR) in accordance with section 12.0 Pharmacovigilance.

11.11 End of Trial

The end of the trial is defined as the date of the collection of the last tissue sample, or 31st December 2021, whichever comes sooner. Tissue block collection will continue until no later than 31st December 2021 but may end before this if the Trial Management Group considers it is not feasible to collect any further tissue blocks.

All evaluable trial participants will be followed up until the 31st December 2020 (defined as the trial follow-up period) with SAEs, SARs and SUSARs collected up until 30 days after this date to be included in the final analysis (see section 12.3.4).

After the end of the trial follow-up period and the 30 day SAE reporting period, the only trial-specific activity will be the collection of tissue blocks for the purpose of future research (see Appendix 4) and the reporting of any SARs and SUSARs that sites become aware of (for regulatory purposes). Tissue block collection will continue until no later than 31st December 2021.

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 CRFs.

11.12.1 Case report forms (CRFs)

Data will be recorded by trial site research staff on trial-specific paper CRFs and the originals submitted by post to the STAR trial team at the CTRU. Only the participant's trial number, 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 which are needed to comply with regulatory requirements – see section 12.3.4). However, any outstanding data applicable to time-points prior to consent 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 consent 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

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 or renal insufficiency), 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 (contrast or non-contrast CT or MRI) and performed using the same technique. Imaging should be reported according to RECIST guidelines V1.1 (see Appendix 3).

Timing of scans

- Baseline (within 42 days prior to starting trial treatment)
- 72 days (± 4 days) post-randomisation and prior to commencement of cycle 3 of sunitinib or pazopanib
- Subsequent scans every 12 weeks from day 72 (± 4 days) after starting trial treatment
- If the scan scheduling becomes out of sync with the cycles of treatment (for example a delay due to toxicity or other medical reason) this can be delayed by up to four weeks to allow the scan to coincide with the usual treatment cycles and schedule of events.

12. Pharmacovigilance

12.1 General Definitions

12.1.1 Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial participant 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[28]
- 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.

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

[28] 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.

Medical judgement should be exercised in deciding whether an AE or Adverse Reaction (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 or pazopanib), in the SPC for that product supplied in the Investigator Site File.

12.2 Reporting Requirements for Adverse Events (AE)

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

Information about AEs, whether volunteered by the participant, 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 or pazopanib, 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) v4.0.[29]

All AEs must be recorded in the 6 Weekly On-Study Review (F05) 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
- 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

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

- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions for serious as given above (section 12.1.2), 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 relevant SPC supplied in the Investigator Site File 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 or pazopanib:

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

Expected SAEs 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 Suspected Unexpected Serious Adverse Reactions (SUSAR)

All SAEs assigned by the local investigator (or following central review) as both suspected to be related to IMP-treatment (sunitinib or pazopanib) 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 Research Ethics Committee (REC) and the Sponsor of SUSARs within the required expedited reporting timescales.

12.3.4 Recording & Reporting SAEs, SARs and SUSARs

Up to 30 days post permanent cessation of sunitinib or pazopanib – SAEs, SARs, & SUSARs

All SAEs (and SARs) occurring from the date of randomisation until 30 days after sunitinib or pazopanib is permanently ceased (strategy failure has occurred) or up to 30 days after the end of the trial follow-up period, whichever is sooner, must be recorded on the SAE (F09) 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).

All SUSARs occurring from the date of randomisation until 30 days after sunitinib or pazopanib is permanently ceased (strategy failure has occurred) or up to 30 days after the end of the trial follow-up period, whichever is sooner, must be recorded on the SUSAR (F10) 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).

Up to the end of trial (see section 11.11 for definition) – SARs & SUSARs

All SARs and SUSARs occurring from 30 days following permanent cessation of sunitinib or pazopanib and up to the end of the trial (see section 11.11 for definition) do not need to be sought, but any that come to the attention of the trial team must, for regulatory purposes, still be reported to the CTRU **within 24 hours** of the trial site becoming aware of the event (this includes participants who have withdrawn consent for data collection, see section 11.2.1). SARs are reported on the SAE (F09) CRF and SUSARs on the SUSAR (F10) CRF.

For each SAE, SAR 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 Serious Adverse Event (SAE) Report (F09) CRF and Suspected Unexpected Serious Adverse Reaction (SUSAR) Report (F10) 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 CRF and this should 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 bisphosphonates 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 hours of the research staff becoming aware of event) to the CTRU. Investigators should 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, e.g. Co-Chief Investigator / Trial Physician):

- 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 (QoL) 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) [36], the FKSI-15 (15 items) [37] and the EuroQol instrument (including EQ-5D™ Index and EQ-VAS™) (all validated in cancer patients to assess health-related quality of life) [38].

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 3a/b. 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 or pazopanib.

During more frequent information collection the EQ-5D™ and EQ-VAS™ (2-page questionnaire) will be completed by participants at home. For both pazopanib and sunitinib, 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 [39], (but not on pazopanib), 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.

It is possible that the impact of the treatment strategies on QoL may differ pre and post treatment strategy failure, e.g. it may be that case that DFIS participants, who will have had less treatment, may respond better later down the line (fewer toxicities, less resistance to treatment, etc.). Thus it is beneficial to continue to collect enough QALY data to be able to explore these potential differences. In order to be able to estimate average QALYs over recruitment and follow-up and compare across the strategy arms, EQ-5D™/EQ-VAS™

information will continue to be collected for all participants post treatment strategy failure at their follow-up clinic visits (where possible) until the end of follow-up.

Quality of life questionnaires during the first 6 months will be administered in clinic in order to support participant 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 should remind participants of the importance of the quality of life assessments at each clinic visit.

Due to the importance of QoL data in this trial, measures will be taken to ensure maximum compliance of questionnaire completion. For the two-weekly questionnaires which participants complete at home from the 24-week time-point, where the participant consents to this, reminders for completion are sent by email or text message to the participant by the research team at CTRU: this is an optional part of the STAR Informed Consent Form. Where a QoL questionnaire would be completed at a hospital clinic visit, but the local research team forget to give this to the participant, of the participant no longer attends clinic visits at hospital during their follow-up period, a questionnaire for the local research team will send this out by post to the participant's home after checking the participant's status and establishing it is appropriate to do so.

15. Economic Evaluation

The star trial will also collect data which will contribute to a cost-effectiveness analysis of a DFIS, 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.

Sunitinib

Extensive QoL data were collected as part of the pivotal sunitinib trial programme [40, 41], 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.

The QoL data collected from the COMPARZ study [17] unfortunately did not collect EQ-5D™ measurements or any of the QoL questionnaires with a validated conversion to EQ-5D™.

As a result these data are all of limited use for estimating the QALY gains from a sunitinib DFIS strategy in the NHS. A small Japanese trial [42] 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.

Pazopanib

For pazopanib there is some EQ-5D™ data from the PISCES patient preference cross-over study [19]. However this data is on a limited number of patients who only received 10 weeks of each treatment in both arms. Measurements were also not performed at equivalent time-points for the sunitinib cycles. The 1st measurement post-baseline was performed after the end of a 2-week treatment break (this is usual for sunitinib and when toxicity is likely to be minimised and QoL maximised), the 2nd measurement was performed at end of a 2nd 4-week block of treatment (when toxicity and QoL are likely to be at their worst). For pazopanib, the 1st measurement post-baseline was performed after end of 2 weeks treatment break (not usual as drug is taken continuously) and the 2nd measurement at the end of 10 weeks of treatment. The data is inconclusive.

There was EQ-5D™ data from the initial Phase III pazopanib study [16], however as this compared pazopanib to placebo (2:1 randomisation ratio) and included a mix of treatment naive and patients previously treated with interferon, it is difficult to interpret. No statistically significant differences were observed between the treatment arms for EQ-5D™ despite the associated active agent toxicities, although this might be expected as the placebo arm QoL, whilst not being affected by drug toxicity, would likely be affected by the presence of disease that is not being treated with an active agent. Also less QoL data was available for placebo patients as a higher proportion discontinued the study early due to progression.

DFIS

Previously collected data are of limited use for estimating the QALY gains from a sunitinib or pazopanib DFIS in the NHS, as such the investigation of such data in the STAR trial is of considerable interest. The COMPARZ [17] data supports the appropriateness of investigating a similar DFIS for pazopanib (i.e. due to the significant amount of dose reductions/discontinuations due to AEs observed for pazopanib as well as sunitinib) and although an improvement in QoL with pazopanib over sunitinib was seen, the time-points used for comparison were day 28 of each cycle which is the time when the QoL difference will be maximised as sunitinib toxicity peaks at this point [18]. Along with this, significant associated toxicities were observed in both COMPARZ arms, supporting the benefit and appropriateness of a planned treatment break for both sunitinib and pazopanib.

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 sunitinib trial data [40, 41] and lack of pazopanib data, means uncertainty remains about the profile, timing and magnitude of the QoL impact of sunitinib and pazopanib treatment. We have therefore retained OS as a primary endpoint after being reassured by the COMPARZ data (whereby pazopanib was shown to be non-inferior to sunitinib in terms of PFS and no significant difference was found for OS), however we plan to analyse the data collected at the Phase II/III decision point to enable modelling to predict, assuming continuation to Phase III, whether we can include the pre-planned averaged QALY over treatment and follow-up as an appropriately powered 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 QALYs; for example NICE report a range for utility values 0.6 to 0.8 for stable/progression free disease states [43]. In addition, the small sample size in previous studies increased 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/Health Economics and standard CRFs 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-week recall period as recall over longer periods has been found inaccurate [44]. We will also ask participants 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 participants 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 Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care[30]. 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 [45]. 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 [46-48], including lambda=20,000 per QALY. In the NHS the manufacturer (Pfizer) estimated the

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

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 [49], 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. [50]. 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 [51]. 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) [52]. 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 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)

- Overall Survival
- QALYs averaged over trial recruitment and follow-up

This trial of sunitinib and pazopanib 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.

At the end of stages A and B a formal (blinded) 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, i.e. potentially downgrade it to a secondary endpoint.

16.2 Stage-Specific Primary Endpoints

Stage A

- Average monthly recruitment rate formally monitored for up to 12 months

Stage B

- Time to Strategy Failure (TSF)

Stages A, B and C

- Overall Survival
- QALYs averaged over trial recruitment and follow-up

16.3 Secondary Endpoints

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

16.4 Trial Definitions

1. Overall Survival (OS) 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. Average recruitment rate is defined as the average recruitment rate per trial site open per month and will be formally monitored for up to 12 months starting from 6 weeks after the first trial site has implemented the new version of the protocol (V4.0).
3. Time to Strategy Failure (TSF) is defined as time from randomisation until:
    a) death;
    b) disease progression[31] on sunitinib or pazopanib;

[31] 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 or pazopanib 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. For participants on the DFIS arm who have recommenced treatment following a treatment break, treatment should

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

d) participant requires use of a new systemic anti-cancer agent for RCC (endpoint measured at the first of either time of disease progression or time of initiation of new agent);

e) clinical deterioration where deterioration is assumed to be due to renal cancer progression and not another co-morbidity and deterioration is sufficient to warrant cessation of sunitinib or pazopanib if on treatment or to preclude restarting sunitinib or pazopanib if on a treatment break on the DFIS arm, without it being clinically appropriate to arrange radiological confirmation of the progression.

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.

4. Time to Treatment Failure is defined as time from randomisation until permanent protocol-based treatment discontinuation for any reason [53].
5. Overall Summative Progression Free Interval (SPFI) is defined as the sum of the intervals from the start of each treatment block with sunitinib or pazopanib until radiological evidence of progressive disease[32] 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 participant-assessed QoL in detail.
8. Progression Free Survival (PFS) 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.

be continued for a minimum of 10 weeks before disease progression on treatment can be confirmed, e.g. if cross-sectional imaging is initially performed after the participant has had a treatment period of < 10 weeks after recommencing treatment, and the scan demonstrates PD (RECIST) then sunitinib or pazopanib should be continued and the decision regarding stopping sunitinib or pazopanib made with the results of the next imaging ≥ 10 weeks after recommencing sunitinib or pazopanib. Please contact the CTRU for further advice in this situation.

[32] 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 or pazopanib 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 (CSG) and the NIHR HTA Programme 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 [54]. There is also further evidence supporting this from a previous lung cancer trial comparing differing durations of chemotherapy [55]. 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. Participants' 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 920 participants will be required, allowing for a 5% drop-out rate, i.e. 874 evaluable participants for final co-primary endpoint analysis.

A total of 249 participants were recruited during stages A/B (phase II) (up until 31st May 2014) from 16 UK renal cancer centres. To reach the required sample size of 920, an additional 671 participants need to be recruited in stage C.

17.3 Primary Endpoints

Update: The trial oversight committees reviewed the results of the Stage A and B analyses in July 2014 and concluded that the both endpoints had been met. As such it was agreed that the trial could continue to stage C.

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.

Originally, recruitment per month during months 10-21 (inclusive) of recruitment (not utilising the initial 9 months to enable site set-up) was going to be formally reviewed. The release of the results of the COMPARZ trial in October 2012 resulted in a decision to delay the period over which recruitment is going to be formally monitored, as agreed with the funder (HTA) and the DMEC. This is to allow for implementation of V4.0 of the protocol, the addition of pazopanib into the treatment schedule and to allow an initial 'settling-in' period for those sites choosing to treat patients with pazopanib. This will also provide a more accurate representation of the feasibility of recruitment into the Phase III study which, at this stage in our understanding, may include pazopanib patients only (although

this will depend upon the ratio of sunitinib/pazopanib use at the time in the clinical community).

Recruitment per month will now be formally monitored for up to 12 months starting from 6 weeks after the first trial site has implemented the new version of the protocol (V4.0) incorporating pazopanib. Should recruitment into the Phase II trial finish early, i.e. the target of 210 participants with 80 on pazopanib, be reached before 12 months, then the period over which recruitment is formally monitored will be modified accordingly.

During this monitoring period, an estimated recruitment rate of approximately 1 participant per trial site per month is anticipated to demonstrate the feasibility of recruiting to the Phase III trial. Approximately 13 sites are expected to recruit to the trial during stages A-B. The 95% CI for a recruitment rate of 1 participant per trial site per month, for example with 13 trial sites for 12 months, is 0.85-1.15. In this case a minimum of 0.85 participants per trial site open per month would be anticipated, i.e. a minimum of 133 participants recruited over the 12 month period, assuming all 13 trial sites opened and commenced recruitment in a timely manner, to demonstrate that achieving the overall recruitment rate of 1000 participants is feasible (original overall target sample size until protocol amendment v10.0). Should the window for monitoring the recruitment rate reduce, then the above estimates will be modified accordingly. So for example if monitoring period is reduced to 8 months, the 95% CI for a recruitment rate of 1 participant per trial site per month, with 13 trial sites for 8 months, is 0.82-1.19. In this case a minimum of 86 participants recruited over an 8-month period would be anticipated to demonstrate the feasibility of recruitment.

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 approximately 29 months of accrual and immediate analysis, 80% power, and assuming proportional hazards, this would require 67 events and a population of 97 participants (approximately 49 in each arm). Assuming approximately 45-50% of participants reach/take up their randomisation allocation at 6 months[33], a minimum of **210 participants are required in total for the stage B analysis**. 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

[33] Allowing for cessation of treatment due to disease progression or toxicity or withdrawal from study.

uses a 1-sided 97.5% confidence interval, as described by Kay [56]. 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 approximately 29 months after start of recruitment) a formal (blinded) 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.

Evaluating this endpoint requires the pooling of both the sunitinib and pazopanib data. As such, a minimum of 80 participants should be receiving pazopanib on the trial. This would give an approximate 3:2 split of sunitinib to pazopanib participants, which is deemed to be sufficient ratio in order to have a sufficient amount data on the pazopanib participants (assuming approximately 45-50% of participants reach/take up their randomisation allocation at 6 months[32]) and to have confidence in the combined results from the stage B analysis. Should the number of participants receiving pazopanib on the trial be less than 80 by the end of Stage A and B, recruitment will continue until this minimum number has been achieved.

There is no current evidence that the treatment break strategy will result in similar efficacy outcomes for the two TKIs but in order to answer the Phase II part of the trial in a reasonable timeframe, a statistical strategy for assessing whether or not the two treatments are similar enough for the data to be pooled has been developed, as detailed below.

A 60% confidence interval (CI) will be calculated around the HR for the TSF point estimate of the sunitinib participants. If the HR for the TSF point estimate for the pazopanib participants lies within this CI, and there are no obvious indications of their differences after evaluating all clinical information, then we would conclude the treatments to be similar enough to be able to pool the data and evaluate the stage B endpoint.

For example, we anticipate that we will have approximately 130 participants receiving sunitinib on the trial compared to 80 pazopanib participants, which would equate to 80 and 50 participants respectively reaching/taking up their randomisation allocation at 6 months[32]. Assuming that no effect was observed on sunitinib, i.e. hazard ratio (HR) = 1, the 60% CI around this HR would be approximately (0.80-1.25). If the HR for pazopanib was 0.9 and therefore fell within this 60% CI, we would conclude that the two treatment regimes were similar enough to pool the data. However, if for example, no effect was observed on sunitinib, i.e. hazard ratio (HR) = 1 and yet the HR for pazopanib was 0.8 (in favour of the continuous strategy), even though this falls within the 60% confidence interval we would be reluctant to continue.

Should the HR for the pazopanib participants fall outside this defined CI, we would continue to recruit fully to the pazopanib arm before evaluating the appropriateness of continuation to Phase III. We have opted for a 60% CI as anything larger would provide us with a CI which we deem to be too wide to be clinically meaningful and conclude similarity of the treatments (e.g. 70% CI: 0.76-1.31), much smaller and we are potentially being too stringent and excluding cases where the results are sufficiently similar that pooling the data would still be appropriate (e.g. 50% CI: 0.84-1.19).

The approach of pooling the sunitinib and pazopanib data has also undergone clinical review by all the sites' Principal Investigators and was considered to be clinically appropriate.

17.3.3 Stage C

Sample Size Calculation and Key Assumptions

There are two primary outcome measures: overall survival (OS) and quality adjusted life years (QALYs). The two null hypotheses are that DFIS is inferior to CCS in terms of OS and QALYs. To calculate a sample size for the co-primary OS endpoint a difference of ≤7.5% in OS at two years between the two arms has been assumed to be an acceptable non-inferiority margin, assuming an OS probability of 48.5% at 2 years in the CCS arm (equivalent to a hazard ratio of 0.812). In order to demonstrate this non-inferiority with 80% power, approximately 920 participants will need to be recruited in order to observe 720 events (allowing for 5% of participants being lost to follow-up). These estimates also remain valid for pazopanib given the results of the COMPARZ study [17] which showed pazopanib to be non-inferior to sunitinib in terms of PFS, where the difference between the treatment arms for OS was not statistically significant.

To calculate a sample size for the co-primary QALY endpoint a difference of ≤10% in mean QALYs between the two arms has been assumed to be an acceptable non-inferiority margin, assuming, from simulations, a mean QALY estimate in the CCS arm of 1.56 years, and further assuming a hazard ratio of 0.9 in favour of the CCS arm. While it is hoped that 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, where such a gain is to be captured through the QALY measure. With a hazard ratio of 0.9 in favour of CCS and 920 participants recruited, simulations give a power of 70% to show non-inferiority in the QALY endpoint for participants treated with sunitinib. Note that this assumption (of a hazard ratio of 0.9) is very conservative, and we would hope for and expect survival in the DFIS arm to be equivalent or only very slightly inferior.

Both non-inferiority sample sizes are calculated assuming a 1-sided 97.5% confidence interval, as described by Kay [56] and assuming participants are recruited in total over approximately 5.8 years, with a further follow-up of at least 2 years before evaluating the data.

Justification of Current Sample Size

The above sample size of 920 is a reduction of the original sample size of 1000 which was the target in previous versions of the protocol. This amendment has come about following a recommendation from both the DMEC (November 2016) and TSC (December 2016) to re-evaluate some of the key assumptions made within the original sample size calculations. Although not a pre-planned review of the sample size estimates, this was deemed appropriate due to the fact that the trial has now accumulated a significant amount of follow-up data since first opening to recruitment in January 2012 and thus we now have more accurate information for some of the required sample size estimation values, specifically the 2-year survival estimate in the CCS arm, the (extended) period of recruitment, and the overall drop-out rate.

The sample size re-estimation was based on 747 participants recruited until the end of October 2016 (373 CCS), followed up until the beginning of January 2017, with a median follow-up of all patients of 19 months. The observed dropout rate within the trial is approximately 2%, thus assuming a rate of 5%, rather than 10%, loss to follow-up is still a conservative estimate. Due to the recruitment extension of the phase II part of the trial, the original recruitment period of 4.5 years has already been extended to approximately 5.5 years, resulting in longer overall follow-up of participants and therefore increased power for the primary endpoint analysis. Finally, the 2 year overall survival rate in the CCS arm is now estimated to be 48.5% rather than the originally assumed 54% (using a modelling based approach to predict the future event rate based on current event rates [59]). To maintain a 7.5% non-inferiority margin at 2 years, gives a hazard ratio of 0.812. Using this updated information, the sample size has reduced to 920 participants, which requires 720 events to maintain the 80% power for the OS endpoint. The reduced sample size reduced the power for the QALY endpoint from 84% to 78%. The additional 15 month extension reduced it further, from 78% to 70% as updated simulations estimated the average QALY in the CCS arm to be 1.56. The additional 15 month extension had no effect on the power for the OS comparison.

Additional Assumptions and Justification for QALY Endpoint

There are a number of additional assumptions involved in the sunitinib QALY endpoint simulations. QALYs were analysed using utilities derived from the EQ-5D^{TM}. Despite strenuous efforts it was not possible to obtain the individual patient data for participants on the registration sunitinib trial [40]. Utility estimates were therefore derived from the EQ-VAS^{TM} data reported in the Japanese sunitinib trial [41] 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 [34], 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.

At the end of phase II, there was a planned informal evaluation of the QoL data (specifically EQ-5D) in order to establish whether the original utility estimates used to derive the power for the QALY co-primary endpoint were still valid, particular in light of the inclusion of pazopanib. Utility estimates for the periods on and off treatment were derived for both sunitinib and pazopanib participants. The original sample size estimates were still deemed to be valid in light of this updated data, and therefore it was established (and agreed by the DMEC and TSC in February 2015) that the QALY endpoint could remain as a co-primary endpoint, and would still be sufficiently powered.

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 18.4. From the published Cella

analysis [41] 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. Similar domains are of interest for pazopanib and so with 920 participants, and assuming 90% power, significance level of 0.05, the trial is powered to detect differences will a small effect size in both physical and functional wellbeing for both sunitinib and pazopanib patients.

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.

For the superiority endpoints an Intention to Treat (ITT) analysis will be given primacy, however for the non-inferiority endpoints, priority will be given to the per-protocol (PP) analysis, as the ITT is likely to be the least conservative approach when testing for non-inferiority. Definitions of all analysis populations (e.g. ITT, PP, safety) will be fully documented within the SAP. Exclusion of participants from any analysis population will be reported within the final analysis report.

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 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 TSC if there is proof beyond reasonable doubt that one treatment is better.

A formal interim analysis will be conducted after the end of stages A/B (approximately 29 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 [57] giving 95% Confidence Intervals (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 (blinded) interim analysis of the utility data so far obtained will also be performed at the end of stages A and B 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 TSC 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.

18.2 Final Analysis

The trial was designed to demonstrate non-inferiority of the DFIS arm compared to the CCS arm in terms of overall survival with 80% power. This required the recruitment of 920 participants in order to observe 720 survival events (allowing for 5% of participants being lost to follow-up) (See Section 17.3.3). 920 participants were recruited and the trial closed to recruitment in September 2017. However, due to multifactorial reasons the survival event rate was lower than predicted, and therefore the study follow-up period was extended by 15 months (until 31st December 2020). This was based on event rate modelling by Renfro et al[34] aiming to still observe 720 survival events.

Ongoing event rate monitoring over the last year has demonstrated that the event rate has reduced further. As we are currently in the tails of any applied distribution we cannot therefore accurately predict when 720 events will be observed, however it is clear that it would not be until a significant additional time after the planned end of follow up. As such it is not feasible to extend the trial for a further fixed duration and after careful consideration the recommendation from the TMG was to complete follow up on 31st December 2020 as planned. This decision was supported by both the DMEC and the TSC and final analysis will proceed at the end of December 2020.

18.3 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 [57], 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 (should the proportional hazards assumption hold).

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

[34] Renfro, L.A., Grothey, A.M., Paul, J., Floriani, I., Bonnetain, F., Niedzwiecki, D., Yamanaka, T., Souglakos, I., Yothers, G. and Sargent, D.J., 2014, December. Projecting event-based analysis dates in clinical trials: An illustration based on the international duration evaluation of adjuvant chemotherapy (IDEA) collaboration. Projecting analysis dates for the IDEA collaboration. In Forum of clinical oncology (Vol. 5, No. 2, pp. 1-7). De Gruyter Open

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, a mixture model will be considered.

18.4 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 [57], 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.

Safety analysis will summarise SAEs, SARs, SUSARs and AEs observed on the trial using the safety population according to CTCAE V4.0. Each of the summaries will present the overall statistics as well as by strategy received (DFIS or CCS) and TKI (sunitinib or pazopanib).

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).

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 [56], 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. The formal interim analysis will be reported to the DMEC after the end of stages A and B. Although the trial will have a formal interim analysis after the end of stages A and B, 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:

- Recruitment rates

- Rates of occurrence of SAEs, SARs, SUSARs and deaths
- Data compliance figures
- Protocol/treatment compliance figures
- Rates of and time to strategy failure/progression.

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 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 GCP 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 participant must remain free to withdraw consent 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 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, participant 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 CTRU. The CTRU will comply with all aspects of the 2018 General Data Protection Regulation 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 participants' 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.
- participant name (via consent form), email address and telephone number will be collected when a participant 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 participant identifiers, usually the participant'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 particiapnt'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, and pharmacovigilance within the trial. The 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 Standard Operating Procedures (SOPs).

The Leeds Teaching Hospitals Trust: During stages A and B of the trial, the Radiology Department at St James's University Hospital had responsibility for reporting all participant CT scans (or MRI scans in cases where these are performed in the place of CT). This reporting was blind to participant's randomisation allocation but took place in real time and the central report generated was 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 Clinical Trial Authorisation (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 International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to 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 (Phase III trial), either for trial publication or oral presentation purposes, without the permission of the TSC. 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 Phase III endpoint.

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Appendix 1: Motzer Score

Definition of risk factors

Score 1 point for each risk factor that applies:

1. Karnofsky performance status: <80% (see table below)
2. Lactate dehydrogenase: >1.5 times Upper Limit of Normal (ULN)*
3. Serum haemoglobin: <Lower Limit of Normal (LLN)*
4. Corrected serum calcium: >2.5mmol/L
5. Prior nephrectomy: No

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

Total Points Scoring
Yes for questions 1-4 = one point each
No for question 5 = one point

Calculation of risk

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

Karnofsky Performance Status[35]

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

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0% death

Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance[36]

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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. 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 Tyrosine Kinase Inhibitors (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 Renal Cell Carcinoma (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 could 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 and pazopanib 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 or pazopanib Tyrosine Kinase Inhibitor (TKI) treatment in metastatic renal cell carcinoma (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 sub-study to map directly onto the both the Phase II/III stages of the STAR trial and to utilise the STAR clinical database and trial infrastructure already established in the Leeds Clinical Trials Research Unit (CTRU).

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 Renal Cell Carcinoma (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 Partial Response (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 Progression Free Survival (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 participants are ideal for this as the clinical trial infrastructure and database already in place can be utilised, and participants will already be having CT assessments at baseline and around 12 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. We anticipate that up

to 100 patients will have undergone contrast enhanced CT including arterial and/or portal venous phases.

Additionally in patients who will have undergone a portal venous phase CT only we would like to test the hypothesis that tumours may demonstrate a heterogeneous response to therapy both within a tumour and across different metastases in the same patient

Aims of the CT Translational Studies

Co-primary objectives:

- 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 approximately 12 weeks after initiation of sunitinib or pazopanib to predict for progressive disease (PD) within 6 months.

Secondary objectives:

- 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 12 week scans to predict time to strategy failure,c) the ability of a novel textural analysis methodology to predict response of mRCC to sunitinib; d) the ability of CT enhancement and histogram distribution to demonstrate the heterogeneity of response within and across lesions.

Recruitment and Informed Consent

This study will be performed at all sites participating in the STAR trial that are able to follow the scanning requirements and use CE-CT as standard of care. Arterial and portal venous phase CT will be collected from sites that perform dual phase imaging as standard of care; portal venous phase CT will be collected from sites where only portal venous phase CT is perfomed as standard of care.No additional CT scans are required over those performed routinely as part of the clinical STAR trial. The study is explained in the main STAR trial Participant Information Sheet 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 Department of Radiology, St James's Institute of Oncology, Leeds and also to the Division of Imaging Sciences, Kings College London to be reviewed and reported for the purposes of the sub-study.

Imaging

In the sub-study, CE-CT will be performed as per STAR clinical trial requirements at baseline and at day 72+/-4 days after starting trial treatment. CE-CT will provide the standard CT scan report information (RECIST) as well additional data on the arterial and venous phase comparison. CT sub-study participants will therefore not need to have any additional scans

compared with STAR trial participants not participating in the CT sub-study. For any 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. CE-CT images will be obtained of the thorax, abdomen and pelvis and will be performed ideally with arterial phase imaging of the thorax/upper abdomen to include the kidneys, and portal venous phase imaging of the abdomen/pelvis.

Scans will be reported using RECIST and alternative published response criteria (including mChoi and Choi criteria).

Transfer of Scans

The CT scans of participants that consent to the CT substudy will be reported by an experienced radiology consultant or fellow within the Division of Imaging Sciences, Kings College London and a subset dual reported by a second experienced consultant or registrar from Leeds.Anonymised scans are to be sent at periodic intervals as agreed with CTRU via standard mail.

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

CT substudy scans must be anonymised and downloaded onto CD prior to transfer by standard post to the CTRU STAR team.

Participant consent for the CT substudy must have been obtained before any scans are sent. Sites must notify the STAR team at CTRU to confirm dispatch of scans and expected delivery:

Fax: 0113 343 6774 Email: CTRU_star@leeds.ac.uk

Endpoints

Primary: Two co-primary endpoints will be evaluated once the required number of suitable scans has been collected. 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 12 weeks to predict patients who have RECIST-defined PD within 6 months of commencing treatment.

Secondary endpoints include the ability of mChoi criteria at 12-week scan to predict time to strategy failure, assessment of the effect of arterial phase and portal 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 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. CT enhancement and histogram distribution will also be evaluated as a tool to demonstrate the heterogeneity of response within and between lesions.

Statistical Analysis

The reproducibility of size and attenuation measurements (test versus retest) i.e the inter-operator variability, will be analysed by the Bland-Altman approach [8] and via the intraclass correlation coefficient (ICC). The ICC is a measure of the reproducibility and level of agreement between operator measurements (test versus retest), and is defined as the proportion of all variation that is not due to measurement error [9]. . 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 50 scans there will be approximately 125 measurable lesions (arterial and/or portal venous phases). The sample size is then based on consideration of the ICC confidence interval. The smallest change we are looking for is a 10% change in lesion size, so we want to be able to attribute changes greater than 10% to underlying biological processes rather than physiological or hardware variability or operator interpretation differences. This would demonstrate a high degree of confidence that patients were being assigned to response groups due to real tumour changes. We therefore require the ICC to be at least 90%. We anticipate that the ICC will be approximately 95%. With 125 measurable lesions, the lower 99% CI on an ICC of 95% comes to 93%, so with this sample size we can exclude an ICC of 90% with >99% confidence.

If the 12-week mChoi assessment is able to predict RECIST progression at 6 months, a high degree of concordance will be required to change practice, i.e. for clinicians to change therapy early before RECIST defined progression is attained. The ability of mChoi defined PD at 12 weeks to predict RECIST defined PD at 6 months will be analysed by kappa measurements in 2x2 contingency tables [10], 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.

Assuming a median time to progression of 11 months gives approximately 30% with PD at 6 months, and this translates to a “by chance” agreement of around 55%. Assuming we are targeting an agreement of 95%, and that an agreement of 80% would be too low, 100 patients would provide approximately 96% power to demonstrate this level of agreement at a 5% significance level. With 75 patients this power drops to 90%, and with 50 patients the power is approximately 76%. Note that with these PD figures (30% at 6 months) an agreement level of 80% corresponds to a Kappa of about 0.56 while an agreement of 95% corresponds to a Kappa of about 0.9.

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 (Case Report Forms) 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 or pazopanib 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 or pazopanib and those who will not, much earlier than with the current Computerised Topography (CT) scanning approach. If this can be done then, in future, instead of continuing to give sunitinib or pazopanib 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 Renal Cell Carcinoma (RCC) treated with sunitinib or pazopanib, early DCE-MRI will be predictive of patients who progress within 6 months and this 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 or pazopanib.

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 or pazopanib 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 or pazopanib 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 25 participants (allowing for 25% attrition) from the main trial. It is anticipated that these functional imaging sub-study participants will be recruited from St James University Hospital, Leeds only but may include up to 5 of the trial sites participating in the STAR trial. A separate participant information sheet and consent form will be provided to potential sub-study participants.

Participant Inclusion Criteria and Registration

The inclusion criteria for the MRI substudy are patients having measurable disease within the abdomen or pelvis. For bony metastasis, only those with measurable soft tissue component can be included. Participants taking part in this sub-study are required to undergo a baseline DCE-MRI scan prior to commencement of sunitinib or pazopanib treatment on the STAR trial. Given the narrow window specified between randomisation and commencement sunitinib or pazopanib (5 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 Clinical Trials Research Unit (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 & Randomisation DCE-MRI Sub-Study Site (F04a) 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 participant 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 post to the STAR team at CTRU along with a scan transfer pro forma 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, and participant date of birth**. Anonymisation of scans will be checked on receipt at the radiology department at St James's University Hospital. 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 or pazopanib 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 or pazopanib to predict participants who have 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 20 participants (25 allowing for 25% attrition) will enable demonstration of a relatively large difference in mean vascularity at 10 weeks of 4 mls/100mg between participants demonstrating RECIST-defined PD and those with RECIST-defined Complete Response (CR) + Partial Response (PR) +

Stable Disease (SD) at 6 months, using a 2-sided t-test, with significance level 5% and 90% power. This would enable us to identify, by MRI at 3 months, approximately half of the patients who will still progress (assessed by RECIST) by 6 months. Detection at 1 month 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.

References

1. Fournier LS, Oudarad S, Thiam R et al. Metastatic renal carcinoma: evaluation of anti-angiogenic therapy with dynamic contrast-enhanced CT. Radiology 2010; 256: 511-8.
2. Kershaw LE, Hutchison CE, Buckley DL. Benign prostatic hyperplasia: evaluation of T1, T2, and microvascular characteristics with T1-weighted dynamic contrast-enhanced MRI. J Magn Reson Imaging 2009; 29: 641-8.

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