TITAN: Trial of Induction TPF Therapy in Advanced Head & Neck Cancer

Randomised controlled open-label trial of TPF induction chemotherapy in the surgical management of locally advanced head and neck cancer
(T = taxane, P = cisplatin, F = 5-fluorouracil)

EudraCT number: 2010-023195-22
Protocol Number: 5

Final Statistical Analysis & Report Template

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Prepared by: Elaine Howarth (Statistician)

1. INTRODUCTION

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the randomised controlled trial of induction chemotherapy (ICT): Docetaxel, Cisplatin, 5-Fluorouracil (5-FU) x 3 cycles for surgical management of locally advanced head and neck cancer (TITAN: Trial of Induction TPF Therapy in Advanced Head & Neck Cancer) funded by Cancer Research UK.

The purpose of the plan is to:

a. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice in general, and minimises bias by preventing inappropriate post hoc analyses.
b. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence
c. Protect the project by helping it keep to timelines and within scope

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post-hoc analysis will be declared.

NOTE:

It was decided by the TSC to close this study to further recruitment on 24 May 2013 due to the extremely slow and poor rate of recruitment observed over the 19 month duration of the trial, compared to the planned rate of recruitment.

This final statistical report documents the data available for the Phase II feasibility study endpoints that was collected for the very limited number of randomised patients.

2. TRIAL DESIGN

2.1 Configuration

TITAN is an open-label randomised controlled trial in patients with previously untreated locally advanced head and neck squamous cell carcinoma. This was a feasibility study with an intention to progress to phase III if feasibility is demonstrated.

2.2 Interventions

Induction chemotherapy (ICT): Docetaxel, Cisplatin, 5-Fluorouracil (5-FU) x 3 Cycles.

2.3 Objectives

Primary

- Rate of recruitment into the TITAN trial over a period of 12 months from at least 4 centres.

Secondary

- Randomisation: Screening Ratio.
- The percentage of patients in the TPF arm who complete the full course of treatment (including post-operative radiotherapy / chemoradiotherapy).

2.4 Eligibility Criteria

Main Inclusion Criteria

1. Age > 18 years
2. Histopathological diagnosis of head and neck squamous cell carcinoma
3. T stage in one of the following site categories:
  i. Lip/ Oral cavity: stage T3 or T4a (and >=4cm in largest dimension)
  ii. Paranasal /nasal: stage T4a
  iii. Larynx: stage T4a
  iv. Hypopharynx: stage T3 or T4a
  v. Cervical oesophagus: stage T3 or T4a
  vi. Oropharynx: stage T3 or T4a and -ve
4. Any N stage
5. M0
6. An MDT decision to offer surgery as primary modality of treatment
7. WHO performance status 0 or 1
8. Resectable by conventional criteria in both primary site and any cervical lymph node involvement

Main Exclusion Criteria

1. Those tumours staged to T4a on the basis of early mandibular invasion *alone*, i.e. <4cm in the maximum dimension
2. Unresectable disease on clinical staging (including imaging) of primary tumour or cervical metastasis
3. Distant metastases (a PET_CT or other conventional imaging methods should be used to exclude pulmonary or hepatic metastases
4. Nasopharynx site
5. HPV +ve Oropharyngeal Site
6. Pregnancy or lactation
7. Patients with haemoglobin < 10g/dl
8. Patients with neutrophil counts < 1.5 x 109/l
9. Patients with thrombocyte counts of <100 x 109/l
10. Patients with significant hepatic impairment (Bilirubin >1.5x upper limit of normal range; ALT >2.5x upper limit of normal range; ALP >5x upper limit of normal range)

11. Patients with significant renal impairment (For the purpose of the study, significant renal impairment is classed as GFR <50ml/min. However, sites may use their local policy if a higher threshold is dictated)
12. Patients who lack mental capacity to give informed consent
13. Patients whose co-morbidities or concomitant medications otherwise preclude TPF chemotherapy
14. All men or women of reproductive potential, unless using at least two contraceptive precautions, one of which must be a condom.

2.5 Sample size estimate

Sample size calculations were carried out for the proposed phase III trial and were undertaken using the NQuery Advisor software version 7.0.

The primary outcome of the phase III trial is overall survival. Sample size calculations are calculated based upon a 2 year overall survival rate in the control arm of 45%. This is equivalent to a median survival time of 1.74 years, assuming an exponential survival distribution.
The aim of the trial is to detect a hazard ratio between the two treatment arms of 0.7. Assuming a 2 year survival rate of 45% in the control arm, a 2 year survival rate of 57% in the treatment arm is required.

Taking a two sided type I error rate of 0.05 (0.025 in each tail) and assuming a power of 85% a sample size of 200 patients in each arm is required. Thus 400 patients are required for the entire trial. This is calculated assuming 4 year recruitment and 2 year follow up periods.

Table 1 shows how the power of any analysis is altered based upon differing survival rates in the control arm but keeping the hazard ratio at 0.7. It is shown that with 200 patients in each arm, the power of any analysis to observe a hazard ratio of 0.7 falls as the 2 year survival rate in the control arm increases. It should be noted however that even with a 2 year survival rate as high as 55%, the power of the analysis to observe a hazard ratio of 0.7 is still approximately 80%.

In the trial, it is also anticipated that a dropout rate of 5% will be observed. To account for this, the sample size is inflated to a total of 420 patients (210 in each arm).

Table 1: Illustrated power differences with varying 2 year survival rates in the control arm

Scenario	**1**	**2**	**3**	**4**	**5**
Control - 2 Year Survival	0.35	0.40	0.45	0.50	0.55
Treatment - 2 Year Survival	0.48	0.53	0.57	0.62	0.66
Hazard Ratio	0.7	0.7	0.7	0.7	0.7
Power	88	87	85	82	79
Sample Size	200	200	200	200	200

2.6 Randomisation procedure

Patients shall be randomised by the method of minimisation using a specially designed computer program at the Liverpool Cancer Trials Unit (LCTU). The minimisation protocol will involve the following stratification factors:

i. Tumour Site (O,PN,OP vs. L&P)
ii. Stage (T3 vs. T4)
iii. Centre

Allocation within the trial is on a 1:1 basis. A random element of 0.8 will be included within the minimisation procedure to remove any remote possibility of predictability within the trial. Central randomisation, by fax, will be undertaken by the LCTU.

2.7 Blinding

No blinding was used as this is an open-label randomised study.

2.8 Endpoints

TITAN Feasibility Study

Primary Endpoint

- The primary endpoint is the feasibility of recruitment into the TITAN trial (specifically the number of patients recruited from at least 4 centres during a 12 month period).

Secondary Endpoints

- Randomisation: Screening ratio
- The percentage of patients in the TPF arm who complete the full course of treatment (including post-operative radiotherapy/chemoradiotherapy).

Planned TITAN phase III trial

It is important to iterate these endpoints as it is envisaged that the data for the 50 patients in the feasibility study will be rolled into the phase III trial i.e. it is necessary to also collect these data.

Primary endpoint

- 2 year overall survival

Secondary Endpoints

- 2 year disease-specific survival
- 5 year overall and disease specific survival
- Degree of tumour response to 3 cycles TPF by RECIST criteria
- Change in mean and maximum SUV on FDG PET-CT after 1 cycle as predictor of response to 3 cycles of TPF ICT by RECIST criteria
- Cost effectiveness (cost per QALY gained)
- Incidence of TPF on overall burden and proportion of local, regional and metastatic relapse in those patients developing recurrence.
- Functional outcomes and quality of life: (EORTC C30 and H&N35)
- Incidence of involved surgical margins and extracapsular spread in cervical lymph nodes (and, by implication the requirement for CRT)
- Volume of surgical resection (as determined by saline displacement in graduated flask)
- Surgical complications: infection rate, fistula rate, length of admission, free flap failure, peri-operative (30 days) mortality.
- Toxicities graded to National Cancer Institute (NRI) – Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

2.9 Trial Oversight Committees

- ***Trial Steering Committee***

The Trial Steering Committee will consist of an independent chairperson, independent experts in the field of head and neck cancer and a biostatistician and up to seven Principal Investigators. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The TSC will first convene and will then define frequency of subsequent meetings (at least annually). The ultimate decision for the continuation of the trial lies with the TSC.

- ***Data Monitoring Committee***

The independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, plus 2 independent members: who are experts in the field of head and neck cancer and an expert in medical statistics.

- Prof. Janet Dunn – Statistics, Professor of Clinical Trials and Head of Cancer Trials Deputy Director WMS Clinical Trials Unit.
- Dr. Andrew Protheroe – Consultant Medical Oncologist, Oxford Cancer Centre
- Dr. Vindh Paleri – Consultant Otolaryngology Surgeon - Newcastle

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC will first convene and will then define frequency of subsequent meetings (at least annually). The ISDMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

- ***Trial Management Group***

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical), trial co-ordinator, pharmacist where possible and representatives of the sponsor. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year.

2.10 Planned Interim analyses

No formal interim analysis of the primary outcome (overall survival) is intended. This is because it is anticipated that by the time that a sufficient number of patients have been monitored for 2 years, the trial itself will be close to, if not past, the end of the recruitment period. It is felt preferable therefore to preserve the type I error rate (0.05) of the study without the need of inflating the sample size.

3. TRIAL HISTORY

3.1. Quality control and data validation procedures

CRF data entered into the MACRO database will be centrally monitored by the LCTU to ensure that data collected are consistent with adherence to the trial protocol. The MACRO database used for this trial includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query is raised within the MACRO database and emailed to site. A complete log of discrepancies and data amendments is automatically generated by MACRO, including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail.

Automated email reminders are generated by the database if follow up data from a scheduled patient visit is overdue. Additional site training will be carried out if recurring problems are noted with data from a certain site, such as consistently incorrect or incomplete data, a backlog of unresolved queries, or unacceptable time delays in submitting CRFs.

Central statistical monitoring will be carried out by the trial statistician prior to the production of each IDSMC report. Eligibility criteria and informed consent are checked to ensure all are documented and satisfied. Monitoring is used to highlight suspicions of fraudulent data (by carrying out range checks for unusual values, checking for consistency within participants and comparing data across sites to highlight inconsistencies), as well as providing a record of the degree of missing CRF and follow up visit, and missing baseline and outcome data. Safety and withdrawal data are also reviewed for completeness. If there is compelling evidence that data from a particular site may be fraudulent, the TC may request a site visit to carry out source document verification of patient case notes and other source documentation.

3.2. Protocol amendments

There were 13 protocol amendments for this study. A summary are provided in the table below.

Table 2: Protocol Amendments Summary

Protocol Number	Level	Brief Description
1	Substantial	Addition of new sites (Glasgow & Clyde; Ayreshire & Arran; Forth Valley; Lanarkshire)
2	Non-substantial	Update labels address; Correction of small typing errors in protocol
3	Substantial	Updates to protocol and informed consent
4	Non-substantial	Addition of a patient identification centre for Aintree (St. Helens & Knowsley)
5	Substantial	Addition of new sites (Imperial College; Newcastle; Sunderland; Devon & Exeter)
6	Substantial	Details of 51-Cr labelled EDTA to measure GFR omitted from ionising radiation section of initial application in error
7	Substantial	Addition of two new sites in Manchester (Christie; Manchester Royal Infirmary)
8	Substantial	Protocol updates
9	Non-substantial	Addition of patient identification centre for Velindre Cancer Centre (Cardiff & Vale)
10	Substantial	Protocol changes
11	Closure to recruitment	Early closure of study due to recruitment. Closed to further recruitment on 24 May 2013
12	End date extension	Extension of study end date from 01/12/2017 to 31/12/2018 to allow time for collection of follow up data
13	End date extension	Extension of study end date from 31/12/2018 to 30/06/2019 to allow time for close-out following follow-up data collection period

3.3. Trial milestones

Table 3: Trial Milestones	
Date of Greenlight	02 Nov 2011
Number of target patients:	50
Number of planned sites to open:	12
Date first site open:	02 Nov 2011
First patient randomised on:	15 Aug 2012
Last patient randomised on:	04 Feb 2013
Number of patients randomised:	7 patients
Number of sites who have randomised:	3 sites (UCL – 2 patients; Bradford Royal Infirmary – 4 patients; Velindre Hospital – 1 patient)
Date study closed due to recruitment:	24 May 2013

4. PROPOSED METHODOLOGY

The phase II study terminated early due to poor recruitment so the final statistical analysis was triggered.

Statistical analyses was performed using SAS version 9.4.

4.1. Patient Groups for Analysis

Full Analysis set: In order to follow the Intention to Treat (ITT) principle this will consist of all randomised patients excepting for a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process and c) patients whose information determining ineligibility existed before randomisation but was not read until after randomisation.

Safety set: All patients who received any trial treatment.

Efficacy analyses will be performed on the full analysis set. Safety summaries will be performed on the safety set.

4.2. Handling of mis-randomised patients, dropouts

For efficacy analyses mis-randomised patients will be analysed as randomised, in order to follow the ITT principle. For safety analyses patients will be analysed as treated.

4.3. Identification and handling of Outliers

As this study is a Phase II feasibility the analyses carried out will focus upon estimation as opposed to hypothesis testing. No identification and handling of outliers will be made.

4.4. Study centre effects

As this study is a Phase II feasibility the analyses carried out will focus upon estimation as opposed to hypothesis testing. In addition, the study was closed early due to poor recruitment with only 7 patients randomised across 3 centres. No identification and handling of study centre effects will be made.

4.5. Adjustment for covariates

As this study is a Phase II feasibility the analyses carried out will focus upon estimation as opposed to hypothesis testing. No adjustment for covariates will be made.

4.6. Multiplicity adjustments

As this study is a Phase II feasibility the analyses carried out will focus upon estimation as opposed to hypothesis testing. No multiplicity adjustments will be made.

4.7. Missing data

As the study has now ended no further attempts to retrieve missing data will be attempted. All missing data will treated as missing. No imputations for missing data will be implemented.

4.8. Sensitivity analyses

As this study is a Phase II feasibility the analyses carried out will focus upon estimation as opposed to hypothesis testing. No sensitivity analyses will be conducted.

4.9. Prespecified subgroup analyses

No pre-specified subgroup analyses will be conducted.

4.10. Definitions & Derived variables

4.10.1 Definitions

No derived variables will be used in the analysis.

4.10.2 Derived Variables

Primary & Secondary Outcome(s)

No derived variables will be used in the analysis.

4.11. Specification and estimation of efficacy parameters

Table 4: Summary of outcome variables and corresponding efficacy parameters

Outcome variable	Efficacy parameter	Comment	Method
Recruitment rate at the end of a 12 month period	Recruitment rate	Recruitment rate over a period of 12 months from at least 4 centres.	Simple summary statistics
Randomisation : Screening ratio	Ratio	randomisation to screening ratio	Simple summary statistics
Percentage of patients in the TPF arm who complete full course of treatment	Percentage	(including post-operative radiotherapy / chemoradiotherapy)	Simple summary statistics

4.12. Primary test of efficacy, Null hypothesis, Levels of significance, width of confidence intervals

As initially the trial is a feasibility study, the analyses carried out will focus upon estimation as opposed to hypothesis testing. Whilst a small degree of hypothesis testing may take place, emphasis will be placed upon the fact that this stage of the trial has not been powered to identify any significant differences.

The primary outcome of the feasibility study is to determine the recruitment rate at the end of a 12 month period. The rate of recruitment shall be analysed, with particular emphasis being placed on the latter months of the feasibility study. Simple summary statistics shall be produced with the intention of demonstrating whether the patient numbers can be recruited within the estimated accrual period for the phase III trial.

4.13. Tests of assumptions, actions to be taken

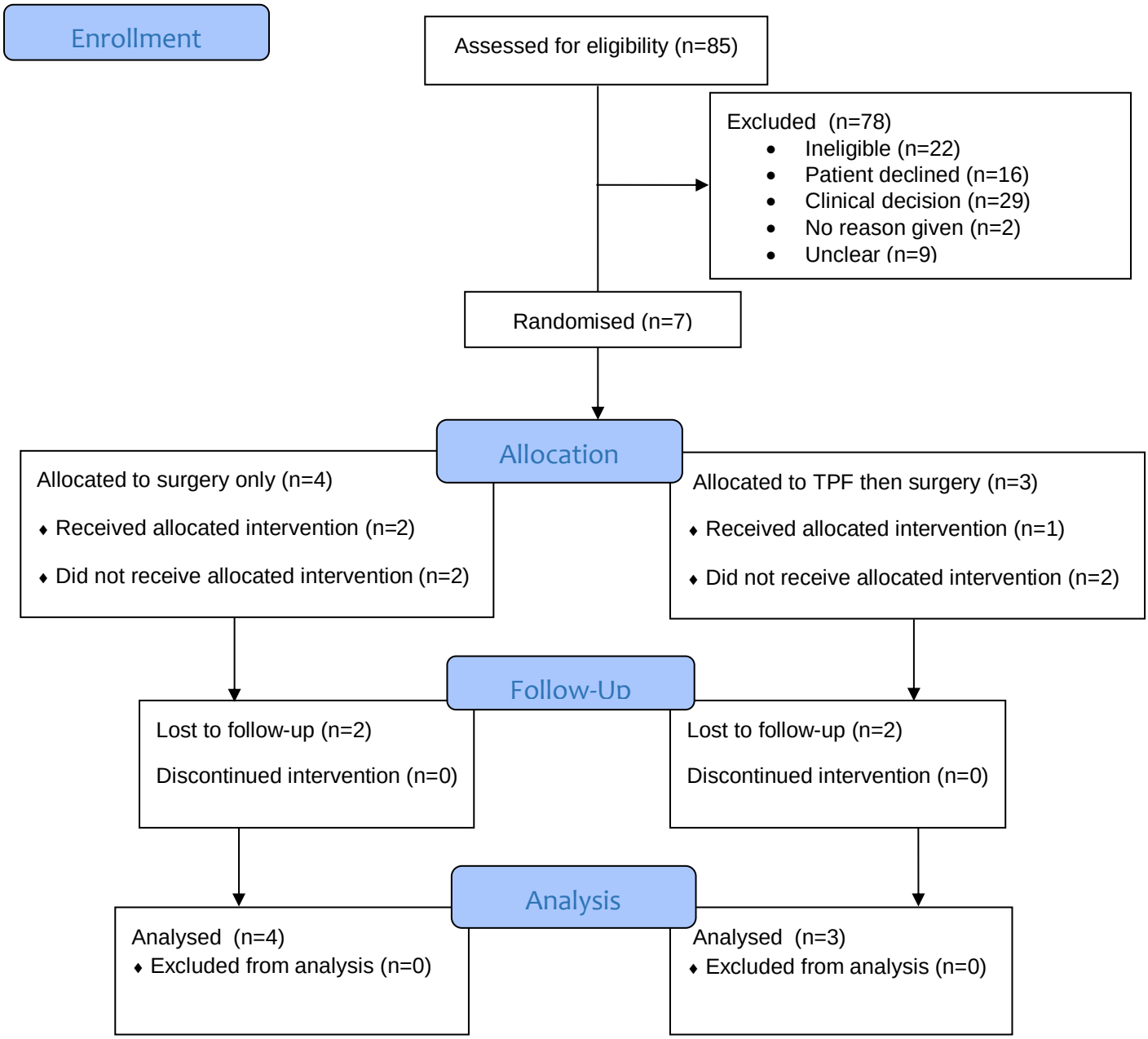
As the analyses carried out will focus upon estimation as opposed to hypothesis testing, no tests of assumptions, actions to be taken will be conducted.

5. RESULTS

5.1.1 Recruitment and disposition

Site Name	Date of First rand	Date of Last rand	N Screened	N Clinical decision	N Ineligible	N Declined	Unclear	No reason given	Rand to Surgery	Rand to TPF	Total Randomised
University College Hospital (London)	15 Aug 2012	21 Aug 2012	2	0	0	0	0	0	1	1	2
St. Luke's Hospital (Bradford)	23 Aug 2012	04 Feb 2013	19	5	6	3	0	1	2	2	4
Velindre Cancer Centre (Cardiff)	19 Nov 2012	19 Nov 2012	1	0	0	0	0	0	1	0	1
Bristol Haematology & Oncology Centre	NA	NA	1	0	0	0	0	1	0	0	0
Guys & St Thomas' Hospital (London)	NA	NA	9	0	2	7	0	0	0	0	0
University Hospital Aintree	NA	NA	53	24	14	6	9	0	0	0	0
Derriford Hospital (Plymouth)	NA	NA	0	0	0	0	0	0	0	0	0
Imperial College (London)	NA	NA	0	0	0	0	0	0	0	0	0
St James Hospital (Leeds)	NA	NA	0	0	0	0	0	0	0	0	0
The Beatson West of Scotland Cancer Centre (Glasgow)	NA	NA	0	0	0	0	0	0	0	0	0
Clatterbridge Cancer Centre (Wirral)	NA	NA	0	0	0	0	0	0	0	0	0
Total			85	29	22	16	9	2	4	3	7

Figure 1: Patient disposition



No End of Treatment forms or End of Study forms were completed for any of the 7 randomised patients.

Of the 4 patients randomised to surgery, 2 patients went on to receive their surgery (Patient ID's 4 & 5). The remaining 2 patients (Patient IDs 2 & 6) have pre-treatment assessments prior to randomisation, but have no further details beyond then.

Of the 3 patients randomised to TPF followed by surgery, only 1 patient (Patient ID 7) received TPF induction chemotherapy and was then assessed for surgery. The remaining two patients (Patient IDs

1 & 3) only completed pre-treatment assessments prior to randomisation and baseline assessments after randomisation, prior to therapy.

5.2 Assessment of data quality

No End of Treatment forms or End of Study forms were completed for any of the 7 randomised patients. As a result we cannot tabulate the End of Treatment reasons to establish total number of patients discontinued treatment and total withdrawn from trial.

Protocol Deviations are accidental or unintentional change to or non-compliance with the trial protocol.

Table 6: Summary of Deviations

Type	Description of Deviation	Category	Arm Surgery	Arm TPF
Major*	Entered but did not satisfy the entry criteria	1	0	0
	Developed withdrawal criteria but not withdrawn	2	0	0
	Received an excluded concomitant treatment	3	0	0
	Received the wrong treatment or incorrect dose	4	0	0
	Deviation from patient management/assessment	5	0	0
	Other	6	0	0
Minor	Protocol Deviations not expected to have an impact on defined endpoints of the trial	7	4	3

*These need to have a potentially major impact on the primary endpoint, such as:
a) extent of treatment deemed inadequate
b) missing primary endpoint, stratification variables or pre-planned covariates

Table 7: Number of Patients with Major Deviations

No. of Major Deviations	Arm - Surgery	Arm - TPF	Overall
0	0	0	0

5.3 Description of baseline subject characteristics

Table 8: Baseline characteristics

		Arm - Surgery (n=4)	Arm - TPF (n=3)	Overall (n=7)
Demographic Characteristics				
Age	Mean (SD)	61.8 (4.4)	60.9 (5.1)	61.4 (4.3)
	Median (Min – Max)	62.4 (56.4 – 65.8)	61.6 (55.6 – 65.6)	61.6 (55.6 – 65.8)
Sex	Female	1	1	2 (29%)
	Male	3	2	5 (71%)
Height	Mean (SD)	176.1 (10.5)	179.7 (7.6)	177.6 (8.8)
	Median (Min – Max)	176.0 (163.4 – 189.0)	183.0 (171.0 – 185.0)	177.0 (163.4 – 189.0)
Weight	Mean (SD)	73.0 (23.7)	70.8 (9.6)	72.0 (17.7)
	Median (Min – Max)	64.2 (55.6 – 108.0)	69.4 (61.9 – 81.0)	64.8 (55.6 – 108.0)
WHO status	0	3	1	4 (57%)
	1	1	2	3 (43%)
Ethnicity	White - British	4	3	7 (100%)
Smoking status	Never smoked	1	1	2 (28.5%)
	Ex-smoker	2	0	2 (28.5%)
	Current smoker	1	2	3 (43%)
Alcohol status	None	0	1	1 (14%)
	Sporadic	2	1	3 (43%)
	Regular	2	1	3 (43%)
Clinical characteristics – prior to treatment				
HIS Stage	3	1	0	1
	4	3	3	6
Diagnosis of squamous cell carcinoma	No	0	1	1
	Yes	2	1	3
	Missing	2	1	3
TNM staging – T stage	04	2	2	4
	Missing	2	1	3
TNM staging – N stage	00	1	0	1
	01	0	1	1
	02	1	1	2
	Missing	2	1	3
TNM staging – M stage	00	1	2	3
	Missing	3	1	4
ECG	Normal	2	2	4
	Missing	2	1	3

5.4 Exposure to treatment & compliance

Table 9: Exposure to treatment			
Measure	**Arm – Surgery (n=4)**	**Arm – TPF (n=3)**	**Overall (n=7)**
TPF Induction chemotherapy			
Cycle 1		1	
Cycle 2		1	
Cycle 3		1	
No record of undergoing TPF induction chemotherapy		2	
Assessed for surgery to primary site & neck(s)			
Assessed for surgery	2	1	3
Re-assessed for surgery	0	1	1
No record of being assessed for surgery	2	2	4
Underwent surgery to primary site & neck(s)			
Underwent surgery	2	0	2
No record of undergoing surgery	2	3	5
Assessed for Post-op Chemo-radiotherapy following surgery			
Assessed for chemoradiotherapy	2	0	2
Not assessed for chemoradiotherapy as did not have prior surgery	2	3	5
Received post-op chemo-radiotherapy			
Received radiotherapy	2	0	2
Received chemotherapy	2	0	2

Notes:

TPF Induction chemotherapy

Only 1 of the 3 randomised patients received the induction chemotherapy (Patient ID 7 completed three cycles of the TPF induction chemotherapy).

Surgery to primary site & neck(s)

Arm – Surgery: Patient ID 4 - underwent surgery for 14 hours
Patient ID 5 - underwent surgery for 10 hours
Patient IDs 2 & 6 – no records of them undergoing surgery

Arm – TPF: Patient ID 7 – no record of then undergoing surgery after being assessed and re-assessed for surgery
Patient IDs 1 & 3 – no records of them undergoing surgery

Post-op Chemo-radiotherapy

Arm – Surgery: Patient ID 4 – received post-op radiotherapy and chemotherapy
Patient ID 5 – received post-op radiotherapy and chemotherapy
Patient IDs 2 & 6 – not assessed as did not undergo prior surgery

Arm – TPF: Patient ID 7 – assessed for prior surgery, but no surgery recorded
Patient IDs 1 & 3 – no records of them undergoing surgery

5.5 Analysis of Primary Outcome

Rate of recruitment into the TITAN trial over a period of 12 months from at least 4 centres

The rate of recruitment was extremely slow over the duration of the trial before it was decided by the TSC to close the study to further recruitment on 24 May 2013.

From 02 Nov 2011 to 24 May 2013, the number of recruiting sites who screened at least one patient was 6, however only 3 of these 6 centres randomised patients onto the TITAN study.

Over the 19 months the recruiting sites were open, only 7 patients were randomised onto the study.

5.6 Analyses of secondary outcomes

Randomisation : Screening ratio

In order for the 7 patients to be randomised into the TITAN trial, a total of 85 patients were screened.

Over the 19 month recruiting period before the trial was closed early this equates to a randomisation : screening ratio of 7 : 85 (i.e. 1 : 12.1 ratio).

Based on this randomisation : screening ratio and rate of recruitment, a total of 605 patients would have needed to be screened over a period of 85 months.

Percentage of patients in the TPF arm who complete the full course of treatment (including post-operative radiotherapy / chemo-radiotherapy)

Of the 7 patients randomised, 3 patients were randomised to the TPF arm.

Of these 3 patients who were randomised to the TPF arm, only one patient received the 3 cycles of TPF induction chemotherapy (patient ID 7). Having completed the 3 cycles of TPF chemotherapy, the patient was assessed and also re-assessed for their surgery on the primary tumour site & neck(s), however, the CRF records received appear to show that this patient did not go on to receive their surgery. As a consequence, they could not be assessed to receive the post-operative radiotherapy / chemo-radiotherapy.

The other 2 patients randomised to the TPF arm (patient IDs 1 and 3) do not appear to have received any TPF induction chemotherapy and subsequently no surgery or post-operative radiotherapy / chemo-radiotherapy.

During the 19 month duration of the trial, before being terminated due to poor recruitment, no patients in the TPF arm completed the full course of treatment (including post-operative radiotherapy / chemo-radiotherapy).

5.7 Analysis of safety & tolerability

Serious Adverse Events

There were no serious adverse events reported by any of the 7 randomised.

Adverse Events

A total of 7 adverse events were reported by 3 randomised patients; 2 patients randomised to the surgery arm and 1 patient randomised to the TPF arm.

Arm – TPF: Patient 1

This patient reported a total of 2 non-serious adverse events (one in CTC category of Infection & Infestation and one in CTC category of Ear & labyrinth disorders). Both with an outcome of 'resolved'.

AE number	CTC event	Severity	Start date	End date
1	Urinary tract infection	02	20 Feb 2013	(not recorded)
2	Tinnitus	01	15 Mar 2013	24 Mar 2013

For the urinary tract infection the investigator causality was recorded as 'possible' for the chemotherapy drugs Docetaxel, Cisplatin and 5-Flurouracil, however no action on any of these 3 drugs was taken.

For the Tinnitus the investigator causality was recorded as 'possible' for the chemotherapy drugs Docetaxel, Cisplatin and 5-Flurouracil. No action was taken against the Docetaxel and 5-Flurouracil drugs, but the dose for Cisplatin was reduced.

Arm – Surgery: Patient 1

This patient reported at total of 1 non-serious adverse event (CTC category of Surgical & Medical procedures). The adverse event had a recorded severity of '02' and an outcome of 'resolved'. The date of their surgery was 19 November 2012.

AE number	**Start date**	**End date**	**Notes**
1	10 Apr 2013	21 May 2018	Exposed bone between lower lip and chin 3-4mm. Notes: 28th May 2017. Secondary reconstruction of anterior mandibular defect with subscapular system (scapular tip + latissimus dorsi) free flap, left neck vascular access and temporary tracheostomy. 21st May 2018. Seen in clinic by Mr Sutton. The procedure to reconstruct his jaw seems to have been broadly successful and the neo mandible is firm. Recurrent chest infections, likely secondary to aspiration.

Arm – Surgery: Patient 2

This patient reported a total of 4 non-serious adverse events (all with a CTC category of Surgical & Medical procedures). All 4 adverse events had an outcome of 'resolved'. The date of their surgery was 10th September 2012. MRO of their rectum (6th August 2018) revealed a T2, or less adenocarcinoma, which would be amenable to local resection. A CT scan performed on the same day has revealed mediastinal and lung metastases. Head and neck MDT 29 August 2018: Lung nodule amenable to biopsy, may be lung primary with mediastinal metastasis (unlikely to be metastases from head and neck primary 2012). Referral to Lung MDT advised.

AE number	Start date	End date	Notes
1	19 Sept 2012	29 Sept 2012	• Exposed plate right lateral aspect of mental sub unit • Hospital acquired pneumonia • Infection around tracheostomy site • Infection left side of chin
2	15 Sept 2012	23 Sept 2012	• Exposed plate right lateral aspect of mental sub unit
3	16 Oct 2013	06 Sept 2017	
4	08 Nov 2013	21 Oct 2014	

FINAL REPORT SIGN-OFF SHEET

This confirms approval of the Final report plan for TITAN

Trial statistician

Signature ……

Date _ _ / _ _ / _ _ _ _

Reviewing statistician

I hereby confirm that I have reviewed and quality controlled the statistical analysis report plan against the trial's current version of the protocol.

Signature ……

Date _ _ / _ _ / _ _ _ _

Chief Investigator

Signature ……

Date _ _ / _ _ / _ _ _ _

Chair of Trial Steering Committee

Signature ……

Date _ _ / _ _ / _ _ _ _

Add: Retain Original Copy of Report & Sign-off sheet in appropriate sections of Statistics File

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(this form should be signed off at first TSC meeting)

FINAL STATISTICAL REPORT SIGN-OFF SHEET

Programming and Reporting Checklist for TITAN Final statistical report	TS	RS
Programming		
Has the relevant analysis plan been written and signed off		
Timescales agreed for database lock, data download into R/Stata/SAS etc, analysis and dissemination		
Have MACRO Queries been created to supply data needed for each table /figure in Report		
Have you checked that the data have been read into SAS/Stata correctly		
Have all SAS/Stata/etc analysis programs been listed in the relevant index?		
Have all SAS/Stata/etc analysis programs been risk-assessed, with appropriate review & sign-off in the validation log		
Have the numbers in the tables been checked against the relevant SAS/Stata output		
Report		
Pagination correct		
All tables/graphs stipulated in Report Plan/subsequent amendments are present/accounted for		
Layout & formatting acceptable (percentages as a whole number, means to 1 d.p. more than unit of measurement)		
Table rows/columns labelled clearly, with units		
Graph axes labelled clearly, with units		
All accompanying text consistent with presented results		
Has report been reviewed and signed off by statistical lead?		

This confirms approval of the Final Statistical Report for TITAN

Signed (TS) **Signed (RS)**

Date **Date**

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Statistics File

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