Kent & Medway Cancer Collaborative

Oncological Treatment of Upper GI Cancer

Pathway of Care

Kent & Medway Cancer Collaborative

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1.0 Introduction and background

This document has been written to provide guidance on the treatment of Upper GI cancer in the Kent & Medway Cancer Collaborative

Radiotherapy schedules are as defined in the Kent Oncology Centre Quality System Clinical Protocols (Disease Management and Radiotherapy Protocols).

See network chemotherapy prescribing proformas for details of chemotherapy / anti-cancer regimens.

All patients will be considered for entry into a clinical trial (see appendix C).

All patients should be discussed within a multidisciplinary team meeting before commencing initial treatment.

Please note, some of the drugs/doses recommended within this document are outside of the U.K. licensed marketing authorisation.

2.0 Oesophageal Cancer

2.1 Neo-adjuvant Treatment

2.1.1 Neo-adjuvant chemotherapy

Indications:
T2-3N0M0
T1-3N1M0
T1-3N0-1M1a

Treatment

- 3 cycles of ECX or one of the regimens listed in table 1 given every 3 weeks
- See chemotherapy prescription proformas for full details of regimens

Table 1

Regimen	Indication
ECX	Standard treatment
ECarboX	• Consider substitution of Cisplatin with Carboplatin (AUC 5) if renal (GFR 30-60 mls/min) or auditory dysfunction.
ECF	• Consider substitution of Capecitabine with 5FU 200 mg/m^2/day continuous infusion if unable to swallow tablets.
ECarboF	• Consider substitution of Cisplatin with Carboplatin (AUC 5) if renal (GFR 30-60 mls/min) or auditory dysfunction. • Consider substitution of Capecitabine with 5FU 200 mg/m^2/day continuous infusion if unable to swallow tablets.
CX	• Omit Epirubicin if significant cardiac impairment (LVEF < 50%).
CarboX	• Consider substitution of Cisplatin with Carboplatin (AUC 5) if renal (GFR 30-60 mls/min) or auditory dysfunction. • Omit Epirubicin if significant cardiac impairment (LVEF < 50%).
CF	• Consider substitution of Capecitabine with 5FU 200 mg/m^2/day continuous infusion if unable to swallow tablets. (5FU 300mg/m^2/day continuous infusion if Epirubicin omitted). • Omit Epirubicin if significant cardiac impairment (LVEF < 50%).
CarboF	• Consider substitution of Cisplatin with Carboplatin (AUC 5) if renal (GFR 30-60 mls/min) or auditory dysfunction. • Consider substitution of Capecitabine with 5FU 200 mg/m^2/day continuous infusion if unable to swallow tablets. (5FU 300mg/m^2/day continuous infusion if Epirubicin omitted). • Omit Epirubicin if significant cardiac impairment (LVEF < 50%).
E	Epirubicin
C	Cisplatin
Carbo	Carboplatin
X	Capecitabine
F	5-Fluorouracil

Tumour assessment
OGD, CT scan, EUS, PET/CT scan and laparoscopy (unless upper or mid oesophagus squamous cell carcinoma) pre-chemotherapy.
CT scan after 2-3 cycles of chemotherapy.
Laparoscopy pre-surgery if not performed pre-chemotherapy.
Surgery
To be performed 4-6 weeks following completion of chemotherapy

2.1.2 Neo-adjuvant chemotherapy radiotherapy

Neo-adjuvant chemoradiation may be considered for selected oesophageal cancer patients and should be agreed at MDT

Indications:

- Potentially operable oesophageal cancer
- Performance status 0-1
- T3 N 0-2. Max 5cm tumour length
- T4 if only involving diaphragmatic crus.
- All nodes above diaphragm
- Minimal comorbidity
- Adeno/Squamous carcinoma
- Agreed at MDT

Chemoradiotherapy regimen:

- Paclitaxel 50mg/m^2 + Carboplatin AUC 2 on days 1, 8, 15, 22 and 29.
- Concurrent radiotherapy as defined in the Kent Oncology Centre Quality Systems Clinical Protocols (Disease management and Radiotherapy Protocols).

2.2 Adjuvant chemotherapy

Indications
Patients with lower third oesophageal or oesophago-gastric junction adenocarcinoma who underwent pre-operative chemotherapy with 3 cycles of ECX (or variant, see table 1) may be considered for 3 cycles of the same chemotherapy postoperatively on the basis of the MRC MAGIC trial results which demonstrated a 13% absolute survival benefit at 5 years for peri-operative chemotherapy.

For patients undergoing surgery for oesophageal carcinoma without pre-operative chemotherapy, there is no proven role for adjuvant chemotherapy. However, in the presence of adverse risk factors (nodal involvement, positive surgical excision margins), adjuvant chemotherapy with 6 cycles of ECX (or variant, see table 1) may be considered on an individual case basis. Patients with positive surgical margins may also benefit from postoperative chemoradiation with continuous infusion 5FU 200-275 mg/m^2/day or Capecitabine 1250 mg/m^2/day with concurrent radiotherapy 50Gy in 25 fractions.

Treatment

- 6 cycles (in total) of ECX or one of the regimens listed in table 1 given every 3 weeks
- Patients with positive surgical margins may also benefit from postoperative chemoradiation with continuous infusion 5FU 200mg/m^2/day or Capecitabine 1250 mg/m^2/day with concurrent radiotherapy

Tumour assessment
End of treatment CT scan

2.3 Radical chemoradiotherapy

Indications
T4N0-1M0
T1-3N0-1M0 unsuitable/unwilling for surgery (may be considered in preference to surgery for squamous cell carcinoma)

Treatment
Primary chemotherapy with ECX (or variant, see table 1) x 3-4 cycles
Chemoradiation with Cisplatin plus 5FU continuous infusion (CF) or Cisplatin plus Capecitabine (CX) x 5 weeks (single agent Capecitabine or infused 5-fluorouracil with concurrent radiotherapy as above may be considered for less fit patients). Carboplatin + paclitaxel to be used in selected patients who are unlikely to tolerate Cisplatin / Fluropyridimine.

Tumour assessment
OGD, CT scan, EUS pre-treatment. Consider PET/CT scan and staging laparoscopy.
CT scan after 4 cycles of chemotherapy or earlier if no symptom response.
CT scan and OGD (plus biopsy) 12 weeks post completion of chemoradiation
Consider surgical resection if residual carcinoma present.

For patients who may be suitable for salvage surgery, 3 monthly OGD and CT scan for 2 years, then 6 monthly for year 3 then annually to 5 years.

2.4 Palliative radiotherapy

Palliative external beam radiotherapy to the oesophagus can be offered for symptom control and for consolidating a good response to chemotherapy. The dose and fractionation depends on the stage of disease and performance status of the patient (refer to radiotherapy protocols). Oesophageal brachytherapy can be offered for re-treatment for symptom control.

2.5 First line palliative chemotherapy

Indications
Metastatic disease
Localised or locally advanced disease and patient unsuitable for or unwilling to receive 24 weeks combination treatment of Oxaliplatin, Fluoropyrimidine, surgery or radical chemoradiation
Performance status 0-2

Treatment
- 6-8 cycles of EOX or one of the regimens listed in table 2 or table 1 (where Oxaliplatin is unsuitable) given every 3 weeks

Table 2

Regimen	Indication
EOX	Standard treatment
EOF	• Consider substitution of Capecitabine with 5FU 200 mg/m^2/day continuous infusion if unable to swallow tablets. (5FU 300mg/m^2/day continuous infusion if Epirubicin omitted).
ECT ECarbo T	• Consider substitution of Fluoropyrimidine with Raltritrexed in the event of Fluoropyrimidine induced chest pain.
E	Epirubicin
O	Oxaliplatin
X	Capecitabine
F	5-Fluoropyrimidine
C	Cisplatin
T	Raltritrexed

Tumour assessment
CT scan pre-treatment
CT scan post 3-4 cycles (consider suitability for surgery if locally advanced disease down-staged)
CT scan post 6-8 cycles

2.6 Second line palliative chemotherapy

Indications
Patients remaining of good performance status (0-1) following disease progression after first line palliative chemotherapy or radical chemoradiation.

Treatment
(i) Disease-free interval from completion of previous chemotherapy > 6 months; consider Platinum/ fluoropyridimine based chemotherapy.
(ii) Disease-free interval < 6 months; There is evidence for-Irinotecan/5FU/Leucovorin (FOLFIRI regimen) or single agent Docetaxel or weekly Paclitaxel (funding approval required for all 3 regimens). Consider referral for phase I/II clinical trials.
(iii) Irinotecan & Capecitabine can be considered in selected patients. (Algorithm deviation)
(iv) Brachytherapy will be considered for patients previously treated with EBR that have local progression and symptoms such as dysphagia and pain.

Tumour assessment
CT scan every 2-3 months

3.0 Gastric/Gastro-oesophageal junction Cancer

3.1 Peri-operative chemotherapy

Indications
Gastric or oesophago-gastric junction adenocarcinoma considered suitable for curative resection:
T1, N1-3, M0
T2a, N0-3, M0
T2b, N0-3, M0
T3, N0-3, M0

Treatment
ECX or variant (see table 1) x 3 cycles preoperative and 3 cycles postoperative.
FLOT (only for patients with PS 0-1) x 4 cycles pre-operative and 4 cycles post -operative

Tumour assessment
OGD, CT scan, laparoscopy pre-treatment. EUS for tumours involving oesophago-gastric junction
CT scan post 3 cycles
CT scan post 6 cycles

Surgery
Surgery should be performed 4-6 weeks after completion of the third cycle of chemotherapy

3.2 Adjuvant chemoradiation

Indications
The Intergroup 0116 study demonstrated a survival benefit for patients who had undergone a microscopically complete surgical resection of gastric adenocarcinoma who received adjuvant chemoradiation therapy compared with no adjuvant treatment.

Adjuvant chemoradiation should therefore be considered a treatment option for these patients, particularly if there is considered to be a high risk of local failure (e.g. no/ limited lymphadenectomy performed, close or microscopically involved surgical excision margins).

Treatment
All cases to be discussed within an MDM. 3 cycles ECX or variant (see table 1) then Capecitabine or infused 5-fluoruracil with radiotherapy for 5 weeks OR chemoradiation without prior chemotherapy (Capecitabine or infused 5-fluoruracil with radiotherapy for 5 weeks).

Tumour assessment
CT scan 3 months post completion of chemoradiation

3.3 Adjuvant chemotherapy

Indications
The role of adjuvant postoperative chemotherapy following resection of gastric cancer remains unclear. A large number of clinical trials have addressed this question, the majority of which have not demonstrated a benefit from treatment. However, many of these trials were of poor methodologic quality, were underpowered to demonstrate a small but clinically relevant survival advantage, and employed chemotherapy regimens with limited activity in the advanced disease setting. Several meta-analyses of these data have been undertaken, which demonstrate a small benefit for adjuvant chemotherapy over no post-operative treatment, with a hazard ratio for survival between 0.72 and 0.88. However, when analysed separately, the positive effect of chemotherapy on survival was confined to Asian trials, with no benefit observed in Western studies.

Therefore at present, adjuvant chemotherapy should not be recommended routinely. However, in the presence of adverse risk factors (nodal involvement, positive surgical excision margins), adjuvant chemotherapy may be considered on an individual case basis.

Treatment
ECX (or variant see table 1) x 6 cycles

Tumour assessment
CT scan end of treatment

3.4 First line palliative chemotherapy

Indications
Metastatic disease
Locally advanced disease
Localised disease and patient unsuitable for or unwilling to receive 24 weeks combination treatment of Oxaliplatin, Fluoropyrimidine or surgery
Performance status 0-2

Treatment
6-8 cycles of EOX or one of the regimens listed in table 2 or table 1 (if Oxaliplatin unsuitable) given every 3 weeks
For HER-2 positive patients (IHC3+)
CX or CF x 6 cycles + trastuzumab until progressive disease in line with NICE TA 208. (N.B .may also be used for patients with HER 2 overexpression as defined by IHC2-positive and a confirmatory SISH or FISH result who have not received prior anti-cancer treatment for their metastatic disease, funding streams for FISH testing are currently under discussion).

For HER-2 negative patients (PS 0-1) with a contraindication to anthracyclines
DCF x 6-8 cycles may be considered as a treatment option

Teysuno® plus cisplatin may be considered for patients with severe fluoropyrimidine toxicities or those with fluoropyridimine induced cardiac toxicity (funding approval required).

Tumour assessment

CT scan pre-treatment
CT scan post 3-4 cycles (consider suitability for surgery if locally advanced disease down-staged)
CT scan post 6-8 cycles

3.5 Subsequent (2nd line and beyond) palliative chemotherapy

Indications
Patients remaining of good performance status (0-1) following disease progression after first line palliative chemotherapy or peri-operative chemotherapy.

Treatment
(i) Disease-free interval from completion of previous chemotherapy > 6 months; consider Platinum/ fluroropyridimine based chemotherapy.
(ii) Disease-free interval < 6 months; Consider Irinotecan/5FU/Leucovorin (FOLFIRI regimen), single agent Docetaxel, weekly Paclitaxel or Ramucirumab with paclitaxel (funding approval required for all 4 regimens). Consider referral for phase I/II clinical trials.

Tumour assessment
CT scan every 2-3 months

3.6 Palliative radiotherapy

Palliative radiotherapy to the stomach can be offered for haemostasis if surgery is not indicated, or for pain management.

4.0 Pancreatic Adenocarcinoma

4.1 Adjuvant chemotherapy

Indications
Macroscopically completely resected pancreatic adenocarcinoma

Treatment
Gemcitabine or Gemcitabine & Capecitabine depending on PS

Tumour assessment
Post treatment CT scan
Monitor Ca19.9 each cycle

4.2 Adjuvant Chemoradiation (after completion of adjuvant chemotherapy)

Consider adjuvant chemoradiation in selected patients with R1 resection

4.3 Chemoradiation for locally advanced disease

Indications
Pancreatic adenocarcinoma confined to pancreas +/- local nodes not amenable to surgical resection
Performance status 0-1

Treatment
All patients should initially be offered 6 months of chemotherapy with a first line advanced disease protocol (see section 3.3)
If disease remains localized and amenable to radical chemoradiation, this may be considered as follows:
Capecitabine with concurrent radiotherapy.

Tumour assessment
Pre-treatment CT scan (plus MRI/ EUS/ laparoscopy as required to determine inoperability)
CT scan following 12 and 24 weeks Gemcitabine chemotherapy and 12 weeks after completion of chemoradiotherapy.

4.4 First line palliative chemotherapy

Indications
Locally advanced inoperable adenocarcinoma of the pancreas
Metastatic disease
Performance status 0-2

Treatment for locally advanced disease:
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- Gemcitabine
- PS 0-1 folfirinox or gemcitabine & capecitabine
- Chemoradiation

Treatment for metastatic disease:

- Albumin bound paclitaxel with gemcitabine can be considered only if other irinotecan or oxaliplatin based combination chemotherapies are unsuitable and the patient would otherwise have gemcitabine monotherapy. (Patients should be PS 0-1 and should have had no previous chemotherapy for early disease unless given as a radiation sensitiser in the adjuvant setting and completed at least 6 months previously).
- Folfirinox
- PS 1-2 -Gemcitabine until progression or intolerance

Patients with prolonged disease control (> 6 months) following adjuvant Gemcitabine who remain of good performance status upon disease relapse may be considered for Gemcitabine re-challenge or Fluoropyrimidine-based therapy.

Tumour assessment
Pre-treatment CT scan
CT scan after 12 weeks
CT scan after 24 weeks
Ca19.9 levels every 4 weeks

4.5 Second line palliative chemotherapy

Treatment
Clinicians' choice of fluoropyridimine/platinum or gemcitabine- based therapy depending on prior therapy**.**

Tumour assessment
CT scan pre-treatment and every 9-12 weeks during therapy

4.6 Palliative radiotherapy

Palliative radiotherapy to the pancreas can be offered for pain control if other measures have failed such as opiates and nerve blocks. It can also be useful for haemostasis if the tumour is involving duodenum.

5.0 Cholangiocarcinoma / Gall Bladder Carcinoma

5.1 Adjuvant chemotherapy

Indications
There is a probable role for adjuvant chemotherapy.

Treatment
Consider Capecitabine as per BILCAP trial or entry to clinical trial

Tumour assessment
Post operative CT scan
CT scan post 6 cycles chemotherapy
Monitor Ca19.9 each cycle

5.2 Palliative Chemotherapy

Indications
Locally advanced inoperable cholangiocarcinoma
Metastatic disease
Performance status 0-2

Treatment
Gemcitabine plus Cisplatin x 6-8 cycles (carboplatin may be used in patients who cannot tolerate cisplatin)
Gemcitabine for a total of up to 24 weeks
ECX or variant (see table 1) x 6-8 cycles

Tumour assessment
Pre-treatment CT scan
CT scan after 12 weeks
CT scan after 24 weeks
Ca19.9 levels every 4 weeks

6.0 Hepatocellular Carcinoma

6.1 Localised disease

All patients should be referred to Kings College Hospital for consideration of resection or chemoembolisation.

6.2 Palliative Chemotherapy

Indications
Locally advanced disease not amenable to loco-regional therapy
Metastatic disease
Performance status 0-2
Child-Pugh status A (or low burden Child-Pugh B for sorafenib)

Treatment
Sorafenib for 1st line treatment in patients with Child–Pugh A disease.

Doxorubicin x 6 cycles
Doxorubicin + Cisplatin x 6-8 cycles
Doxorubicin + Carboplatin x 6-8 cycles

Tumour assessment
CT scan pre-chemotherapy

CT scan post 3 cycles
CT scan post 6 cycles
AFP levels before each cycle

7.0 Small Bowel Carcinoma

7.1 Adjuvant chemotherapy

Indications
There is no established role for adjuvant chemotherapy, but for selected patients with poor prognostic features, 6-8 cycles of ECX or variant (see table 1) as above may be considered.

7.2 Palliative chemotherapy Indications

Advanced disease not amenable to surgical resection
Performance status 0-2

Treatment
There is no standard treatment regimen.
Suitable patients may be considered for ECX x 6-8 cycles or variant (see table1) or EOX x 6-8 cycles

Tumour assessment
CT scan pre-treatment
CT scan post 3-4 cycles
CT scan post 6-8 cycles

8.0 Gastroenteropancreatic Neuroendocrine Tumours

8.1 Adjuvant therapy

Indications
There is no role for adjuvant therapy following surgical resection of gastroenteropancreatic neuroendocrine tumours.

Goblet cell carcinoid tumours of the appendix (adenocarcinoids) with lymph node involvement or T3N0 disease should be considered for adjuvant chemotherapy with 8 cycles of Capecitabine.

8.2 Palliative systemic anti-cancer therapy

A number of therapeutic options exist as follows:
(i) Surgical resection of hepatic metastatic disease (Refer to Kings College Hospital)
(ii) Embolisation (refer to Kings College Hospital) or radiofrequency ablation of hepatic metastatic disease (Refer to Maidstone Hospital or Kings College Hospital)
(iii) Somatostatin analogue therapy
(iv) Radiolabeled MIBG/ octreotide (Funding approval required.)
- Peptide receptor radionuclide therapy (Lutetium 177 octreotate) should be considered for the treatment of unresectable or metastatic, progressive, well differentiated and somatostatin receptor positive gastroenteropancreatic neuroendocrine carcinoma.

(v) Selective internal radiotherapy (SIRT) (Refer to Kings NET MDT) Funding approval required.
(vi) Systemic anti-cancer therapy

Indications
Active therapy should be considered for:
(i) symptomatic metastatic disease (e.g. symptoms of the carcinoid syndrome, local symptoms due to tumour mass/ invasion such as pain, haemoptysis, cough, biliary obstruction)
(ii) Rapidly progressive metastatic disease

Treatment
The choice of treatment will be dictated by the clinical situation.

(i) Somatostatin analogue therapy
Highly symptomatic patients should be commenced on a short acting preparation initially (e.g. octreotide 50 mcg s/c bd increased as necessary to 200 mcg s/c tds)
Responding patients should then be converted onto a long acting preparation (e.g. Sandostatin LAR 20 mg im 4-weekly, increased if necessary to 30 mg im 4-weekly or Somatuline autogel 60 mg s/c 4-weekly, increased if necessary to 120 mg s/c 4-weekly
(ii) Systemic anti-cancer therapy
There is no standard chemotherapy regimen for this disease. Patients with increased likelihood of response to chemotherapy are those with poorly differentiated tumours, particularly those with a high proliferative rate (Ki67>10%), pancreatic neuroendocrine carcinomas.
The following regimens may be considered.
Streptozocin plus Capecitabine x 6 cycles
Streptozocin plus Doxorubicin x 4 cycles
Steptozocin plus Capecitabine plus Cisplatin x 6-8 cycles
Carboplatin plus Etoposide x 6 cycles
Capecitabine plus Temozolomide x 6-8 cycles

There is increasing evidence for the use of targeted therapies in neuroendocrine tumours.
Sunitinib may be considered as 1st, 2nd or 3rd line treatment for well differentiated pancreatic neuroendocrine tumours.
Everolimus may be considered for well differentiated pancreatic, non-fractionated gastrointestinal or lung neuroendocrine tumours.

Tumour assessment
Baseline CT scan, octreotide scan, MIBG scan, 24-hour urinary 5-HIAA and VMA, investigation of neuropeptide hormone secretion as clinically indicated, fasting gut hormone profile including chromogranin A and B.

Repeat CT scan and 24-hour urinary 5-HIAA and serum chromogranin A every 3-12 months depending on rate of disease growth.

Repeat CT scan every 12 weeks while receiving cytotoxic chemotherapy

9.0 Gastrointestinal Stromal Tumours

9.1 Adjuvant therapy

Imatinib 400mg od is recommended as an option as adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD117)-positive gastrointestinal stromal tumours, as defined by the Miettinen 2006 criteria (based on tumour size, location and mitotic rate).

9.2 First line metastatic therapy

Patients presenting with advanced inoperable disease should have tumour specimens sent to the Royal Marsden Hospital for mutational analysis.

Imatinib 400mg daily is currently considered standard therapy for all patients.
However, for patients with exon 9 c-kit mutations or wild type, there is emerging evidence for a benefit from higher initial Imatinib doses e.g. 600-800mg daily.

<u>Monitoring for patients receiving imatinib</u>
The occurrence of toxicity following institution of imatinib is unpredictable. The following schedule of assessments should be undertaken ,with clinical assessment, FBC, U+E and LFT performed at each of 2 weeks, 4 weeks, 8 weeks, 12 weeks then 3 monthly thereafter.
Tumour assessment should be performed with CT T/A/P every 12 weeks during imatinib therapy (May be extended to every 24 weeks in prolonged stable disease)

9.3 Second line metastatic therapy

Options for second line treatment include high dose Imatinib 800 mg daily or Sunitinib 37.5 mg daily continuously.
Treatment will be decided on the basis of testing for exon-9 mutation:

- If the patient is exon-9 +ive then high dose imatinib 800mg daily is the option of choice (funding approval required)
- If the patient is exon-9 –ive (or if funding is not available for an exon-9 +ive patient) then Sunitinib 50mg daily for 4 of every 6 weeks will be the option of choice.

9.4 Third line metastatic therapy

Regorafenib should be considered for patients PS 0-1 who have disease progression or intolerance to imatinib and disease progression on sunitinib.

10.0 Guidelines on the Management of Drug-specific Toxicity

10.1 DPD testing

Fluoropyridimines are rapidly degraded by dihyropyrimidine dehydrogenase (DPD). Therefore, DPD deficiency can lead to severe toxicity or death following treatment with, for example, 5-FU or capecitabine. Homozygotes to DPD are rare (but likely to have severe toxicity or die). However, there are 3-5% of patient who are heterozygotes and are likely to develop toxicity; the clinician may reduce the fluoropyrimidine starting dose in this cohort.

The clinical recommendation of the NOG is to test all patients prior to treatment with a fluoropyrimidine.

Work is in process to identify whether there is equitable access to this test across Kent & Medway.

The following are intended as guidelines only. Individual cases should be discussed with the relevant consultant.

10.2 Gemcitabine

Haematological toxicity
On the day of Gemcitabine administration, the following dose should be given according to the absolute neutrophil and platelet counts on that day:

Absolute neutrophil count ($x10^9$/l)	Dose modification
>1.0	100% dose
0.5-1.0	75% dose
<0.5	Omit for one week

Platelet count (x 10^9/l)	Dose modification
>100	100% dose
50-100	75% dose
<50	Omit for one week

Dose reduction
Patients who have had a dose reduction due to decreased neutrophil or platelet count should have their next dose according to neutrophil and/or platelet count on the day of Gemcitabine administration, i.e. they can have their dose escalated back to 100% dose if their blood count is adequate. However, if after dose reduction to 75%, their blood count in the next Gemcitabine administration is still inadequate i.e. neutrophil count between 0.5-1.0 or platelet count between 50-100, same dose at 75% should be given.

Omission of Gemcitabine administration for one week:
On the day of next Gemcitabine treatment, give above dose according to neutrophil and/or platelet count on that day.

Omission of Gemcitabine administration for two or three weeks:
Give 75% of dose in all subsequent cycles even if neutrophil and/or platelet count has recovered completely.

Neutropenic sepsis:
Gemcitabine should be omitted during an episode of fever associated with a neutrophil < 0.5 x 10^9/l. Following an episode of febrile neutropenia, all subsequent cycles should be given at 75% dose.

Non-haematological toxicity:
Modifications are not required normally. In exceptional cases treatment delay may be necessary until the toxicity has resolved. If this happens, a 25% dose reduction should be made for subsequent cycles.

Gastrointestinal:
a) Abnormalities of liver transaminase enzymes occur in about two thirds of patients, but they are usually mild, non-progressive and rarely necessitate stopping treatment. However, Gemcitabine should be used with caution in patients with impaired liver function.
b) Nausea and vomiting are reported in one third of patients and are easily manageable with standard anti-emetics.

Renal:
Mild proteinuria and haematuria are reported in 50% of patients, but are rarely clinically significant and are not usually associated with any change in serum creatinine. However, in very rare instances, cases of haemolytic uraemic syndrome have been reported. Hence, Gemcitabine should be used with caution in patients with impaired renal function.

Allergy:
A rash is seen in approximately 25% of patients and sometimes associated with pruritus. The rash is usually mild and not dose-limiting. Anti-histamines may provide relief.

Oedema:
It occurs in approximately 30% of patients. Sometimes facial or pulmonary oedema may occur. It is usually mild to moderate, rarely dose-limiting and is usually reversible after stopping Gemcitabine treatment.

Flu-like illness:
20% of patients complain of fever, headache, back pain, chills, myalgia, asthenia and anorexia. Paracetamol may produce symptomatic relief.

10.3 Protracted venous infusion 5-FU

Dose Modification for infusional 5-FU Non Haematological Toxicity:

These guidelines apply to the use of protracted infusion 5FU in the following regimens:

CF, CarboF, ECF, ECarboF, MCF, EOF, continuous infusion 5FU

	Grade I	Grade II	Grade III	Grade IV
Stomatitis	Supportive measures	Stop chemo. Restart with 50mg/m^2 dose reduction	Stop chemo. Restart with 100mg/m^2 dose reduction.	Stop chemo. Restart with 150mg/m^2 dose reduction
	Commence Sucralfate mouthwash			
***Plantar-Palmar syndrome**	Supportive measures	Stop chemo. Restart with 50mg/m^2 dose reduction	Stop chemo. Restart with 100mg/m^2 dose reduction	- N/A -
	Commence Pyridoxine 50-150 mg po tds.			
Diarrhoea	Supportive measures	Stop chemo. Restart with 50mg/m^2 dose reduction	Stop chemo. Restart with 100mg/m^2 dose reduction	Stop chemo. Restart with 150mg/m^2 dose reduction

*The development of chronic toxicity, in particular, plantar palmar erythema with protracted venous infusion 5-fluorouracil is well recognised. In view of this, and knowledge of toxicity profiles with protracted venous infusion 5-FU, patients developing CTC grade 2 or 3 toxicity unresponsive to symptomatic measures after 10 weeks of treatment have been completed, should have treatment stopped until resolution of the toxicity. They do not need to have a dose reduction.

Chest pain: If patients develop angina during the 5FU treatment stop 5FU. Consider substitution of 5FU with Raltritrexed, e.g. Epirubicin 50mg/m^2 d1, Cisplatin 60 mg/m^2 d1, Raltritrexed 1 mg/m^2 d1 & 8 every 3 weeks.

Haematological Toxicity

Protracted infusion 5-FU is rarely associated with significant myelosuppression. When used in combination with Epirubicin, Mitomycin C or platinum drugs, haematological toxicity is likely to result from the other agent(s), so dose modification of 5-FU is rarely indicated.

For regimen-specific dose modifications see section10. Patients receiving protracted infusion 5-FU in combination with other agents presenting with myelosuppression at the time of the day 8 or day 15 pump change should be managed as follows:

ANC (x10^9/l)	Platelets (x10^9/l)	5-FU dose
≥0.5	≥50	100%
<0.5	<50	Omit 5-FU for 1 week and reassess

10.4 Bolus 5-FU Haematological Toxicity

- WBC <3.0, Neutrophils <1.5 or Platelets <100, delay dose for 1 week.
- If there are 2 delays for haematological toxicities- all subsequent doses should be at 75 %.
- Any further delays require doses to be 50% of 5 FU.

Non Haematological Toxicity

	Grade I	**Grade II**	**Grade III / Grade IV**
Stomatitis	Supportive measures	Stop until recovery, reduce dose to 75% for remainder	Stop until recovery then reduce dose to 50% for remainder
	Commence Sulcrulfate mouthwash		
Planter-Palmar syndrome	Supportive measures	Stop until recovery, reduce dose to 75% for remainder	Stop until recovery then reduce dose to 50% for remainder
	Commence Pyridoxine 50-150 mg po tds		
Diarrhoea	Supportive measures	Stop until recovery, reduce dose to 75% for remainder	Stop until recovery then reduce dose to 50% for remainder
	Commence codeine phosphate and/or loperamide		

10.5 Capecitabine

These guidelines apply to the use of Capecitabine in the following regimens: EOX, CX, CarboX, ECX, ECarboX, MCX, gemcitabine and capecitabine, streptozocin and capecitabine, single agent Capecitabine.

Non haematological toxicities:

Toxicity grading according to NCIC-CTC	**During a course of therapy**	**Dose adjustment for next cycle (% of starting dose)**
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
First appearance	Interrupt until resolved to grade 0-1	100%
Second appearance	Interrupt until resolved to grade 0-1	75%
Third appearance	Interrupt until resolved to grade 0-1	50%
Fourth appearance	Discontinue treatment permanently	
Grade 3		
First appearance	Interrupt until resolved to grade 0-1	75%
Second appearance	Interrupt until resolved to grade 0-1	50%

Third appearance	Discontinue treatment permanently	
Grade 4		
First appearance	Discontinue permanently *or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

All patients should be prescribed symptomatic treatment such as Loperamide, Sucralfate and Ppyridoxine for diarrhoea, stomatitis and hand-foot syndrome respectively.

Renal function:
For creatinine clearance 30-50 mls/min the dose of Capecitabine should be reduced by 25%. Capecitabine should not be administered to patients with creatinine clearance < 30 mls/min

Bilirubin:
Capecitabine can cause an increase in bilirubin and liver transaminases. This is usually mild and of no clinical significance. However, if the bilirubin increases to >3 x normal or AST / ALT increases to >2.5 x normal the Capecitabine should be withheld until the abnormalities correct, at which point treatment can recommence without dose reduction. If patients (with liver metastases) have abnormally elevated liver transaminases prior to commencing Capecitabine, then only changes in the bilirubin should be taken into account. If the bilirubin is >27 prior to commencing treatment then discuss with the consultant.

Chest pain: If patients develop angina during the Capecitabine treatment stop Capecitabine. Consider substitution of Capecitabine with Raltritrexed, e.g. Epirubicin 50mg/m^2 d1, Cisplatin 60 mg/m^2 d1, Raltritrexed 1 mg/m^2 d1 & 8 every 3 weeks.

Haematological toxicity
Capecitabine is rarely associated with significant myelosuppression. When used in combination with Epirubicin, Mitomycin C or platinum drugs, haematological toxicity is likely to result from the other agent(s), so dose modification of Capecitabine is rarely indicated. Regimen-specific dose modification guidelines are outlined in section10.

10.6 Cisplatin

Haematological Toxicity
Cisplatin at the doses used in the treatment of upper gastrointestinal cancers is rarely associated with significant myelosuppression. Regimen-specific dose modification guidelines are outlined in section 10.

Non-haematological Toxicity
Renal:
Cisplatin is nephrotoxic. Patients require assessment of GFR prior to Cisplatin administration, and the following dose adjustments instituted.

GFR (mls/min)	Cisplatin Dose
>60	100%
40-60	Dose (mg) = GFR (mls/min) Consider substitution with Carboplatin
30-40	Substitute with Carboplatin
<30	Omit platinum agent

Ototoxicity:
Cisplatin is associated with high frequency hearing loss and tinnitus. In the event of grade 2 or greater ototoxicity, Cisplatin should be substituted with Carboplatin. If grade 2 or greater ototoxicity persists, consideration should be given to discontinuing platinum therapy.

Other non-haematological toxicity:
Other grade 3 or 4 non-haematological toxicity should be managed by delaying further treatment until recovery to grade 1 or less and subsequent dose reduction by 25-100% dependent on assessment of causality.

10.7 Carboplatin

Haematological Toxicity

Neutrophils ($x10^9$/l) day Rx due	**CTC Grade**	**ACTION**
>1.5	0-1	Full dose
1.0-1.4	2	Delay until count recovers and restart at same dose.
0.5-0.9	3	Delay until recovery. Reduce to AUC 4 on subsequent cycles.
< 0.5 or neutropinic sepsis	4	Delay until recovery. Reduce to AUC 3 for subsequent cycles

Platelet Count (x10^9/l) day Rx due	CTC Grade	Action
>100	0	Full dose
75-99	1	Delay until count recovers and restart at same dose.
50-74	2	Delay until recovery. Reduce to AUC 4 on subsequent cycles.
<50	3-4	Delay until recovery. Reduce to AUC 3 for subsequent cycles.

Non-Haematological Toxicity
No dose modification is required for non-haematological toxicity.

Renal function should be monitored and in the event of elevation in serum creatinine to greater than 1.5 x baseline, the dose of Carboplatin should be recalculated using the Cockcroft/Gault formula initially, and if considered appropriate, the EDTA clearance repeated.

10.8 Epirubicin / Doxorubicin

Haematological Toxicity

Neutrophils (x10^9/l) day Rx due	CTC Grade	ACTION
>1.5	0-1	Full dose
1.0-1.4	2	Delay until count recovers and restart at same dose.
0.5-0.9	3	Delay until recovery. Reduce 25% on subsequent cycles.
< 0.5	4	Delay until recovery. Reduce by 50% for subsequent cycles.

Platelet Count (x10^9/l) day Rx due	CTC Grade	Action
>100	0	Full dose
75-99	1	Delay until count recovers and restart at same dose.
50-74	2	Delay until recovery. Reduce by 25% on subsequent cycles.
25-49	3	Delay until recovery. Reduce by 50% for subsequent cycles.
<25	4	Omit Epirubicin/doxorubicin in subsequent cycles

Non-Haematological Toxicity

Neutropenic Sepsis:

Grade 3 infection/fever associated with neutropenia (ANC<1) at any time on treatment requires a subsequent 25% dose reduction.

Grade 4 infection/fever associated with neutropenia at any time on treatment requires a subsequent 50% dose reduction**.**

Liver Function:

If bilirubin increases to > 1.5 ULN, Epirubicin/Doxorubicin should be omitted until bilirubin returns to acceptable levels.

Cardiac toxicity:

Any patients who develop unexplained cardiac failure while on treatment should undergo evaluation of cardiac function with a MUGA scan or echocardiogram. If left ventricular function is less than the lower limit of normal range then Epirubicin/Doxorubicin should be omitted.

Other non-haematological toxicity:

Other grade 3 or 4 non-haematological toxicity should be managed by delaying further treatment until recovery to grade 1 or less and subsequent dose reduction by 25-100% dependent on assessment of causality.

10.9 Mitomycin C

- If neutrophils <1.0x10^9/l or platelets <100x10^9/l delay for 1 week but recommence at full dose.
- If neutrophils remain <1.0x10^9/l or platelets <100x10^9/l delay for a further week and then proceed with a 25% dose reduction of MMC.
- If more than 2 weeks delay is required for recovery, omit that cycle of MMC and all following doses given with a 25% dose reduction.

Toxicity grading NCI CTC	Dose adjustment for next cycle (% of starting dose)
Grade 3 neutropenic sepsis	75%
Grade 4 neutropenic sepsis	50%
Incipient haemolytic uraemic syndrome (HUS: red cell fragments on blood film) / HUS	Cease MMC

10.10 Streptozocin

Haematological Toxicity

Neutrophils ($x10^9$/l) day Rx due	**CTC Grade**	**ACTION**
>1.5	0-1	Full dose
1.0-1.4	2	Delay until count recovers and restart at same dose.
0.5-0.9	3	Delay until recovery. Reduce 25% on subsequent cycles.
< 0.5	4	Delay until recovery. Reduce by 50% for subsequent cycles.

Platelet Count ($x10^9$/l) day Rx due	**CTC Grade**	**Action**
>100	0	Full dose
75-99	1	Delay until count recovers and restart at same dose.
50-74	2	Delay until recovery. Reduce by 25% on subsequent cycles.
25-49	3	Delay until recovery. Reduce by 50% for subsequent cycles.
<25	4	Omit in subsequent cycles

Non-Haematological Toxicity

Renal:
Streptozocin is nephrotoxic. Serum creatinine should be monitored, and GFR estimated prior to each cycle. If GFR<60 mls/min, discuss with consultant.

Hypoglycaemia:
This may be a problem during infusion and it is therefore important to monitor blood glucose readings during treatment.

10.11 Oxaliplatin

Haematological Toxicity
See section 10 for dose modifications of oxaliplatin for haematological toxicity when used in combination regimens.

Non-haematological Toxicity
Renal:
Oxaliplatin can be safely continued unless creatinine clearance falls below 30mls/minute; in which case it should be omitted until renal function recovers.

Neurotoxicity:

Toxicity	Duration of toxicity 1-7 days	Duration of toxicity >7days	Persistent between cycles
Cold-related dysaesthesia	No reduction	No reduction	Withhold oxaliplatin until recovery then restart at 100mg/m^2. Omit oxaliplatin if recurs.
Paraesthesia without pain	No reduction.	No reduction.	Withhold oxaliplatin until recovery then restart at 100mg/m^2. Omit oxaliplatin if recurs.
Paraesthesia with pain	No reduction.	Reduce to 100mg/m^2. Omit oxaliplatin if recurs.	Omit oxaliplatin.
Paraesthesia with functional impairment	No reduction.	Reduce to 100mg/m^2. Omit oxaliplatin if recurs.	Omit oxaliplatin.

If oxaliplatin is omitted due to neurotoxicity, consider substitution with Carboplatin AUC5 (i.e. ECarboX/F or CarboX/F regimen).

11.0 Guidelines on the Management of Haematological Toxicity of Combination Chemotherapy Regimens

11.1 Cisplatin + 5FU/Capecitabine (CF/X)

Treatment may proceed if Neutrophils >1.0 x 10^9/l, Platelets >100 on day 1

If treatment delay is required as a result of haematological toxicity then appropriate dose reduction should be discussed with the consultant.

11.2 Carboplatin + 5FU (Carbo F/X)

Neutrophils (x10^9/l) on day 1 of cycle	**CTC Grade**	**ACTION**
>1.5	0-1	Full dose of Carboplatin and 5FU/Capecitabine
1.0-1.4	2	Continue 5FU/Capecitabine and delay Carboplatin until count recovers and restart at same dose.
0.5-0.9	3	Stop 5FU/Capecitabine and delay Carboplatin until recovery. Restart 5FU/Capecitabine at the same dose and reduce Carboplatin to AUC 4 on subsequent cycles.
< 0.5	4	Stop 5FU/Capecitabine and delay Carboplatin until recovery. Restart 5FU/Capecitabine at same dose and reduce Carboplatin to AUC 3 for subsequent cycles.

Platelet Count (x10^9/l) on day 1 of cycle	**CTC Grade**	**Action**
>100	0	Full dose of Carboplatin and 5FU/Capecitabine.
75-99	1	Continue 5FU/Capecitabine and delay Carboplatin until recovery. (>100) Restart at same dose.
50-74	2	Continue 5FU/Capecitabine and delay Carboplatin until recovery Reduce Carboplatin to AUC 4 on subsequent cycles.
25-49	3	Stop 5FU/Capecitabine & delay Carboplatin until recovery. Restart 5FU/Capecitabine at same dose and reduce Carboplatin to AUC 3 for subsequent cycles
<25	4	Stop 5FU/Capecitabine & delay Carboplatin until recovery. Restart 5FU/Capecitabine at same dose and reduce Carboplatin to AUC 3 on subsequent cycles

11.3 ECF/X

Neutrophil count ($x10^9$/l) on day 1 of cycle	CTC Grade	Action
>1.5	0-1	Full dose of all drugs
1.0-1.4	2	Continue 5FU/Capecitabine and delay Epirubicin and Cisplatin until count recovers and restart all drugs at same dose.
0.5-0.9	3	Stop 5FU/Capecitabine and delay Epirubicin and Cisplatin until recovery. Restart 5FU/Capecitabine and Cisplatin at full dose. Reduce Epirubicin by 25% on subsequent cycles.
<0.5	4	Stop 5FU/Capecitabine and delay Epirubicin and Cisplatin until recovery. Restart 5FU/Capecitabine and Cisplatin at full dose. Reduce Epirubicin by 50% on subsequent cycles.

Platelet Count ($x10^9$/l) on day 1 of cycle	CTC Grade	Action
>100	0-1	Full dose of all drugs
75-99	1	Continue 5FU/Capecitabine and delay Epirubicin and Cisplatin until count recovers and restart all drugs at same dose.
50-74	2	Stop 5FU/Capecitabine and delay Epirubicin and Cisplatin until recovery. Restart 5FU/Capecitabine and Cisplatin at full dose. Reduce Epirubicin by 25% on subsequent cycles.
25-49	3	Stop 5FU/Capecitabine & delay Epirubicin and Cisplatin until recovery. Restart 5FU/Capecitabine and Cisplatin at full dose and reduce Epirubicin by 50% on subsequent cycles
<25	4	Stop 5FU/Capecitabine and delay Cisplatin until recovery. Restart 5FU/Capecitabine and Cisplatin at full dose. Omit Epirubicin on subsequent cycles.

11.4 ECarboF/X

Neutrophil count (x10^9/l) on day 1 of cycle	CTC Grade	ACTION
>1.5	0-1	Full dose of all drugs
1.0-1.5	2	Continue 5FU/Capecitabine and delay Carboplatin and Epirubicin until recovery restart at same dose.
0.5-0.9	3	Stop 5FU/Capecitabine and delay Epirubicin and Carboplatin until recovery. Restart 5FU/Capecitabine at same dose. Reduce Epirubicin by 25%, Carboplatin AUC 4 on subsequent cycles.
<0.5	4	Stop 5FU/Capecitabine and delay Epirubicin and Carboplatin until recovery. Restart 5FU/Capecitabine at same dose. Reduce Epirubicin by 50%, Carboplatin AUC 3 on subsequent cycles.

Platelet Count (x10^9/l) on day 1 of cycle	CTC Grade	Action
>100	0	Full dose of all drugs
75-99	1	Continue 5FU/Capecitabine and delay Carboplatin and Epirubicin until recovery (>100) restart at same dose
50-74	2	Stop 5FU/Capecitabine and delay Epirubicin and Carboplatin until recovery. Restart 5FU at same dose. Reduce Epirubicin by 25%, Carboplatin AUC 4 on subsequent cycles.
25-49	3	Stop 5FU/Capecitabine & delay Epirubicin and Carboplatin until recovery. Restart 5FU/Capecitabine at same dose. Reduce Epirubicin by 50% and Carboplatin AUC 3 on subsequent cycles
<25	4	Stop 5FU/Capecitabine and delay Carboplatin until recovery. Restart 5FU/Capecitabine at full dose. Omit Epirubicin and reduce Carboplatin to AUC 3 on subsequent cycles

11.5 EOF/X

Neutrophil count ($x10^9$/l) on day 1 of cycle	**CTC Grade**	**ACTION**
>1.0	0-2	Full dose of all drugs
0.5-0.9	3	Stop 5FU/Capecitabine and delay Epirubicin and Oxaliplatin until recovery. Restart 5FU/Capecitabine at same dose. Reduce Epirubicin by 25%, Oxaliplatin 100mg/m^2 on subsequent cycles.
<0.5	4	Stop 5FU/Capecitabine and delay Epirubicin and Oxaliplatin until recovery. Restart 5FU/Capecitabine at same dose. Reduce Epirubicin by 50%, Oxaliplatin 100mg/m^2 on subsequent cycles.

Platelet Count ($x10^9$/l) on day 1 of cycle	**CTC Grade**	**Action**
>75	0-1	Full dose of all drugs
50-74	2	Stop 5FU/Capecitabine and delay Epirubicin and Oxaliplatin until recovery. Restart 5FU/Capecitabine at same dose. Reduce Epirubicin by 25%, Oxaliplatin 100mg/m^2 on subsequent cycles.
25-49	3	Stop 5FU/Capecitabine and delay Epirubicin and Oxaliplatin until recovery. Restart 5FU/Capecitabine at same dose. Reduce Epirubicin by 50%, Oxaliplatin 100mg/m^2 on subsequent cycles.
<25	4	Stop 5FU/Capecitabine and delay Oxaliplatin until recovery. Restart 5FU/Capecitabine at full dose. Omit Epirubicin and reduce Oxaliplatin to 100mg/m^2 on subsequent cycles

12.0 Appendix A: Clinical Trials

Refer to the local research team who will provide on request an orientation handbook, list of current trials and associated trial protocols and summaries.

Contact numbers

MTW – Clinical Trials Office	01622 225033
Darent Valley Hospital – Clinical Trials Office	01322 428100 ext 4810
Medway Maritime Hospital – Clinical Trials Office	01634 825094

East Kent Hospitals – Clinical Trials Office:

Solid Tumours (excluding Gynae)	01227 866393
Gynae Clinical Trials	01843 234343
Haematology Clinical Trials	01227 864129

13.0 Appendix B: KMCN guidelines on managing cardiac toxicity for patients receiving trastuzumab

- The same monitoring modality should be used throughout the course of treatment and, where possible, this should also include the same operator, machine, and calculation algorithm. Each institution should establish a normal range for the methods used. On the basis that an echocardiogram exposes the patient to less radiation and is usually less expensive than a MUGA scan, the NOG recommend this as the method used to assess cardiac function. ECHOs are reported as a range not an absolute figure, but it is generally accepted that the lower limit of normal (LLN) for cardiac function when measured by an ECHO is 55%.

- Patients developing signs and symptoms of heart failure should have their trastuzumab treatment interrupted, have ACE inhibitor therapy initiated by the oncologist and be referred to a cardiologist. Investigation and treatment is recommended in accordance with present guidelines (NICE, 2003; Bonow et al 2005; Swedberg et al 2005).

- It is the prescriber's responsibility to check that the ECHO/MUGA is satisfactory before continuing treatment.

    - An ECHO/ MUGA should be carried out every 6 months

NB When an ECHO is used to measure cardiac function, LLN can be assumed to be 55%. For MUGA scans, the LLN for the institution should be used.

Comment [JW1]: These guidelines don't quite fit the UGI situation as we don't give chemo prior to the start of Herceptin and would not plan anthracycline chemotherapy in patients having trastuzumab

Comment [WS2]: We have amended slightly and removed traffic light guidance – are you happy with this?

14.0 Personnel and Contact Information

A comprehensive, up to date list of MDM contact details can be found on the KMCN website via the following link: http://www.KMCC.nhs.uk

15.0 Glossary

Acronyms in common usage throughout KMCN documentation

CNB	Cancer Network Board
CYP	Children & Young People (in relation to the IOG)
DCCAG	Diagnostic Cross Cutting Advisory Group
DOG	Disease Orientated Group (NSSG/TSSG/TWG)
DVH	Darent Valley Hospital
EK	East Kent
EKHUFT	East Kent Hospitals University Foundation Trust
HoP	High Level Operational Policy
IOSC	Improving Outcomes: A Strategy for Cancer
K&C	Kent & Canterbury Hospital, Canterbury, (EKHUFT)
KMCN	Kent & Medway Cancer Network
KMCRN	Kent & Medway Cancer Research Network
LSESN	London & South East Sarcoma Network
MFT	Medway Foundation Trust
MTW	Maidstone & Tunbridge Wells NHS Trust
NOG	Non Surgical Oncology Group *(Permanent oncologist sub group of the DOGs with a specific responsibility for chemo/rad pathways and advice to the DOG, Network and GEOGRAPHICAL LOCATIONs on new drugs)*
PoC	Pathway of Care *(Network agreed disease site specific clinical guidelines)*
QEQM	Queen Elizabeth the Queen Mother Hospital, Margate (EKHUFT)
QoL	Quality of life
RAT	Research and Trial Group *(Permanent sub-group of the DOGs with a specific responsibility for taking forward the clinical trials agenda)*
RMH	Royal Marsden Hospital
RNOH	Royal National Orthopaedic Hospital
QVH	Queen Victoria Foundation Trust Hospital East Grinstead
UCLH	University College Hospital London
WHH	William Harvey Hospital, Ashford (EKHUFT)
WK	West Kent

16.0 Document Administration

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