CLINICAL PRIORITIES ADVISORY GROUP
06 and 07 November 2018

Agenda Item No	02.1
National Programme	Cancer
Clinical Reference Group	Chemotherapy
URN	170101P

Title
Clinical Commissioning Policy: Gemcitabine and capecitabine for adjuvant treatment in resected pancreatic cancer (all ages).

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
The policy proposition recommends that capecitabine, an off-label chemotherapy drug, be made routinely available in conjunction with gemcitabine to treat pancreatic cancer following potentially curative surgery where histology confirms that the resection has achieved either microscopic clearance (R0) or microscopic infiltration (R1) margins. It is important to note that gemcitabine is the current pancreatic cancer standard of care adjuvant treatment (which means a treatment given after an initial treatment) where potentially curative surgery has been undertaken. Therefore, in practice, the policy proposition recommends that capecitabine is added to the current standard of care. This is in accordance with Clinical Guideline 85 (National Institute of Health and Care Excellence, 2018).

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report

2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Operational Delivery Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

No	*Metric*	*Summary from evidence review*
1.	Survival	Overall survival (OS) is a measure of how long from the start of treatment people are expected to live. It is not restricted to deaths that are disease-related; deaths of any cause are accounted for. The median (a particular way of measuring the average) OS was 25.5 months in the gemcitabine group. The result provides an estimate of the true value of OS of the treatment. The probability that the true value is contained within the range of 22.7 – 27.9 months is 95%. The median OS was 28.0 months in the gemcitabine plus capecitabine group. The probability that the true value is contained within the range of 23.5 – 31.5 months is 95%. The results mean that people having gemcitabine plus capecitabine instead of gemcitabine alone after potentially curative surgery for pancreatic cancer could expect to live on average for an extra 2.5 months. In people who had negative resection margins after surgery (this means no cancer cells were seen at the outer edge of the tissue that was removed and suggests that all of the tumour was taken out) gemcitabine plus capecitabine was shown to have a significant treatment effect on OS compared with gemcitabine alone. However, in those who had positive resection margins after surgery (some cancer cells were seen at the outer edge of the tissue that was removed suggesting

		that some of the tumour was left behind), gemcitabine plus capecitabine was not shown to have a significant treatment effect on OS compared with gemcitabine alone. Caution should be exercised when looking at the results for these subgroups of people with negative and positive resection margins as the study was powered (a way of planning how many participants or events need to be in a study to show a difference between 2 treatments) for the outcome of overall survival for the whole group. In people who had negative resection margins after surgery, gemcitabine plus capecitabine increased median OS by 11.6 months compared with gemcitabine alone. Median OS was 27.9 months in the gemcitabine group compared with 39.5 months in the gemcitabine plus capecitabine group. In people who had positive resection margins after surgery, median OS was 23.0 months in the gemcitabine group compared with 23.7 months in the gemcitabine plus capecitabine group. At 12 months an estimated 80.5% of people in the gemcitabine group and 84.1% in the gemcitabine plus capecitabine group were still alive. At 24 months an estimated 52.1% of people in the gemcitabine group and 53.8% in the gemcitabine plus capecitabine group were still alive. At 5 years an estimated 16.3% of people in the gemcitabine group and 28.8% in the gemcitabine plus capecitabine group were still alive. This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 730 adults with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The study ran for approximately 7.5 years but participants could be recruited to the study at any time during the first 6 years. The median follow-up time (the time a person was in the study from study entry until they died or if they were still alive the study ended) was 43.2 months.
2.	Progression free survival	Progression free survival (or relapse free survival) is a measure of how long from the start of treatment people can expect to remain both alive and free of disease progression or relapse.

		The median progression free survival was 13.1 months in the gemcitabine group. The result provides an estimate of the true value of progression free survival of the treatment. The probability that the true value is contained within the range of 11.6 – 15.3 months is 95%. The median progression free survival was 13.9 months in the gemcitabine plus capecitabine group. The probability that the true value is contained within the range of 12.1 – 16.6 months is 95%. The results mean that people taking gemcitabine plus capecitabine instead of gemcitabine alone after potentially curative surgery for pancreatic cancer can expect no difference in how long they live without disease progression or relapse. At 3 years 20.9% of people in the gemcitabine group and 23.8% in the gemcitabine plus capecitabine group were still alive and had not had disease progression or relapse. At 5 years 11.9% of people in the gemcitabine group and 18.6% in the gemcitabine plus capecitabine group were still alive and had not had disease progression or relapse. This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 730 adults with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The median follow-up time was 43.2 months.
3.	Safety	Adverse effects of treatment: There was no difference between gemcitabine alone and gemcitabine plus capecitabine for treatment-related serious adverse events: 151 events reported by 26% of people in the gemcitabine group compared with 154 events reported by 24% of people in the gemcitabine plus capecitabine group. The study did not report how it defined treatment-related serious adverse events. Adverse events were graded according to the National Cancer Institute common toxicity criteria, which grades adverse events on a scale of 1 to 5 with 4 being the most serious adverse event and 5 being death. There were 481 grade 3-4 adverse events reported by 54% people in the gemcitabine

		group compared with 608 events reported by 63% people in the gemcitabine plus capecitabine group. Frequencies of grade 3-4 adverse events were also presented by symptom or system type. There was a higher percentage of people who had grade 3-4 adverse events of diarrhoea, neutropenia (a low level of neutrophils, a type of white blood cell), and hand-foot syndrome (a skin reaction) in the gemcitabine plus capecitabine group compared with the gemcitabine group. There was a lower percentage of people who had grade 3-4 adverse events of infection and other infestations (adverse event category not defined in the paper) in the gemcitabine plus capecitabine group compared with the gemcitabine group: • Diarrhoea: 2% in the gemcitabine group compared with 5% in the gemcitabine plus capecitabine group • Neutropenia: 24% in the gemcitabine group compared with 38% in the gemcitabine plus capecitabine group • Hand-foot syndrome: No people in the gemcitabine group compared with 7% people in the gemcitabine plus capecitabine group • Infections and other infestations: 7% in the gemcitabine group compared with 3% in the gemcitabine plus capecitabine group. For the other grade 3-4 adverse events of anaemia, fatigue, fever, decreased lymphocyte count (a type of white blood cell), platelets, thromboembolic events (blood clots), decreased white blood cell count, acute kidney injury, multi-organ failure, cardiac disorders and benign, malignant and unspecified neoplasms there was no difference in the percentage of people who had these events between the 2 groups. There were 6 grade 5 events (death due to an adverse event); 5 in the gemcitabine group and 1 in the gemcitabine plus capecitabine group. These results mean that if people had gemcitabine plus capecitabine instead of gemcitabine alone: • the percentage of people who have a grade 3-4 adverse event of diarrhoea could rise from 2% (2 in 100 people) to 5% (5 in 100 people) • the percentage of people who have a grade 3-4 adverse event of neutropenia could rise from 24% (24 in 100 people) to 38% (38 in 100 people) • the percentage of people who have a grade 3-4 adverse event of hand-foot syndrome could rise from 0 to 7% (7 in 100 people)

		• the percentage of people who have a grade 3-4 adverse event of infections and other infestations could fall from 7% (7 in 100 people) to 3% (3 in 100 people). This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 725 adults in the safety analysis with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The median follow-up time was 43.2 months.

Other health metrics determined by the evidence review		
No	Metric	Summary from evidence review
1.	Participants who stopped treatment	This outcome considered how many people had to stop taking their treatment before completing the full 6 cycles of chemotherapy because of side-effects, 14% of people in the gemcitabine group and 22% of people in the gemcitabine plus capecitabine group stopped treatment early due to side-effects. This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 730 adults with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The median follow-up time was 43.2 months.
2.	Quality of life	Quality of life was assessed using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ). This questionnaire asks questions about how symptoms or side-effects impact on a variety of aspects of daily living, family life and social activities and asks questions about how people feel and their mood. There was no difference on quality of life questionnaire results by treatment group. The results mean that people taking gemcitabine plus capecitabine instead of gemcitabine alone after potentially

		curative surgery for pancreatic cancer can expect no difference in their quality of life. This evidence is from a study which clearly stated and described the research questions, aims, design and methods. The study population included 730 adults with the indication and characteristics of interest and the results are generalisable to a UK population (76% of participants were from the UK). The study was randomised, so neither the people in the study nor the study investigators could choose which treatment a person had. However, the study was open label; participants and study investigators knew what treatment people had and so there is a high risk of bias. The median follow-up time was 43.2 months. The figures reported in the study, for the number of people who completed the questionnaire were inconsistent. The study did not report the questionnaire results from each group.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This policy recommends gemcitabine and capecitabine as adjuvant treatment for resected pancreatic cancer. This is an off label use for this combination. Both are excluded from tariff.

Considerations from review by National Programme of Care
The proposal received the full support of the Cancer PoC Board on Wednesday 12th September 2018.