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Mr D.M. Salter
Oxfordshire Coroner's Office
The Oxford Register Office
2nd Floor
1 Tidmarsh Lane
Oxford
OX1 1NS

31st January 2020

Dear Mr Salter,

Re: Regulation 28 Report to Prevent Future Deaths – pneumonia due to chemotherapy toxicity in consequence to gall bladder cancer (14 February 2019)

Thank you for your Regulation 28 Report dated 20 August 2019 concerning the death of Thelma Joyce on 14 February 2019. Firstly, I would like to express my deep condolences to Mrs Joyce's family.

The regulation 28 report concludes Thelma Joyce's death was a result of pneumonia due to chemotherapy toxicity in consequence to gall bladder cancer.

Following the inquest you raised concerns in your Regulation 28 Report to NHS England regarding the possible need for updated guidance in respect of testing for dihydropyrimidine dehydrogenase (DPD) deficiency for patients due to embark on capecitabine or 5FU chemotherapy.

Gall bladder cancer is a rare cancer and in the UK there are around 1,000 new cases diagnosed each year. Where diagnosed at an early stage, surgical removal is the preferred treatment and offers the potential of cure or long-term survival. In some cases, surgery is supplemented with either chemotherapy or radiotherapy treatment. Where chemotherapy is used, the medicines used are typically off label, i.e., licensed for another condition. This is the case for both capecitabine and 5FU.

Where using off label medicines, Trusts are required to consider and agree internal governance arrangements prior to treating patients. Both Trusts and individual prescribers are also expected to have and adhere to policies relating to the safe prescribing and monitoring of off-label licensed medications, including compliance with MHRA safety alerts. In this case, [redacted] written evidence sets out that the risks of treatment were explained and that Mrs Joyce received written material produced by Macmillan about capecitabine.

More broadly, both capecitabine and 5FU belong to a group of chemotherapy medicines known as fluoropyrimidines. These medicines are known to present increased risks for patients that have either a complete or partial DPD deficiency and, although very rare, such complications can be fatal. While a complete deficiency is extremely rare and is usually diagnosed in childhood, it is thought that between 2 and 8 in every 100 people have a partial deficiency (Cancer Research UK).

In relation to the matter of concern raised, evidence as to the adequacy of DPD testing has hitherto been far from compelling, which is alluded to in your report. Underlining this, the European Medicines Agency (EMA) in March 2019 began a review of the evidence for testing and use of these medicines under Article 31 of Directive 2001/83/EC. Ultimately, the review may result in changes to marketing authorisations of the relevant medicines which would be mandatory. While these medicines are unlicensed for use in gall bladder cancer, it would be normal practice for marketing authorisation requirements, such as for testing and patient monitoring, to also apply to off label uses and would be managed through Trust arrangements for off label medicines. The EMA review is not yet complete.

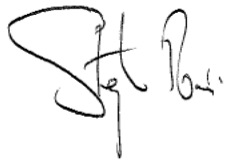
In England, the NHS Long Term Plan sets out the ambition and commitment to establish a genomics service providing access to cutting edge genomic technologies which will help to pave the way for wider advances, particularly in relation to personalised medicine. The introduction of an effective testing strategy for DPD deficiency, to better tailor treatment decisions to individual patients, is a clear example of this. To that end, I can confirm that work to review the evidence for DPD testing is underway within NHS England and NHS Improvement, with a view to reaching a decision about whether to routinely commission DPD testing and include the testing within the National Genomic Test Directory. A decision is expected to be made by April 2020 and, if approved, will be supported with a plan for implementation in order to achieve equitable access to testing across England.

Alongside this, steps have been taken to ensure a supply of a medicine called uridine triacetate within England. The medicine can sometimes reverse the complications of serious toxicity following exposure to fluoropyrimidines, when it is administered within 96 hours of exposure. The treatment is not currently licensed in the UK or Europe and has not, until recently, been readily available outside North America. An urgent policy statement, setting out NHS England and NHS Improvement's commissioning arrangements for this medicine is expected to be published in March 2020.

In line with our normal practices, both the updated Test Directory and the urgent policy statement will be published on NHS England and NHS Improvement's website and Trusts will receive written notification of changes.

Thank you for bringing this important patient safety issue to my attention and please do not hesitate to contact me should you need any further information.

Yours sincerely,



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NHS England and NHS Improvement