A R W Forrest LLM, FRCP, FRCPath
GMC Number: 1333523
Her Majesty's Senior Coroner for South Lincolnshire

REGULATION 28: REPORT TO PREVENT FUTURE DEATHS (1)

*NOTE: This form is to be used **after** an inquest.*

	REGULATION 28 REPORT TO PREVENT FUTURE DEATHS **THIS REPORT IS BEING SENT TO:** 1. [redacted] **Chair, Standard Safety Quality Committee, Intensive Care Society** 2. [redacted] **Senior Secretary, British Society of Gastroenterology** 3. [redacted] **Senior Medical Advisor, British National Formulary Publications** 4. [redacted] **Director, Vigilance and Risk Management of Medicines MHRA** 5. [redacted] **Clinical Director, TPP** 6. [redacted] **Medical Director, Lincolnshire Community Health Services** 7. [redacted] **Medical Director, United Lincolnshire Hospitals NHS Trust**
1	**CORONER** I am ARW Forrest, Senior Coroner for the Coroner's area of South Lincolnshire.
2	**CORONER'S LEGAL POWERS** I make this report under paragraph 7, Schedule 5, of the Coroners and Justice Act 2009 and regulations 28 and 29 of the Coroners (Investigations) Regulations 2013.
3	**INVESTIGATION and INQUEST** On 21st December 2012 I commenced an investigation into the death of Craig Adam

Unit 1, Gilbert Drive, Endeavour Park, Boston PE21 7TQ
Tel: 01522 553374 Fax: 01522 516717
Email: HMCoroner_Southlincolnshire@lincolnshire.gov.uk

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	WHITE, age 21. The investigation concluded at the end of the inquest on 10th January 2014. The conclusion of the inquest was MISADVENTURE due to disseminated tuberculosis.
4	**CIRCUMSTANCES OF THE DEATH** Craig Adam White was a 21 year old student, in his final year at Lincoln University. He was born and brought up in Lincolnshire, an area with a low incidence of tuberculosis. He received BCG immunisation as a child. He developed Crohn's disease at the age of 16. Eventually good control of the disease was achieved with a regimen that included treatment with Azothioprine and infusions of Infliximab every 8 weeks. Infliximab was administered in hospital by a nurse on a gastro-intestinal ward. A letter was not sent to Craig's general practitioner after each infusion. Infliximab is a monoclonal antibody which inhibits the activity of the Cytokine Tumour Necrosis Factor Alpha. This blocks part of the pathological mechanism of Crohn's disease, but also inhibits the body's response to infection and, in particular Tuberculosis. Because the drug was prescribed and administered entirely by secondary care practitioners, it did not appear on the System One Home screen that would be consulted when Craig consulted his primary health care providers. Before starting treatment with Infliximab he had been screened for latent tuberculosis by Chest X-ray, history and his BCG immunisation scar being noted. His Crohn's disease was biopsy proven and review of the biopsies after his death confirmed the diagnosis and excluded his gastro-intestinal illness being an atypical presentation of tuberculosis. From September 2012 onward Craig presented to the University Health service at Lincoln with recurrent chest infections. He did not see a registered medical practitioner there. The experienced nurse practitioner / independent nurse provider who saw him on several occasions gave evidence that she knew Craig was on Infliximab, that she knew it was an immunosuppressant but did not know of the increase risk it posed of tuberculosis. At the inquest she took roughly 7 minutes to find the relevant section (10.1.3) of the British

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National Formulary that draws attention to the increased risk of tuberculosis.

Craig did not respond to first line antibiotic treatment for his chest infection. Treatment with two second/third line antibiotics, Clarithromycin and Ciprofloxacin, which have some limited activity against tuberculosis, produced temporary improvement in his condition. On 31st October 2012, Craig consulted a general practitioner with 10 years experience in Boston (Lincolnshire) with a history of recurrent chesty cough. Only a subset of Craig's clinical record was available on the System One E-records available to the GP. Craig told the GP that he was being treated with Infliximab and Azothioprine for his Crohn's disease. The GP gave evidence that he was aware of the association of treatment with Infliximab and tuberculosis. He was aware from his own practice of the very low incidence of TB in those born and brought up in Lincolnshire. He arranged for blood tests including full blood count, urea and electrolytes and a C- reactive protein and a Chest X-Ray. These showed a raised C reactive protein, a low white blood cell count, a marginally reduced plasma sodium and a small right sided pleural effusion. The doctor decided to prescribe a 3rd line antibiotic (Ciprofloxacin) and to wait and see if the clinical picture improved.

On 30th November Craig became acutely ill, he was confused, he fitted in the Accident and Emergency department at Pilgrim Hospital and was taken to the Intensive Therapy Unit. After a CT scan, done primarily to establish it was safe to perform a lumbar puncture, a lumbar puncture was done. This only showed a small elevation in protein concentration. Craig was sedated and treated with antibiotics and the anti-viral drug Acyclovir. The following day he was extrubated and transferred to a general medical ward. Whilst there, he had a fluctuating level of consciousness. An MRI done on 5th November 2012 showed changes suggestive of Leptomeningitis. He was prescribed further antibiotics, including Co-trimoxazole. A further CT scan was done on 9th December 2012. Again this was primarily to assess the safety of a lumbar puncture. On this occasion the tests requested on the CSF included a Polymerase Chain Reaction

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	(PCR) test for tuberculosis. Specific treatment for tuberculosis meningitis was not initiated at that point. Craig was readmitted to the ITU on 9th December 2012. Review by Intensivists, Gastroenterologists and a Neurologist on 9th and 10th December 2012 produced a differential diagnosis of Multi-Focal Leukeoencephalopathy, Listeria Meningitis, Crytococcal Meningitis, TB Meningitis and Aseptic Meningitis. Amphotericin was added to his treatment. Specific treatment for tuberculosis was not administered. Evidence was given that at that point "Gold Standard" treatment for tuberculosis meningitis would have had a less than 80% chance of resulting in Craig's survival. Craig's condition deteriorated and at 17.30 hours on 12th December 2012, just before the first set of tests to confirm a diagnosis of Brain Stem Death were to be carried out, the consultant Intensivist received a call from the Microbiology Laboratory informing him that a positive result for tuberculosis had been found on PCR testing of the cerebro-spinal fluid sample obtained on 9th December 2012. At Post Mortem Craig was found to have widely disseminated tuberculosis in his chest and abdomen as well as Tuberculosis Leptomeningitis, early Cerebritis and abscess formation in his brain with an acute thrombosis in the sigmoid sinus. An epidemiological investigation by Public Health England has not revealed how Craig came to be infected with tuberculosis.
5	**CORONER'S CONCERNS** During the course of the inquest the evidence revealed matters giving rise to concern. In my opinion there is a risk that future deaths will occur unless action is taken. In the circumstances it is my statutory duty to report to you. The **MATTERS OF CONCERN** are as follows. – 1 Protocols for pre-Infliximab treatment screening for tuberculosis 2 Awareness of Health Care Professionals, in particular prescribers of the increased risk of TB inherent Infliximab treatment

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	3 The need for continuing patient education about the risks of Infliximab treatment 4 The need for prompt treatment to be initiated when tuberculous meningitis is suspected
6	**ACTION SHOULD BE TAKEN** In my opinion action should be taken to prevent future deaths and I believe you and/or your organisation have the power to take such action.
7	**YOUR RESPONSE** You are under a duty to respond to this report within 56 days of the date of this report, namely by **13th March 2014**. I, the coroner, may extend the period. Your response must contain details of action taken or proposed to be taken, setting out the timetable for action. Otherwise you must explain why no action is proposed.
8	**COPIES and PUBLICATION** I have sent a copy of my report to the Chief Coroner and to the following Interested Persons [redacted] I have also sent it to [redacted] Prescribing Advisor, Great East Midlands Commissioning Support Group, and to [redacted] Public Health Physician, who may find it useful or of interest. I am also under a duty to send the Chief Coroner a copy of your response. The Chief Coroner may publish either or both in a complete or redacted or summary form. He may send a copy of this report to any person who he believes may find it useful or of interest. You may make representations to me, the coroner, at the time of your response, about the release or the publication of your response by the Chief Coroner.
9	**14th January 2014** **ARW Forrest**..... **H M Senior Coroner for South Lincolnshire**

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