Coroners Act, 1996
[Section 26(1)]

Western  ***Australia***

RECORD OF INVESTIGATION INTO DEATH

Ref No: 20/16

I, Rosalinda Vincenza Clorinda FOGLIANI, State Coroner, having investigated the death of ***Jared Charles OLSEN****, with an Inquest held at Perth Coroner's Court, 501 Hay Street Perth on 8-10 June 2016 and 28 June 2016 and 13 October 2016 find that the identity of the deceased person was* ***Jared Charles OLSEN*** *and that death occurred on 5 March 2015 at Fiona Stanley Hospital, Murdoch as a result of fulminant sepsis (Klebsiella pneumoniae) with multi-organ failure complicating severe pancytopenia following the administration of 6-Mercaptopurine in a man with acute severe exacerbation of chronic colitis (Crohn's) and TPMT deficiency, in the following circumstances -*

Counsel Appearing:

Ms Kate Ellson assisting the State Coroner

Mr David Harwood (State Solicitors Office) appeared on behalf of Fiona Stanley Hospital Group and PathWest Laboratory Medicine WA, Department of Health, and the doctors from both of those entities.

Mr Daniel Brand (MDA National) appeared on behalf of Dr J Ravet

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INTRODUCTION

1. Mr Jared Charles Olsen (the deceased) died at Fiona Stanley Hospital (FSH) on 5 March 2015 after suffering complications from sepsis, brought on by a serious adverse reaction to a medication that had previously been prescribed to him at that hospital. He was 41 years old.

2. The deceased had a history of digestive problems and he had developed a mental health condition. Shortly before his death he was in severe pain and it is now known he was suffering from Crohn's colitis (one of the inflammatory bowel diseases). Untreated, Crohn's colitis can be an overwhelmingly debilitating condition. Its impact upon him was magnified by his depression and anxiety, all of which made him a vulnerable patient shortly before his death.

3. In early February 2015 the deceased sought medical attention for his escalating symptoms related to his digestive problems. This was the first time that he sought and received specialist treatment for what was subsequently identified to be Crohn's colitis. He initially presented to St John of God Murdoch (SJOG Murdoch) with a one-week history of abdominal pain, diarrhoea, and vomiting. He reported similar episodes over the previous four to five years but they had usually resolved spontaneously after one day. Those episodes had occurred approximately every four to six months.

4. A computed tomography (CT) scan was performed at SJOG Murdoch that showed colitis affecting the descending, transverse and ascending colon. He was transferred to FSH for further care, with a provisional diagnosis at that stage of new onset colitis.

5. The deceased was admitted to FSH upon his presentation at the emergency department (ED) on 4 February 2015. Following medical testing he was diagnosed with Crohn's colitis, though the possibility of ulcerative colitis could not be excluded. He also displayed symptoms of worsening depression.

6. Over the next few days, the deceased was initially treated with corticosteroids (steroids) but concerns emerged about the possible deleterious effect upon his mental state. The day before his discharge, the deceased was taken off the

steroids and commenced on the immunosuppressant drug 6-Mercaptopurine (6-MP) to help control inflammation of the bowel and maintain disease remission.

7. On 10 February 2015 the deceased was discharged from FSH because his treating clinicians felt that his colitis had sufficiently responded to treatment. In light of his ongoing mental health condition, arrangements were also made for him to be followed up by the community mental health team.

8. His father supported him after his discharge. The deceased continued to experience pain and discomfort, but was reluctant to draw attention to it. Alarmingly, on 1 March 2015, the deceased collapsed at his father's home. He was promptly transferred by ambulance to FSH.

9. Upon arrival at FSH ED he was in a critical and unstable condition. After initial resuscitation he was transferred to FSH's intensive care unit (ICU) and intubated the following day. A specialist medical team treated him around the clock.

10. Blood tests revealed the deceased had a severely low level of white cells and platelets. The 6-MP was withdrawn. The deceased was found to have ongoing gastrointestinal bleeding and he was diagnosed with septic shock and marrow aplasia (the causative organism was *Klebsiella pneumoniae*).

11. Very tragically, despite extensive resuscitation efforts, the deceased died on 5 March 2015. The bone marrow aplasia was attributed to 6-MP toxicity. The FSH clinician issued a death certificate, which has since been voided.

12. The deceased's death was unfortunately not reported to me until his father, Mr Phillip Charles Olsen wrote to me by letter dated 31 March 2015 and received by the court on 9 April 2015, outlining his concerns about medical treatment given to the deceased at FSH shortly before he died.

13. The deceased's father expressed a concern to the effect that his son died as a result of being prescribed the 6-MP medication by a clinician at FSH to treat his Crohn's colitis, in circumstances where he was unable to metabolise this

medication due to a severe and inherited deficiency in his enzyme activity.

14. The deceased's father was of the view that his son should have been tested for this enzyme activity before the drug was prescribed and administered to him. His letter included detailed information concerning his observations about his son's medical condition and treatment.

15. After inquiries were made, it became readily apparent that the deceased's death was a "*reportable death*" within the meaning of section 3 of the Coroners Act 1996 (the Coroners Act). I took jurisdiction and commenced a coronial investigation.

16. The delay in having this matter brought to my attention, and the burden upon the deceased's father in having to arrange for the notification himself, was wholly undesirable. The evidence concerning the possible reasons for this delay is addressed later in this finding.

17. The circumstances surrounding the deceased's death required careful and detailed examination. Regrettably by the time I received notification of this death, it was no longer practicable for me to direct a pathologist to perform a post mortem examination on the deceased's body and/or remove tissue samples for analysis.

18. It became necessary to examine the deceased's medical history, with particular focus on the detail of his medical treatment at FSH on his first admission between 4 and 10 February 2015, and the detail of the information disclosed by the results of his medical tests on his second admission between 1 and 5 March 2015. The medical information disclosed by those results, being proximate to his time of death, was critical in assisting me in making my finding on the cause of death.

THE DECEASED

19. The deceased was born in East Fremantle in 1973 into a close and loving family. He was one of two children, and like his mother, who was artistically gifted, he had planned to devote himself to a career in the arts. He attended the National Institute for Dramatic Art in Sydney (NIDA) graduating in 2005 with a Bachelor of Dramatic Arts (props).

20. The deceased began working in Sydney for theatres and the opera company. He specialised in stage props and make-up. Although he was very talented, and his work was used in many theatre and television productions, it was difficult for him to maintain continuous full time work in his chosen field.

21. His father's work took him to Sydney regularly and he had been able to visit his son often while he lived there. It was clear to him that his son had loved being at NIDA, he was engaged with his friends and the community around him, and he was enjoying his career in the arts.

22. Several years after the deceased graduated in Sydney, his mother, to whom he was very close, was diagnosed with cancer. This had a severe impact upon the deceased. He sold up and moved back to Western Australia to help care for her. Sadly after a time the deceased's mother died; her son's presence by her side as she bore her illness must have been a great comfort to her.

23. When the deceased moved to Perth, he struggled to find steady work in the arts. In order to be gainfully employed, he began working in the stores of Osborne Park Hospital. There, he appeared to enjoy his work, and he was popular with his colleagues. He worked at the Osborne Park Hospital for around two years, and rented a small unit close by. However, in around mid-2014, his contract came to an end.

24. At around this time, the deceased's pre-existing problems with his digestive system started to become worse, and he spent some periods of time staying with his father, who supported him emotionally. The deceased had suffered from depression and anxiety for a number of years. He had a history of significant alcohol consumption, would have exacerbated his conditions.

25. By early 2015, the deceased's physical and mental health conditions were becoming complex and difficult for him to bear without focussed and specialist medical intervention. Specialist treatment commenced for him in early February 2015. Approximately one month later, he very tragically died.

THE INQUEST

26. The deceased's death was a reportable death within the meaning of s 3 of the Coroners Act because it appeared to have been unexpected in that it followed the administration of a medication. It also appeared to have resulted at least indirectly from injury, being the damage to his immune system from medication that was unsuitable for him and that resulted in profound bone marrow suppression. Initially, it also appeared to be unnatural because CT imaging performed shortly before his death detected the presence of at least 20 tablet-like bodies in his bowel that could suggest a possible overdose, or an accumulation of tablets due to his bowel condition.

27. I held an inquest into the death and heard evidence from 15 witnesses between 8 to10 June 2016, and 28 June 2016, and 13 October 2016. I received 18 exhibits into evidence. Exhibit 1 contained 45 tabs. Exhibit 2 contained 3 tabs. Exhibit 3 contained 11 tabs. The final relevant exhibits were received into evidence on 19 April 2017 as Exhibits 18.1 and 18.2 respectively.

28. The focus of the inquest was on the deceased's first admission at FSH, and traversed his diagnosis, the initial treatment with steroids to treat his inflammation, the decision to prescribe the 6-MP medication, the steps taken to address his consent to treatment, the timing of medical tests undertaken to detect his enzyme activity, the reasons as to why the test results were not ascertained by the FSH clinicians, the plans for his follow up medical care after discharge, and the reasons as to why those plans failed in their implementation.

29. It is important that I state at the outset that I have no concerns about the deceased's medical treatment at FSH during his second admission. He was conveyed there by ambulance after his collapse at home, and despite all reasonable and proper efforts by the clinicians over a number of days, he was unable to be saved.

30. My primary function has been to investigate the deceased's death. It is a fact-finding function. Pursuant to s 25(1)(b) and (c) of the Coroners Act, I must find, if possible, how the deceased's death occurred and the cause of his death.

31. Pursuant to s 25(2) of the Coroners Act, in this finding I may comment on any matter connected with the deceased's death including public health, safety or the administration of justice. This is the ancillary function.

32. Section 25(5) of the Coroners Act prohibits me from framing a finding or comment in such a way as to appear to determine any question of civil liability or to suggest that any person is guilty of an offence. It is not my role to assess the evidence for civil or criminal liability, and I am not bound by the rules of evidence.

33. After some of the oral evidence was taken at the inquest, submissions were provided to me between 14 July 2016 and 4 August 2016. After the completion of the oral evidence on 13 October 2016, further submissions were provided to me between 10 and 16 November 2016.

34. My findings appear below.

6-MERCAPTOPURINE (6-MP)

35. The deceased died from complications following treatment with the medication 6-MP.

36. It is important to understand how the medication 6-MP is used to treat inflammatory bowel disease (IBD) and the reasons why a small proportion of the population may experience a toxic effect, resulting in bone marrow suppression. Untreated, this can be fatal. This is what happened in the case of the deceased because he came within that small proportion of patients who are not able to metabolise 6-MP. At the inquest I was assisted by expert evidence in this area.

37. IBD encompasses two different conditions, namely ulcerative colitis and Crohn's disease. They both result in inflammatory disorders of the intestine. The cause is presently unknown. IBD can create both acute severe conditions and also chronic disease. The principal symptoms are diarrhoea, bleeding from the bowel, abdominal pain, weight loss, and sometimes vomiting.[1]

[1] ts 12 to 13

38. Whilst ulcerative colitis and Crohn's disease have been viewed as two distinct entities, a large proportion of patients share the characteristics of the two conditions. The essential distinction is that ulcerative colitis is confined to the lining of the surface of the bowel and the colon, and spreads in a continuous distribution. In contrast, Crohn's disease is a full thickness disorder of the intestine, not only involving the superficial lining, but also the deeper layers of the intestine, and commonly occurs in a patchy distribution.[2]

39. A flexible sigmoidoscopy, being a limited examination of the lower part of the bowel for a variable distance (essentially a limited colonoscopy), can be helpful in distinguishing between ulcerative colitis and Crohn's disease. The distinction is important from a prognostic perspective, to assist in stratifying therapeutic options. However, in an acute setting, such as that faced by the deceased in February 2015, the distinction is not as important because treatment is the same.[3]

40. Medical investigations established that the deceased had a severe case of Crohn's disease or Crohn's colitis. Infection was excluded. In such a case there are various treatment options. Clinicians may commence with intravenous steroids in an effort to defuse the degree of inflammation. The next step would depend on whether the patient responds to that treatment after approximately two or three days.[4]

41. Steroids in high doses over a period of time can be noxious. Another treatment option is to commence a patient on the medication 6-MP for the longer-term treatment of the medical condition, with the aim of limiting the duration of the steroids, and to obtain a clinical remission. The deceased would have required ongoing treatment to avoid similar flare-ups of the condition in the future.[5]

42. At the inquest, independent expert gastroenterologist Dr William Connell described the medication 6-MP as a thiopurine, in the following terms:

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[2] ts 13 to 14
[3] ts 15
[4] ts 18 He clearly had IBD.There was an outside possibility that it was ulcerative colitis, but it was more likely Crohn's disease or Crohn's colitis
[5] ts 18 to 19

> *"....it's an immunosuppressive drug....it is a drug that has – interferes with DNA production and is a powerful anti-inflammatory drug. However, in high doses it's also a cytotoxic drug, so depending on the doses chosen it can actually just – it has the potential to destroy cells, but when it's used in the context of this condition and other inflammatory conditions it is used as an anti-inflammatory drug and it's reserved for people with chronic inflammatory conditions."*[6]

43. At the inquest expert clinical pharmacologist and toxicologist Professor Joyce explained that the medication 6-MP was designed in the late 1940's and early 1950's to look structurally very much like one of the pieces of DNA. Its function is to inhibit the metabolic formation of DNA, and is referred to as an antimetabolite. Its worldwide primary use is in the treatment of leukaemia.[7]

44. Professor Joyce also explained that 6-MP can commonly, and properly, be used "*off-label*" for other purposes, including the treatment of IBD and specifically Crohn's disease. In the context of Crohn's disease its function is to reduce the number of certain types of white blood cells: "*....so that they can't do their mischief in the bowel.*" Slowing down the production of white cells to a certain degree has been shown to stop inflammatory conditions that are harmful to cells.[8]

45. Consultant gastroenterologist Dr Callum Pearce, under whose care the deceased was admitted at FSH ICU on 1 March 2015, provided the court with information about his experience of prescribing 6-MP. He was not involved in the deceased's care prior to 1 March 2015. Dr Pearce has a sub-specialty in IBD and he has been prescribing 6-MP since about the late 1990's for IBD. In his estimation he would have prescribed it on thousands of occasions.[9]

46. The evidence of Dr Connell, Professor Joyce and Dr Pearce persuades me that the medication 6-MP is well known and frequently and appropriately utilised as a medication for the management of IBD conditions. The medication 6-MP is also used in several other medical conditions, such as rheumatoid arthritis, systemic lupus erythematosus,

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[6] ts 20
[7] ts 399
[8] ts 400; Exhibit 15.1
[9] ts 152 to 153

autoimmune hepatitis, organ transplantation and psoriasis.[10]

47. The medication 6-MP, as a thiopurine drug, is metabolised by the enzyme thiopurine methyl transferase (TPMT). In other words, the body breaks down 6-MP using the enzyme TPMT. Approximately 0.3% of people have two non-functioning copies of the TPMT gene and have little or no detectable enzyme activity which in turn can lead to toxicity of the drug and profound bone marrow suppression.

48. A TPMT gene test can identify whether an individual has one or two of the non-functioning copies of the gene. Normal metabolisers have two active components of the TPMT gene. However, some people are genetically deficient in TPMT. They have either a defective (low activity) TPMT gene on one chromosome 6 (heterozygotes) or they have defective TPMT genes on both of their copies of chromosome 6 (homozygotes).[11]

49. The reason that TPMT deficiency confers such a risk relates to the way 6-MP is metabolised in the body. The site of action for 6-MP is inside the rapidly dividing cells, such as the cells of the bone marrow that have to supply the blood's platelets, red cells and white cells. The dosages were historically chosen once it was understood that most of the 6-MP is actually wasted. In other words, it gets metabolised before it has a chance to act. The most important metabolic pathway for wasting 6-MP is the TPMT pathway.[12]

50. However, if a person is genetically deficient in TPMT and takes a standard dose of 6-MP, that medication will build up in the body so most of it is forced through into active forms. The consequence of this accumulation can be the complete inhibition of the production of blood cells in the bone marrow.[13]

51. Without white blood cells a person cannot fight off infection. Without blood platelets blood will not clot. The deceased came within the 0.3% of people who have defective TPMT genes on both copies of chromosome 6 (homozygote). In his case, the 6-MP medication was therefore contraindicated.

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[10] Exhibit 5
[11] Exhibit 15.1
[12] Exhibit 15.1
[13] Exhibit 15.1

52. Professor Joyce explained that the deficiencies in blood cells take time to appear, because it takes time for the effect of the excessive medication to accumulate (in a person with defective TPMT genes). It takes time for the white cells, platelets and red cells that are already in the circulating blood to complete their natural lives and disappear.

53. In Professor Joyce's experience, historically it has been found that a full blood count at two weeks after starting 6-MP will identify the patients who are destined for bone marrow aplasia. A full blood count at one week might give early warning. In his opinion, this testing regimen is very reliable and has been employed as the safeguard throughout the approximately 60 years in which thiopurines have been used in clinical medicine.[14]

54. The product information for mercaptopurine (being 6-MP) states that:

> "*there are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelo suppressive effect of mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with mercaptopurine. …….Some laboratories offer testing for TPMT deficiency although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary."*[15]

55. It is readily apparent that there are two potential safeguards to alert clinicians to the potentially toxic effect of 6-MP in a patient. One involves testing for TPMT deficiency, the other involves follow up testing by full blood count. In the deceased's case, for reasons that are explored in this finding, neither follow up was completed.

56. Dr Paul Mark, Acting/executive director of FSH and the Fremantle Hospitals Group, gave evidence at the inquest. He was responsible for running both hospitals and described his role as the single point of accountability to the area chief executive. At the inquest, he was asked for his views as to the contribution of 6-MP to the deceased's death:

> *"What contribution do you believe it made?---A very major contribution. Mr – in order of the sequence of events, Mr Olsen had severe inflammatory bowel disease. He was treated with a*

[14] Exhibit 15.1
[15] Exhibit 1, tab 34

range of drugs, and one of them was 6-Mercaptopurine. The side effect of the 6-Mercaptopurine was marrow suppression. The result of that was overwhelming sepsis, and the result of that was untimely death."[16]

57. Within this context, the medical treatment of the deceased is examined.

FIRST ADMISSION TO FSH

58. An outline of the salient aspects of the deceased's first admission to FSH appears below. Later in this finding, under the heading "ANALYSIS" some of these aspects are more closely examined.

59. On 4 February 2015, the deceased presented to FSH ED and was initially seen and assessed by the ED staff. Upon arrival the deceased reported abdominal pain, diarrhoea and said he had not eaten for three days. His normal weight was 100 to 110 kilograms. His weight was later recorded as 93 kilograms.

60. At FSH numerous clinicians saw him, and a variety of tests were conducted. He was initially admitted to FSH's acute medical unit and a surgical review was requested because a significant proportion of patients with Crohn's or ulcerative colitis will eventually need to undergo surgery.[17]

61. Following surgical review, he was admitted under the care of consultant gastroenterologist Dr Andre Chong, a doctor of medicine for 21 years and a consultant gastroenterologist for 11 years. Dr Chong had started with Fremantle Hospital in 2006 and he moved to FSH when it opened at the start of 2015. He was the consultant gastroenterologist rostered at FSH from 8.00 am Monday 2 February 2015 to 8.00 am Monday 9 February 2015.[18]

62. Investigations showed that on admission to FSH the deceased had a raised C-reactive protein (CRP, a marker of inflammation). His CRP was 220 [<5]. He was suspected of having IBD on the basis of a recent CT scan.

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[16] ts 303
[17] Exhibit 7
[18] ts 124; Exhibit 7

63. In accordance with Dr Chong's advice, a flexible sigmoidoscopy was performed on 5 February 2015. It showed moderate inflammation of the proximal sigmoid colon, severe inflammation of the descending colon and very severe inflammation of the distal transverse colon. The findings were so severe that a decision was made not to continue the examination beyond the transverse colon for safety reasons.[19]

64. The deceased was diagnosed with Crohn's colitis, an IBD (though the possibility of ulcerative colitis could not be excluded). He was commenced on IV steroids (100mg hydrocortisone four times a day) and pain medication.

65. The surgical team that reviewed the deceased's case concluded that no surgery was indicated and that conservative management of the deceased's condition should continue.

66. An entry in the deceased's medical progress notes of the afternoon of 6 February 2015 reflected that his pain was improving. Consistent with this, his CRP had improved.

67. At 11.57 am on 7 February 2015 a medical progress note stated "*immunomodulator screen tomorrow.*" I am satisfied that this entry was intended to be a reference to a test for TPMT enzyme activity and TPMP genotyping, which was ordered by FSH the next day. As it transpired, the clinician who later read it did not interpret it in the manner that had been intended.

68. Records reflect that on 8 February 2015, FSH sent PathWest laboratories a request for TPMT testing in relation to the deceased. The requesting form sought a number of tests, including the one for "*Thiopurine-S-Mth Transfe*". The requesting form stated clinical history was: "*Colitis; Crohns; Crohns workup for immunomodulator.*" The purpose was to ascertain whether the 6-MP was contraindicated for the deceased.[20]

69. By 8 February 2015 the deceased's CRP was continuing to improve. His medical progress notes reflect a decision to the effect that he could be switched to oral steroids the following day (40 mg prednisolone once a day). However, there is also reference to the possibility that his depressive symptoms

[19] Exhibit 1, tab 18
[20] Exhibits 16.1 and 16.4

had become worse from steroid therapy. His clinicians therefore explored the possibility of treating him with 6-MP in preference to the steroid treatment.

70. At 8.00 am on 9 February 2015, as per the roster, there was a handover by Dr Chong to the next consultant. The deceased then came under the care of consultant gastroenterologist Dr Oyekoye Ayonrinde, who took over from Dr Chong.[21]

71. Dr Ayonrinde has been a doctor of medicine for 22 years. He practiced as a specialist in gastroenterology at Fremantle Hospital since 2006 and then moved to FSH when it opened in early 2015.[22]

72. The medical progress notes of 9 February 2015 reflect a plan to treat the deceased with 6-MP and that the risks and benefits of lifelong 6-MP were discussed with him. It was documented that he was happy to start this medication. There was no written consent form signed by the deceased.[23]

73. Having regard to his verbal consent, his clinicians made the decision to commence the deceased on 6-MP (50 milligrams once a day; 0.5 milligram/kilogram). Medication charts record his first dose was given at 7.00 pm on 9 February 2015. Discharge was planned for the following day because it was felt that his colitis was sufficiently responding to treatment. Medication charts record the deceased's second dose of 6-MP was given at 8.00 am on 10 February 2015, the day of his discharge. No other doses of 6-MP were administered to the deceased at FSH.

74. On 9 February 2015 the deceased had also been reviewed by a dietician and a social worker who noted that the deceased was unemployed, on Newstart Allowance and that he lived alone in a private rental. The deceased reported that he was supplementing his Centrelink income with the inheritance he had received from his mother. He reported that he felt financial stress and described his mood as the "*lowest*" it had ever been.

75. In fact, during this admission to FSH the deceased had repeatedly expressed a worsening of his depression and reported insomnia and nightmares. The psychiatric team

[21] Exhibit 5
[22] ts 227 to 228
[23] Exhibit 2 Tab 3M

had also reviewed the deceased on 9 February 2015. He reported to them a long history of depressive symptoms that had been exacerbated in the last 18 months.

76. The deceased disclosed that he experienced fleeting suicidal thoughts and told the psychiatric team that he was looking for ways to take his life. However, he guaranteed his safety (meaning that he undertook that he had no active plan to take his life). The psychiatric team considered that he appeared future orientated. He had no prior history of self-harm.

77. The deceased's psychiatric team considered him to be a chronic suicide risk, but not acutely. The case was discussed with the consultant psychiatrist. The deceased was diagnosed with dysthymia/major depressive disorder. He was noted to have problems with alcohol use. The recommendations were to continue on the antidepressant escitalopram and to start another antidepressant mirtazapine at night to help with his sleep. It was also suggested that his GP wean him off oxazepam. He was referred to the community mental health services for follow up.

78. The alcohol and drug service had also reviewed the deceased on 9 February 2015. He reported to them that over the past four years he had been consuming one to two bottles of wine daily. He felt that he had not dealt with the passing of his mother and he was experiencing a lot of grief. He claimed he would stop drinking in view of his Crohn's disease and he was willing to engage with the Southeast Metro Community Drug Services for follow up.

79. The gastroenterology team reviewed the deceased on 10 February 2015 at about 10.15 am. It was noted that his symptoms continued to improve and that he could be discharged that day with a plan that included ongoing analgesia, his GP to perform specific blood tests in two weeks, review by IBD clinic in four weeks, and follow up with psychiatric and drug and alcohol services.

80. Unfortunately the deceased then spent about seven and a half hours in FSH's transit lounge awaiting his discharge. Nursing progress notes during this period reflect that the deceased was complaining of pain which he described as 9/10 severity, post tramadol, and that he was groaning. The deceased's pain decreased to 7/10 by the time he left

the transit lounge. His father took him home in the early evening.

81. Before he left, the deceased was provided with his discharge summary, diet education and literature regarding Crohn's disease. The deceased was unhappy with his medical management at FSH and verbalised his wish to complain about the system to the head of the department.

82. A copy of the prescription for the deceased's discharge medications dated 10 February 2015 reflected that he was prescribed:

- the immunosuppressant 6-MP, 50 milligrams; one tablet in the morning (total of 50 tablets);
- the narcotic analgesic buprenorphine, 200 microgams; one tablet dissolved under tongue up to four times day (total of 10 tablets);
- the analgesic tramadol 50 milligrams; one to two capsules every four hours if required (total of 20 capsules);
- the antidepressant mirtazapine, 15 milligrams; one tablet at night (total of 30 tablets);
- the steroid prednisolone, 25 milligrams (total of 30 tablets) and 5 milligrams (total of 60 tablets) at a reducing dose until ceased.

FSH ORDERS TPMT TEST

83. Whilst FSH did not have a practice of ordering a TPMT test before (or after) commencing an IBD patient on 6-MP, as it transpired, one of the doctors, adopting the practice of another hospital he trained at, and assuming FSH operated on the same basis, ordered a TPMT test for the deceased.

84. It was ordered electronically, and the confusion generated by the sequence of events that followed highlights the risks of over-reliance on electronic communications. The TPMT test was ordered by FSH, a critical result was received, and no clinician became aware of it until it was too late. The results of the TPMT test sent by PathWest to FSH on 19 February 2015 showed, unequivocally, that the 6-MP would have a toxic effect on the deceased. The details appear below.

85. The decision to treat the deceased's IBD with 6-MP was made after his care was handed over from Dr Chong to Dr Ayonrinde on the morning of 9 February 2015. At that

time, FSH did not have a written policy regarding the prescription of 6-MP, hence there was no written guidance on whether TPMT tests were to be ordered in such circumstances.

86. Despite the absence of a written policy, some practices had developed at FSH around the prescription of 6-MP and the manner in which potentially toxic effects were to be ascertained. Instead of TPMT testing, the FSH clinicians monitored the potentially toxic effects of 6-MP by arranging for full blood counts at regular intervals following its commencement.

87. However, in an environment where it is not uncommon for doctors from other hospitals to work rostered shifts, and in the absence of a written policy, it is not surprising to discover that when a member of the deceased's treating team at FSH did in fact order a TPMT test for him, the consultant in charge did not find out about it.

88. Dr Gan, then a registrar/hepatology fellow at FSH (now a consultant gastroenterologist) had developed a practice of performing a TPMT test in such circumstances by reason of his clinical training at another hospital. He therefore assumed, based upon his prior experience, that similar procedures would apply at FSH and that he ought to order the phenotype and genotype TPMT testing for the deceased. As it transpired, different hospitals had different practices on this point.[24]

89. Dr Gan was of the view that a TPMT test did not replace diligent blood monitoring, but supplemented it. At the material time he was also aware that low or negligible TPMT activity could cause 6-MP to be preferentially metabolised which can lead to bone marrow suppression.[25]

90. Dr Gan was involved in the deceased's care on the weekend of 7 and 8 February 2015 by reason of being rostered on duty. In his role as hepatology registrar, he supported the gastroenterology ward team for hepatology (liver) related issues. The gastroenterology ward team for that period included Dr Marius van Rijnsoever (advanced gastroenterology trainee), Dr Syed Shah (resident medical officer) and Dr Rowan Ellis (intern).

[24] ts 339 to 340
[25] Exhibit 12

91. On the morning of 7 February 2015 Dr Gan reviewed the deceased with Dr Shah during the ward round and concluded that he was suffering from Crohn's colitis. In Dr Gan's experience, given a clinical response to steroids, the usual path of management is to consider long-term steroid free maintenance therapy, one of the options being immunomodulatory therapy.[26]

92. In anticipation of the gastroenterology ward team being likely to consider commencement of immunomodulatory therapy with 6-MP or azathioprine, on the morning of 7 February 2015 Dr Gan asked Dr Shah to arrange for immunomodulatory screening over that weekend. This comprised varicella zoster and hepatitis B screening, serum TPMT enzyme level, baseline full blood count and liver function test. This was normal practice for Dr Gan.[27]

93. Dr Shah was also rostered on the weekend of 7 and 8 February 2015, and he executed Dr Gan's instructions regarding the screening for the deceased. The request for the TPMT test is reflected in Dr Shah's entry in the deceased's medical records at approximately midday on 7 February 2015: "*Immunomodulator screen tomorrow*".[28]

94. Dr Shah, as a resident medical officer with the gastroenterology team at the material time, did not make management decisions such as what tests to order. He acted on instructions from senior colleagues. This entry was a reference to blood samples that were to be collected from the deceased on the ward phlebotomy round the next morning.[29]

95. In addition to the arrangements for collecting the deceased's blood samples, Dr Shah ordered the actual TPMT test for the deceased upon Dr Gan's instructions, after the ward round on 7 February 2015. Dr Shah ordered the TPMT test electronically at FSH, through the iSoft clinical manager database (iCM), from PathWest. Dr Shah had no previous knowledge of TPMT testing, having only worked in gastroenterology for two weeks at that time.[30]

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[26] Exhibit 12
[27] Exhibits 12 and 13
[28] Exhibits 12 and 13
[29] Exhibits 12 and 13
[30] Exhibit 13

96. As it transpired, the immunomodulatory screening test in the iCM database did not automatically include TPMT activity. Dr Shah believes Dr Gan must have specifically instructed him to include the TPMT test, otherwise he would only have ordered the tests that automatically appear in the iCM standard immunomodulatory screening. This is consistent with Dr Gan's evidence.[31]

97. The iCM database records reflect that Dr Shah made the following entry at 11.26 am on 7 February 2015: "*TPMT activity – AM – phlebotomy*". Records reflect that the deceased's blood specimen for this TMPT test was collected at 7.35 am on 8 February 2015.[32]

98. However, when the iCM database generated Dr Shah's request for the TPMT test to PathWest, it went under Dr Ellis' name as the requesting clinician. The clinical pathology order form requesting the TPMT test was generated electronically from FSH and dated 8 February 2015.

99. Somewhat confusingly, the clinical pathology order form recorded Dr Chong as being in charge (although at this stage Dr Ayonrinde was in charge) and Dr Ellis as making the request in relation to the deceased's blood sample (although Dr Shah made the request). The order was in respect of a number of tests, including TPMT.[33]

100. Dr Ellis was the gastroenterology intern at FSH on duty between 4 to 6 February 2015 and 9 to 10 February 2015. Dr Ellis confirmed that whilst PathWest subsequently generated a TPMT report directed to him at FSH, he did not request this particular test and he described it as an "*add on*".[34] Dr Ellis, who was not working on 8 February 2015 provided the following explanation.

101. One of Dr Ellis' routine daily tasks was to ensure that all patients on the ward had daily blood tests. At 8.44 pm on 6 February 2015, before he completed his shift, Dr Ellis had entered a request on iCM for routine blood tests for the deceased to be performed for dates over the coming weekend and the next Monday morning. Those routine tests

[31] Exhibit 13
[32] Exhibits 10 and 13
[33] Exhibit 10
[34] Exhibits 10 and 11

comprised a full blood count, urea and electrolytes, liver function tests and C-reactive protein.[35]

102. The iCM records reflect that the deceased's blood for the daily routine tests ordered by Dr Ellis on 6 February 2015 was to be collected at 8.00 am on 7, 8 and 9 February 2015.[36]

103. The next request appearing on the iCM records was by Dr Shah, who requested "*TPMT Activity – AM – phlebotomy*" for the deceased at 11.26 am on 7 February 2015 (and three minutes later he added some other tests under his name). [37]

104. Dr Ellis explained that since the deceased's blood was initially taken for the routine tests that he requested, the specific TPMT test request entered by Dr Shah nonetheless remained on the iCM system with Dr Ellis' name attached to it (despite Dr Ellis not having requested the TPMT test and knowing nothing of it).[38]

105. Consequently, when PathWest in accordance with its usual procedures later proceeded to genotype testing of the deceased's blood for TPMT due to an abnormal phenotype result, it was recorded on the iCM system at 9.02 am on 17 February 2015 as having been requested by Dr Ellis: "*TPMT Genotype – routine*". However, in reality it was in relation to Dr Shah's request on Dr Gan's instructions.[39]

106. Given the iCM system recorded Dr Ellis as the requesting doctor, PathWest generated a TPMT report addressed to him at FSH on 19 February 2015. However, the first time that Dr Ellis became aware of a TPMT test being ordered was when he was in ICU with the gastroenterology team seeing the deceased after his second admission to FSH following his collapse on 1 March 2015.

107. Dr Ellis had not requested TPMT genotype testing for the deceased, knew nothing of it, and was therefore not expecting to receive any such results for the deceased. Dr Shah, in his role as registered medical officer, had input the TPMT test request upon Dr Gan's instruction, and was

[35] Exhibit 11
[36] Exhibit 11
[37] Exhibits 11 and 13
[38] Exhibit 11
[39] Exhibits 11 and 13

not previously aware of the function of that test having only worked in gastroenterology for two weeks. Dr Shah did not himself have a role in following up the TPMT test result.

108. Dr Gan who did request the TPMT test with full knowledge of its function and purpose completed his rostered role as hepatology registrar supporting the gastroenterology team on 9 February 2015, well before PathWest generated its TPMT report. Dr Gan was not involved in the deceased's care after 9 February 2015. Dr Gan therefore did not have a role in following up the TPMT test result either.

109. Dr Gan recalled that on the morning of 9 February 2015, when his shift concluded, he verbally handed the deceased's care back to the gastroenterology ward team during a routine handover. Dr Gan was unable to recall exactly what he said during the handover, but believed he would have informed the team that he had organised immunomodulatory screening.

110. Dr Gan could not recall whether he specifically told the team that a TPMT test had been ordered, but believed it would have been his usual practice to do so. Dr Gan pointed to the entry made by Dr Shah in his instruction in the deceased's medical progress notes at 11.57 am on 7 February 2015: "*Immunomodulator screen tomorrow*". There was no written record of the handover.[40]

111. Dr van Rijnsoever was the most senior member of the four-person team, being the gastroenterology advanced trainee (now an interventional endoscopic fellow in gastroenterology). In February 2015, Dr van Rijnsoever worked in a number of hospitals, including FSH. He was in his sixth postgraduate year and in his second year of core gastroenterology training.

112. Dr van Rijnsoever was not expecting a TPMT test to be ordered, as it was not the practice at FSH at that time. He remained unaware that a TPMT test had been ordered for the deceased until after his collapse and admission to ICU on 1 March 2015.[41]

113. Dr van Rijnsoever did not recall Dr Gan mentioning that he had requested a TPMT test at the ward round on 9 February 2015, when he gave instructions for the prescription of 6-MP

[40] Exhibit 12
[41] Exhibit 4

for the deceased. His understanding of the entry of 7 February 2015: "*Immunomodulator screen tomorrow*" was that it meant hepatitis serology and quanteferon gold (tuberculosis test). He did not understand it to refer to, or include, a TPMT test.[42]

114. Accordingly, whilst Dr Gan believed he had informed the gastroenterology team that he had ordered a TMPT test, as part of his handover of medical care, Dr van Rijnsoever, being the most senior member of that team after the consultant in charge, did not form that view from the handover communications and medical records.

115. Dr Chong, who was the gastroenterology consultant in charge between 4 and 8 February 2015 only became aware that a TPMT test had been ordered for the deceased after he discussed the deceased's management with Dr Gan during the deceased's re-admission in March 2015.[43]

116. Finally, Dr Ayonrinde who became the gastroenterology consultant in charge on 9 February 2015 did not know that a TPMT test had been ordered for the deceased and only became aware of the deceased's TPMT results when his case was discussed at a gastroenterology morbidity meeting after the deceased's re-admission in March 2015.[44]

117. Regrettably, none of the FSH clinicians who could have directed the deceased to stop taking 6-MP were able to do so, because they did not become aware of the TPMT test results until after his collapse and re-admission to FSH.

PATHWEST's TPMT TEST RESULTS

118. PathWest Laboratory Medicine WA (PathWest) is the Western Australian public pathology testing provider with laboratories in metropolitan and regional areas across the state. PathWest provides pathology and laboratory medicine services to a range of entities, including FSH.[45]

119. As stated above, FSH sent PathWest laboratories the request for TPMT testing on 8 February 2015. Given the type of testing involved, there was no result available to FSH by the time the deceased was discharged.

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[42] Exhibit 4
[43] Exhibit 7
[44] Exhibit 4
[45] Exhibit 1, tab 32

120. It is necessary to assess the PathWest's procedures for TPMT testing by reference to its testing policy as it applied in February 2015, and its understanding of the reasons for such a test being requested.

121. At a general level, PathWest understood that the reasons for such a test, performed at a clinician's request, may be related to commencing or amending the dose of a range of medications for a range of conditions including organ transplantation, cancer patients, and those with autoimmune disease states such as rheumatoid arthritis, pemphigus, IBD, multiple sclerosis, autoimmune hepatitis and restrictive lung disease.[46]

122. In the deceased's case, I am satisfied that the PathWest medical scientist carrying out the TPMT test will have understood that it related to IBD given the reference to "*Colitis*" and "*Crohns*" on FSH's requesting form.[47]

123. However, for reasons that are outlined later in this finding, I am not satisfied that the PathWest medical scientist would have also understood that the deceased had already been commenced on 6-MP, because FSH's requesting form stated "*Crohns workup for immunomodulator*". It was submitted to me that this would indicate to PathWest that the deceased had not been commenced on 6-MP.[48]

124. Self-evidently where a person has already been commenced on 6-MP, the TPMT test results become time critical, as there is a need to more promptly ascertain whether this medication is contraindicated.

125. In the deceased's case, the request for TPMT testing was generated on 8 February 2015 and entered onto PathWest's Laboratory Information System (LIS) at 8.01 am on that date. FSH despatched the deceased's blood samples to PathWest which recorded them as being received at 11.44 am on that date. Three samples were received.[49]

126. On 10 February 2015, PathWest Special Chemistry sent two of the three samples to Diagnostic Genomics should there be a requirement for further testing (in fact, that requirement did eventuate). After the necessary preparations of the

[46] Exhibit 1, tab 31
[47] Exhibit 1, tab 31; Exhibits 16.1 and 16.4
[48] Exhibit 1, tab 31; Exhibits 16.1 and 16.4
[49] Exhibit 1, tab 31

remaining sample, the analytical procedure for TPMT activity occurred on 11 February 2015.[50]

127. On 12 February 2015 the deceased's initial phenotype result showing a TPMT activity of 0.04 nmol/gHb/min became available. The normal range is 0.57 to 1.08 nmol/gHb/min. It is obvious that the deceased's TPMT activity was abnormally low. One expert witness described it as profoundly low and I accept that.[51]

128. At that time, PathWest's written policy was that phenotype test results below the threshold of 0.57 nmol/gHb/min were repeated in the next run of testing, and for genotype testing to also be conducted.[52]

129. The repeat phenotype testing would normally occur the following week, but the deceased's sample was randomly selected for quality control and so this testing was repeated on the same run of testing. The confirmation phenotype test returned the same result.[53]

130. The threshold of 0.57 nmol/gHb/min represented the lower limit of the 95% confidence limits for the range in a healthy population (full range being 0.57 to 1.08 nmol/gHb/min). However, despite its written policy, PathWest had also developed a clinical review practice whereby for a period of 12 months from August 2014, it was decided that phenotype and genotype testing on results of 0.62 nmol/gHb/min or below would occur.[54]

131. At the material time, PathWest's default reporting practice was that phenotype results would not be released until genotype results were available, for those cases that had gone to genotyping (that is, where the phenotype result was abnormal). This has now changed and addressed later in this finding.

132. PathWest's rationale as at February 2015 for not releasing the phenotype results until the genotype results were available was that any number of factors may give rise to erroneous results. PathWest's scientist in charge of Special Chemistry Dr Joseph explained that it was considered that

[50] Exhibit 1, tab 31
[51] Exhibit 16.1
[52] Exhibit 16.1
[53] Exhibit 1, tab 31; Exhibit 16.1
[54] Exhibits 15.1 and 16.1

good laboratory practice was to ensure that results are reliably reported. Professor Joyce confirmed that the genotyping would be an absolute confirmation of the phenotyping, thereby providing the clinician with reliable information.[55]

133. In Mr Joseph's experience, erroneous results may arise as a result of sample integrity issues or from errors in the analysis process. Abnormal (unusually high or low) results were often repeated for confirmation. If there was a sample integrity issue this would not have been picked up by the repeat phenotype test (the repeat is done to pick up errors in analysis). If, as in the deceased's case, the repeat phenotype testing merely confirmed the initial phenotype test result, genotype testing would be conducted.[56]

134. In preparation for the genotype testing, DNA was extracted from the deceased's sample on 13 February 2015. The request by Special Chemistry was sent to Diagnostic Genomics on 17 February for genotypic studies on the deceased's sample. The DNA sequencing results first became available on 19 February 2015. The genotyping identified a homozygous *3A genotype.[57]

135. This result made clear the fact that the deceased could not metabolise 6-MP and that this medication should have been promptly discontinued to avoid the bone marrow toxicity and the dire consequences that did eventuate. Unfortunately the deceased's treating team at FSH did not become aware of this result at the material time and the deceased, oblivious to this state of affairs, continued to take his 6-MP.

136. How this managed to happen has already been outlined under the heading "FSH ORDERS TPMT TEST" and is summarised below. It goes back to the manner in which the electronic ordering and retrieval system operated at FSH.

137. PathWest's TPMT report of the phenotype and genotype results, directed to Dr Ellis at FSH, was uploaded onto iCM on 19 February 2015. Specifically the TPMT report became electronically available to FSH at 12.56 pm on 19 February 2015, with a red flag indicating an abnormal result. The

[55] ts 416 to 417; Exhibit 16.1
[56] Exhibit 16.1
[57] Exhibit 1, tab 31; Exhibit 15.1

treating clinicians had access to iCM. It contained the following commentary:

> *"TPMT activity is low and the presence of TWO variant alleles for TPMT indicates a very substantially impaired clearance of thiopurines (azathioprine or mercaptopurine). If thiopurine therapy is essential, the literature suggests the starting dose of azathioprine or mercaptopurine should be reduced to approximately 5% of the dose otherwise indicated, and therapy must be closely monitored for clinical and haematological response (full blood picture)…."*[58]

138. Dr Ellis did not know that a TPMT test had been requested by Dr Shah but attributed to him as the requesting doctor on the iCM system. Dr Ellis was not expecting a TPMT report in relation to the deceased and did not see the report outcome on the iCM system on 19 February 2015, or indeed at any time prior to the deceased's collapse on 1 March 2015. Records reflect that receipt was "*acknowledged*" on the iCM at 12.36 am on 2 March 2015.[59]

139. Regrettably no member of the gastroenterology team was aware of the deceased's TPMT report results until after the deceased's collapse and admission to ICU on 1 March 2015. The evidence at the inquest begged the question of how such a critical test can be ordered and results received at a hospital without any treating clinician becoming aware. Even if it was not then the general practice to order a TPMT test prior to prescribing 6-MP, the fact is that this test was ordered, and a materially important result was received, that contraindicated the use of 6-MP in the deceased's case.

140. At the inquest Dr Mark, FSH's A/executive director, posited that the majority of relevant staff who transitioned to FSH came from Fremantle Hospital, and at Fremantle it was departmental policy not to do TPMT testing under these circumstances. On the other hand, Dr Gan came from another hospital where it was departmental policy to do it.[60]

141. Dr Mark proceeded to give evidence about how this risk of miscommunication has now been mitigated by FSH after the deceased's death, and that is addressed later in my finding, in connection with improvements since the deceased's death.

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[58] Exhibit 1, tab 31; Exhibit 11
[59] Exhibit 1, tab 31
[60] ts 311

142. The relevant improvements relate to the expansion of services provided by FSH's IBD clinic following an increase in its staffing levels, and they comprehensively address the tracking of blood test monitoring and results. FSH has also entered into some arrangements with PathWest regarding the communication of such results, and these are outlined immediately below.

143. At the inquest Dr Ee Mun Lim, head of the Biochemistry Department at PathWest QEII explained that as at February 2015, they believed that when a TPMT test was ordered, the person would not yet have been started on 6-MP. This belief was held at PathWest because of their knowledge of a recommendation to the effect that when specialists are prescribing thiopurines they should be ordering the TPMT test first.[61]

144. Mr Joseph, scientist in charge, special chemistry at PathWest testified that the words "*Crohn's workup for immunomodulator*" on the clinical pathology electronic order for the deceased's TPMT test would suggest to him that the patient is being worked up prior to being put on treatment, but would not amount to a clear indication on whether or not the patient was already on 6-MP.[62]

145. It is to be borne in mind that when the clinical pathology electronic order form requesting the TPMT test was generated, on 8 February 2015, the deceased had not in fact been commenced on 6-MP. The author of that request form did not know whether the deceased would be prescribed 6-MP. Dr Ayonrinde approved its use to treat the deceased the next day, on the morning of 9 February 2015, and the deceased was administered his first dose that evening.

146. It is therefore reasonable for PathWest to have operated on the basis that the deceased's treating team were awaiting the results of the TPMT testing before commencing the deceased on 6-MP. Further, whilst a clinician with expertise in gastroenterology may have apprehended the critical importance of the abnormally low TPMT activity result (phenotype result), the PathWest scientists' efforts were aimed at generating a reliable result based upon the genotyping.

[61] ts 283
[62] ts 394 to 395; Exhibit 10

147. I am satisfied that this was, and continues to be, an evolving area of medicine and at that the material time PathWest was applying best practice, as far as it was known and understood. It is also to be borne in mind that whilst PathWest was generating the test results, the deceased remained in the care of FSH. He was due for follow up at the IBD clinic four weeks post discharge. FSH's role in his care did not end at the time of his discharge on 10 February 2015. There was an outstanding request from FSH for a TPMT test as at that date.

148. Dr Lim accepted that in hindsight the TPMT activity result should have been made available to FSH on 12 February 2015, and also that it would have been better for PathWest to have phoned through the results of the genotype testing to FSH on 19 February 2015. This approach was supported by Professor Joyce.[63]

149. Dr Lim and Mr Joseph outlined the subsequent changes in PathWest's procedures following a review of this case, and these are addressed later in my finding in connection with improvements since the deceased's death.[64]

SECOND ADMISSION TO FSH

150. After the deceased's discharge from FSH on 10 February 2015 he saw his GP, but for reasons outlined later in this finding under the headings "Discharge arrangements" and "Follow up with GP," he did not have the full blood count testing at two weeks post discharge. The deceased continued to experience pain and discomfort, but he did not re-present to FSH until after he collapsed on 1 March 2015. Tragically by that time, it was too late for the clinicians to save him.

151. St John Ambulance (SJA) received a call at 6.37 pm on 1 March 2015 reporting that the deceased had been complaining of increasing pain and nausea and had been found by his father collapsed on the bathroom floor in a pool of dark, blood stained, diarrhoea. SJA departed immediately and arrived at 6.51 pm. Records disclose that the paramedics found the deceased to be alert but weak, cold and clammy, with an increased respiratory rate and heart

[63] ts 287; ts 416 to 417
[64] ts 287

rate. His BP was 80 palpable, his oxygen saturations were only around 75% and his temperature was only 34.6.

152. The deceased reported pain in his abdomen and was given IV fentanyl, fluids and oxygen. He was promptly conveyed by ambulance to FSH in a critical and unstable condition, arriving at the ED at 7.30 pm on 1 March 2015.[65]

153. The deceased was immediately taken to the resuscitation room. He was seen by the ED Consultant, and a history of bloody diarrhoea over the last few days was obtained. It was initially felt that the deceased had suffered haemodynamic instability from hypovolaemia, secondary to bleeding from Crohn's disease. Bloods were taken, a CT scan of the abdomen was performed and the deceased was given IV fluids and blood products.

154. The deceased was started on a metaraminol infusion to maintain his blood pressure and transferred to ICU, under the gastroenterology team. Specifically he was admitted under the care of Dr Callum Pearce, who was the ward consultant gastroenterologist for that week. The deceased was diagnosed with renal failure and active bleeding from the gastrointestinal tract.

155. The CT scan dated 1 March 2015 showed the following:

- mild to moderate wall thickening of the caecum, ascending, transverse, splenic flexure and descending colon with luminal narrowing/stricture at the splenic flexure and a more saccular dilatation of the proximal descending colon;
- no evidence of bowel ischaemia;
- no free air to suggest bowel perforation;
- left sided pleural effusion and patchy peripheral streaky consolidation;
- accentuation of the interlobular septa; and
- multiple (at least 20) dense bodies, presumed tablets, in the lumen of the large bowel. Self-evidently, overdose was a consideration.

156. Initial blood tests showed anaemia (Hb 86) [135 – 180] and an extremely low white cell count (0.17) [4 – 11], neutrophils (0.01) [2 – 7.5] and platelet count (2) [150 – 400]. His creatinine level was also significantly raised (324) [60 – 110].

[65] Exhibit 1, tab 10

157. The deceased was reviewed by the surgical team who felt there was no need for surgical input as the CT scan showed no sign of perforation.

158. The deceased was diagnosed with septic shock, coagulopathy (abnormal clotting function) and pancytopenia (a deficiency of all three cellular components of the blood, namely red cells, white cells, and platelets). His case was discussed with the haematologist and he was given G-CSF (granulocyte-colony stimulating factor, a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells). He was also started on IV antibiotics Tazocin, hydrocortisone and noradrenaline metaraminol and adrenaline.[66]

159. Consultant Gastroenterologist Dr Waters was consulted and he advised that neutropenia (low neutrophil count) was a side-effect of 6-MP but that it was not usually that severe.

160. Early on 2 March 2015 the deceased's condition was discussed with his father and it was explained that the immunosuppression was most likely drug-related, and that his son remained critically unwell and that he may not survive.

161. At approximately midday the deceased was reviewed by the gastroenterologist who stated that it was not appropriate to perform a scope at that time due to the risk of perforating the bowel and that allopurinol was not useful due to risk of worsening his myelosuppression.

162. That evening it was noted that the deceased's condition had worsened. Further advice was sought from the haematologist regarding the replacement of blood products. By this stage the deceased had already received five units of packed red blood cells (PRBC), three units of platelets and two units of fresh frozen plasma (FFP). He had on-going gastrointestinal bleeding and further units of PRBC, platelets and FFP were given along with tranexamic acid, vitamin K, and an infusion of octreotide.

163. The next day, 3 March 2015, the deceased remained critically unwell. Gram-negative bacilli were isolated from his blood culture and his antibiotics were changed to

[66] Exhibit 2, tab 3

Merapenem. He was receiving continuous renal replacement therapy.

164. The deceased continued to have episodes of rectal bleeding and the nasogastric aspirates were also suggestive of bleeding. Dr Pearce still maintained that the risks of a gastroscopy were too great, given his low platelet count and raised INR, and there was not much else that could be done to stop the bleeding.

165. Throughout the next day, 4 March 2015, a number of the deceased's relatives were in attendance. Further history was obtained to the effect that the deceased had spoken of the deterioration in his condition over the last weeks. He had been suffering increasing abdominal pains but it appears he was reluctant to seek further medical treatment.

166. A record was made of the admission CT scan result showing multiple tablet-like bodies in his bowel. It was noted that this could be due to impaired transit, due to him being critically unwell, or possibly due to an overdose of his medication. It was also recorded that he could have been extremely sensitive to the 6-MP due to TPMT deficiency. The doctor writing this entry, Dr van Rijnsoever, had also commented: "*would be useful to see how many unused 6-MP tablets are left.*"

167. A further entry by Dr Van Rijnsoever on the morning of 4 March 2015 stated that: "*TMPT (sic) levels are low confirming the enzymatic deficiency"* and that the family have been counselled regarding this genetic enzyme deficiency. Dr Van Rijnsoever also recorded that he had asked the deceased's father to bring in the 6-MP medication packets to assess how many tablets he had actually taken.

168. On 4 March 2015 *Klebsiella pneumoniae* was isolated from cultures. The deceased continued to deteriorate and died at 6.40 am on 5 March 2015.[67]

ANALYSIS

169. Having found the facts outlined above, and the events leading to the deceased's death, it is necessary to focus on particular aspects of the deceased's treatment, insofar as

[67] Exhibit 1, tab 33

they affect my conclusions on the question of whether the deceased's death was preventable, and quality of his care.

170. These aspects concerned the factors affecting the decision to prescribe the 6-MP to the deceased, the fact that there was no policy at FSH concerning the safe prescription of 6-MP, the efforts made to obtain the deceased's informed consent to treatment with 6-MP, the efficacy of the known safeguards against 6-MP toxicity (TPMT test or full blood count), the discharge arrangements and the follow up with the deceased's GP. These are outlined below.

Decision to prescribe 6-MP

171. Dr van Rijnsoever proposed that 6-MP be prescribed to the deceased, and consultant in charge Dr Ayonrinde approved this plan before the medication was administered. Expert evidence at the inquest persuades me that the decision to prescribe 6-MP as at 9 February 2015 for the purpose of treating the deceased was based on sound medical practice.

172. The problems arose afterwards because a system breakdown resulted in the deceased not being followed up to ascertain whether he was able to metabolise, and therefore tolerate, the 6-MP.

173. Dr van Rijnsoever reviewed the deceased at 2.40 pm on 5 February 2015 on behalf of the gastroenterology team. Dr Chong was the consultant in charge on that date, and he was also the admitting consultant for the deceased. After examining the deceased and taking his history Dr van Rijnsoever's impression was that he had colitis with non-bloody diarrhoea of acute onset. His differential diagnosis was either infective colitis or Crohn's disease.[68]

174. Dr van Rijnsoever made the arrangements for the deceased to have the flexible sigmoidoscopy on the same day, to assess for IBD. Results became available that day and a diagnosis of Crohn's disease was made, which was confirmed by biopsy later.[69]

175. Dr van Rijnsoever recommended a plan to Dr Chong that included commencing the deceased on IV hydrocortisone,

[68] Exhibits 2 and 4
[69] Exhibits 2 and 4

and reviews by surgical team and psychiatric team. His CRP was raised at that stage. The deceased had depression and Dr van Rijnsoever specifically took account of the fact that steroids can aggravate mental health conditions. Medical records as at 5.35 pm on 5 February 2016 reflect that Dr Chong agreed with this plan. The deceased was duly commenced on IV hydrocortisone.[70]

176. Dr van Rijnsoever reviewed the deceased at 9.41 am on 6 February 2015 during the gastroenterology ward round. The deceased reported having a low mood, with insomnia and nightmares. Dr van Rijnsoever was aware the deceased had been prescribed medications for his mental health condition.[71]

177. Dr van Rijnsoever reviewed the deceased again later on 6 February 2015, at 2.06 pm, along with Dr Chong during the consultant review ward round. The deceased reported being in less pain. His CRP had improved, which indicated to Dr van Rijnsoever that there had been a positive response to the steroid treatment.[72]

178. Dr van Rijnsoever next reviewed the deceased with Dr Gan and Dr Ellis during the morning ward round on 9 February 2015. During this consultation he discussed with the deceased the risks and benefits of going on lifelong immunomodulatory medication 6-MP. The entire discussion lasted approximately 20 minutes. Dr van Rijnsoever had previously prescribed 6-MP to patients, and he had observed different IBD consultants explain the risks and benefits of 6-MP to patients on many occasions. Medical records made by Dr Ellis as at 9.21 am on 9 February 2015 reflect: "*Discussed lifelong 6-MP. Risks and benefits. Patient is happy to have 6-MP.*"[73]

179. Dr van Rijnsoever recalled explaining to the deceased that in the long term immunomodulatory medications such as 6-MP are required to control Crohn's disease since long term steroid use has severe side effects. However, there can also be severe side effects in the case of 6-MP.[74]

[70] Exhibits 2 and 4
[71] Exhibits 2 and 4
[72] Exhibits 2 and 4
[73] Exhibits 2 and 4
[74] Exhibit 4

180. Dr van Rijnsoever recalled informing the deceased there are common side effects with 6-MP that include nausea, vomiting and photosensitivity. He also recalled informing the deceased that there are more serious, less common side effects, including bone marrow suppression and pancytopenia (a reduction in the number of red and white blood cells, as well as platelets), deranged liver function, pancreatitis and a very small increase in skin cancers and lymphoma.[75]

181. On the other hand, the risk of not having 6-MP treatment included perforated bowel or a higher risk of developing bowel cancer, and Dr van Rijnsoever also recalled explaining this to the deceased.[76]

182. At the inquest, independent expert gastroenterologist Dr Connell outlined the reasons for needing to balance the risk of keeping the deceased on steroids for a few more days or a week as opposed to the clinical imperative for starting him on the 6-MP. He gave the analogy of needing to withstand the effects of a bushfire or storm as quickly as possible:

> "*….as a general rule …. the emphasis in someone with severe colitis is to try to curtail the use of steroids as much as possible, and the reason is because although it - it reduces the acute infection it actually doesn't do anything to control the actual underlying disease. The disease will continue to smoulder on and people not only have to withstand the effects, the unpleasant effects, of the disease but they are at a high risk then of getting secondary infection, of …. having a higher mortality and a higher need for surgery, and …. this is the overwhelming imperative that we are …. trying to avoid Mr Olsen having to have a …. colectomy, which is removal of your bowel, and - well, the longer that his condition goes on untreated the higher the likelihood that surgery is required and - and mortality.*"[77]

183. In Dr Connell's opinion, the decision to commence the deceased on 6-MP was not unreasonable given the context of his disease severity and a need to introduce a steroid sparing agent quickly. He explained that 6-MP's onset of action is slow, and that it can take up to three months for it to become effective. He regarded the prescription of 6-MP to the deceased as a decision that most other experts in IBD would concur with.[78]

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[75] Exhibit 4
[76] Exhibit 4
[77] ts 47
[78] Exhibit 1, tab 18

184. One of the central questions in the inquest concerned the need for the deceased to have follow-up blood tests as a safeguard to check for any toxicity from the 6-MP, and the reasons as to why this did not occur. This was examined from a number of perspectives. The starting point concerns the information conveyed to the deceased when Dr van Rijnsoever discussed risks and benefits of 6-MP with him.

185. Dr van Rijnsoever recalled that with regard to bone marrow suppression and pancytopenia, during that ward round on 9 February 2015 he also discussed with the deceased how these conditions can be detected, including the need for regular blood tests (initially fortnightly, but lifelong at least a blood test every three months), to look out for abdominal pain from pancreatitis and to present to ED or his GP of he was feeling unwell.[79]

186. At the end of that discussion, Dr van Rijnsoever formed the view that the deceased clearly understood the risks and benefits of 6-MP as well as the requirements for regular blood tests.[80]

187. Dr van Rijnsoever was next in attendance during the consultant review ward round with the incoming consultant in charge, Dr Ayonrinde later on the morning of 9 February 2015, at 10.37 am. During this consultation, Dr van Rijnsoever's treatment plan for the deceased, including the prescription of 6-MP, was agreed to by Dr Ayonrinde, consultant in charge. Medical records reflect that the deceased felt that he was: "….*improving slightly*…." and his CRP, as an objective indicator, had also improved.[81]

188. Dr Ayonrinde also noted improvements in the deceased's condition. He was informed that the risks and benefits of 6-MP had already been discussed with the deceased, who had consented to being prescribed the 6-MP. Dr Ayonrinde, having agreed with the plan to prescribe 6-MP, proceeded to explain to the deceased that they were trying to get him off the steroids and onto the 6-MP instead, given his mood disorder.[82]

189. Medical records and evidence before me establishes that Dr Van Rijnsoever directed Dr Ellis to prescribe the 6-MP to

[79] Exhibit 4
[80] Exhibit 4
[81] Exhibits 2 and 4
[82] Exhibit 5

the deceased and Dr Ellis executed that instruction. This was done with Dr Ayonrinde's approval. The deceased was commenced on 6-MP at 7.00 pm on 9 February 2015.

No policy regarding prescription of 6-MP

190. Whilst I have concluded that the decision to prescribe the 6-MP was based upon sound medical practice, there was a failure to implement appropriate safeguards for monitoring its side effects. Unfortunately, as at February 2015, FSH did not have a written policy addressing the safe prescription of 6-MP, which self-evidently includes monitoring for potential toxicity. Clinicians on the deceased's treating team took different approaches to the safe prescription of 6-MP.

191. Dr Gan on the one hand ordered a TPMT test to ascertain whether the deceased was able to metabolise the 6-MP, believing it was the usual practice. Dr Ayonrinde and Dr van Rijnsoever on the other hand had no such practice, and intended that there be full blood count testing within two weeks in order to ascertain whether the deceased was metabolising the 6-MP, or having a toxic reaction to it. Neither side knew of the others' approach.

192. At the inquest I explored the question of whether FSH ought to have had a policy in place for the safe prescription of 6-MP. On the evidence before me I have concluded that a relevant policy ought to have been in place. The reasons are outlined immediately below.

193. In October 2012, the Australian Commission on Safety and Quality in Health Care had published a Safety and Quality Improvement Guide concerning Medication Safety (NSQHS Standards, Standard 4). The NSQHS Standards were developed in consultation and collaboration with jurisdictions, technical experts and a wide range of organisations and individuals including health professionals and patients.[83]

194. The primary aims of the NSQHS Standards are to protect the public from harm and improve the quality of care provided by health service organisations. They provide a quality assurance mechanism that tests whether relevant systems are in place to ensure minimum standards of safety and

[83] Exhibit 1, tab 35

quality. In terms of implementing systems to improve medication safety, Standard 4 provides:

> *"The Medication Safety Standard requires health service organisations to implement systems that reduce the occurrence of medication incidents and improve the safety and quality of medicines use. The intention of the Standard is to ensure that competent clinicians safely prescribe, dispense and administer appropriate medicines to informed patients and monitor the effects."*[84]

195. At the inquest Dr Mark, FSH's A/executive director, explained that the NSQHS Standards outline the standards that FSH has to meet. In relation to medication safety, it provides for a range of standards and actions that are to be completed to ensure safe prescription and management of medications.[85]

196. In September 2014 the Office of Patient Safety and Clinical Quality of the WA Department of Health published the WA Health High Risk Medication Policy. It outlined a range of precautions, and included the following:

> *"All chemotherapeutic agents are considered high risk medications"*
>
> *"Procedures and policies must be in place regarding the safe prescription, preparation, administration and monitoring of chemotherapeutic agents."*
>
> *"Procedures and policies should be in place to provide direction and clear instruction on working practices to staff involved in providing chemotherapy and targeted therapy."*[86]

197. In that same month, September 2014, the then Director General of the Health Department issued Operational Directive OD 0561/14 attaching the WA High Risk Medication Policy, stating that it was based upon NSQHS Standards, with a period of effect from 31 August 2014 to 31 August 2017. The directive outlined that: "*The purpose of identifying high risk medications is to establish locally-based safeguards and strategies to reduce the risk of errors with these medications during all phases of the medication use process.*"[87]

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[84] Exhibit 1, tab 35
[85] ts 294
[86] Exhibit 1, tab 36
[87] Exhibit 1, tab 37

198. At the inquest Dr Mark explained that FSH is required to comply with the WA High Risk Medication Policy. He agreed that 6-MP is a chemotherapeutic agent. His attention was drawn to the requirement for procedures and policies to be in place for FSH staff involved in providing chemotherapy and targeted therapy. He conceded that: "*There was none in place at the time.*"[88]

199. Dr Mark proffered the explanation that the treatment of the deceased was led by the consultant assisted by two experienced registrars and that if FSH were to write policies and procedures (as they subsequently did) they would be consulting with them because they are the content experts.[89]

200. I am not satisfied that this explanation adequately addresses the lack of policies and procedures at FSH regarding the prescription of 6-MP in February 2015. The terms of the WA High Risk Medication Policy and the Operational Directive of the Director General of the WA Health Department required that there be written policies and procedures, as from September 2014.

201. After the deceased's death FSH proceeded to develop a policy and procedure concerning "*Inflammatory Bowel Disease Patients commencing on Mercaptopurine or Azathioprine*" (FSH's Mercaptopurine Policy). The first version was before me in evidence at the inquest and dated December 2015. An amended and updated version was provided to the court on 18 April 2017 and received by me into evidence on 19 April 2017.[90]

202. The details of FSH's Mercaptopurine Policy are addressed later in this finding in connection with the improvements since the deceased's death.

Consent to treatment with 6-MP

203. There is no signed or written consent form relating to treatment with 6-MP in the deceased's medical records at FSH. The deceased's medical records document the fact that the risks and benefits of lifelong 6-MP were discussed with him and that he was happy to start this medication.

[88] ts 302
[89] ts 302 to 303
[90] Exhibit 1, tab 38 and Exhibit 18.1

However, there is no detail of the discussion in the medical records.[91]

204. The deceased's father is concerned that his son was not comprehensively alerted to the potentially adverse effects of 6-MP and questions whether he consented to it being prescribed to him. Allied to this is his concern that his son, being in a fragile mental state, may not have been capable of apprehending the risks involved in giving his consent to this type of medication.

205. At the inquest I explored the questions of whether the deceased provided his consent to treatment with 6-MP, how it was sought, obtained and documented, and whether those communications could have been better.

206. On the evidence before me I have concluded that the deceased gave his consent, but that in the circumstances it would have been desirable to have it recorded by way of written informed consent. Again, the absence of a written policy at FSH regarding the safe prescription of 6-MP impacted upon the manner in which this was addressed.

207. The Department of Health's Office of Safety and Quality in Healthcare developed the Consent to Treatment Policy for the Western Australian Health System, which was first released in October 2006. The version that applied as at February 2015 was the 2011 third edition (the 2011 DOH Consent Policy). It is now superseded, and a copy with that notation is available at the Health Department's website.

208. The 2011 DOH Consent Policy provided that all WA Health facilities (as expressed in that policy) will obtain written consent using an approved consent form (except for emergency treatment) …. for:

> *"administration of medications with known high risk complications or new unusual medications which may have risks."*

209. The 2011 DOH Consent Policy went on to explain that (self-evidently) while a consent form is merely evidence of consent, its absence could lead to the conclusion that the procedure has not been discussed with the patient or that the patient has not given his/her informed consent. For this reason, where the patient is conscious and able to give

[91] Exhibit 2

written consent, the 2011 DOH Consent Policy outlined that it is always preferable that consent be obtained in writing. Furthermore it was noted that if consent was only obtained verbally there is a risk for ambiguity around what was said and agreed to.

210. Separately to the written consent in those cases, the 2011 DOH Consent Policy outlined that it was essential that the consent process and the outcome be always documented in the patient's health care record. That record was to include all essential and key points of the discussion, including questions raised by the patient and responses provided, and a list of any material risks discussed with the patient.

211. It is arguable that 6-MP was a medication with known high risk complications as at February 2015. The medication was prescribed in a wide range of circumstances, and the high-risk complication was in the small proportion of the population who are unable to metabolise 6-MP by reason of having two non-functioning copies of the TPMT gene.

212. The medical records in their totality, considered together with the evidence of Dr Ayonrinde and Dr van Rijnsoever persuade me that the risks and benefits of lifelong 6-MP were discussed with the deceased, that he had capacity to understand the information conveyed to him, and that he consented to being prescribed 6-MP on 9 February 2015.

213. However, this is not the end of the matter. With a medication such as 6-MP there needs to be ongoing assessment and discussion with the patient. Side effects may emerge over time. There was a lot of information for the deceased to process when he was informed of the risks of 6-MP on 9 February 2015. Whilst I am satisfied that he had capacity, he was prone to both anxiety and depression, which together with his debilitating illness, made him a vulnerable patient.

214. If the deceased had been asked to consider and sign a consent form that outlined the risks of treatment with 6-MP, and the safeguards (such as the need for regular blood tests), there would have been a document available to him in the longer term that he could refer back to. It might have prompted him to take action when he continued to feel unwell post-discharge. At his election, he might have shown it to his father, who was taking care of him post-discharge.

215. At the inquest, Dr Mark did not consider specific written consent from the patient was required as at February 2015, preferring instead that consent be documented:

> *"….If you look at the Department of Health Consent Policy 2011 it did say high risk medications should have written consent.* ***It didn't specifically note chemotherapeutic agents****. If you look at the 2016 policy – which of course wasn't around at the time of this unfortunate incident – it doesn't require written consent, but it does require a specific effort and documentation of the information given to the patient …. that the patient had agreed to the consent.* ***And the 2016 document does specifically mention chemotherapeutic agents****".*[92] [emphases added]

216. In this regard, Dr Mark was referring to 2016 DOH Consent to Treatment Policy, which was issued after the deceased's death. His focus was on the documentation of consent in the patient's medical record. The 2016 DOH Consent to Treatment Policy provides as follows:

> *"It is imperative that the details relevant to consent be documented, regardless of whether the patient consents to or declines the proposed treatment. Well-documented consent communications will assist in verifying that a health professional has met his/her obligations in providing relevant information to the patient about their treatment options. The more complex or risky the procedure, the more important it is that specific details are captured in the patient's medical record."*

217. The 2016 DOH Consent to Treatment Policy requires that prior explicit consent be obtained and recorded in respect a range of treatments that relevantly include: *"….off-label use of medications …. with known high risk complications*". This more clearly includes the 6-MP that was prescribed to the deceased in February 2015.

218. The 2016 DOH Consent to Treatment Policy goes on to require certain minimum documentation requirements in the medical record that include details about the information provided to the patient, all key points of the discussion, material risks discussed with the patient and signature of patient and person who determined that consent process has occurred. Consent forms form part of the medical record.

219. I am therefore satisfied that in the case of the prescription of 6-MP off-label, the 2016 DOH Consent to Treatment Policy

[92] ts 297

requires both written and signed consent, together with documentation in the medical records. The 2016 DOH Consent to Treatment Policy also makes it clear that the prescription of 6-MP off-label comes within the ambit of the treatments requiring explicit consent.

220. I am satisfied that as at February 2015 it was Western Australian health policy that written informed consent be obtained using an approved consent form when prescribing medications with known high risk complications or new and unusual medications which may have risks. This would arguably include 6-MP.

221. It is submitted to me that it was a legal requirement. It was not a legal requirement. The matter was addressed by state-wide policy. There was no specific policy addressing written and signed informed consent to treatment with 6-MP at FSH as at February 2015. However, this is now addressed in the 2016 DOH Consent to Treatment Policy.

222. It is noteworthy that the 2017 FSH Mercaptopurine Policy outlines a specific procedure for the patient's written and signed consent to commence an immunosuppressant (such as 6-MP) and this is addressed later in this finding in connection with the improvements since the deceased's death.

TPMT test or Full Blood Count

223. Another central question at the inquest concerned whether or not TPMT testing ought to have been undertaken for the deceased prior to prescribing 6-MP. The evidence disclosed that hospitals had different practices for addressing the question of whether 6-MP was contraindicated in a patient, and not all of them performed TPMT testing.

224. Broadly speaking, one approach was to test for TPMT activity before prescribing 6-MP, bearing in mind that whilst only a small proportion of population is genetically deficient in TPMT, the adverse reaction that is to be anticipated in such persons is significant and likely to be fatal if the 6-MP is not withdrawn in time.

225. Another approach was to start the 6-MP, which will take some months to become effective, and follow up with a full

blood count screening within at least two weeks, to ascertain whether the particular patient is at risk of bone marrow aplasia. This allows the patient to be commenced on an important treatment, and in the case of the small proportion of the population that has non-functioning copies of the TMPT gene, this will be identified through the blood screening and the 6-MP can be withdrawn in time. The evidence established that this is the primary safeguard, even if a TPMT test is done.

226. Self-evidently, the third option is to do both. The manner in which monitoring for toxicity is to now occur is addressed later in this finding in relation to the improvements since the deceased's death, as outlined in FSH's Mercaptopurine Policy.

227. For the purposes of analysing the role of the clinicians at the time of the deceased's death, care must be taken to understand the generally accepted approach to TPMT testing in connection with the prescription of 6-MP as at February 2015.

228. The first point to note, as already outlined, is that FSH had no written policy regarding the prescription of 6-MP and relied upon the expertise of the clinicians. The evidence disclosed that clinicians had different approaches to monitoring the potentially toxic effects of 6-MP.

229. At the inquest I heard evidence directed to establishing the generally accepted approaches by specialised clinicians to TPMT testing in such circumstances. This aspect of the inquiry became critical because a TPMT test was ordered by FSH and results received, and they showed unequivocally that the deceased should have been instructed to cease his 6-MP, by reason of his homozygous TPMT mutation. However, the results did not become known to his clinicians until after his collapse, by which time it was too late, as the toxicity had become insurmountable. Two questions arose:

- why was it not the practice at FSH to order a TPMT test prior to prescribing 6-MP?
- how was the potential toxicity of 6-MP to be addressed?

Royal College of Pathologists' recommendation

230. The position of the Royal College of Pathologists of Australia (RCPA) as at February 2015 was (and remains) that all patients should be assessed for TPMT activity prior to the commencement of any thiopurine (such as 6-MP). Dr Michael Harrison, president of the RCPA gave evidence at the inquest. The RCPA regulates the specialty of pathology within Australia, New Zealand and parts of South East Asia. Its main role is educational. They set curricula, assess candidates and grant fellowship to those who meet the qualifications.

231. Pathology is the study of the basis of disease, and pathologists are involved predominantly in performing tests to detect and diagnose disease. The RCPA issues a manual of use and interpretation of pathology tests. Dr Harrison regards the manual as an aid to doctors in other specialities (which would include gastroenterology).[93]

232. The manual contains an entry that outlines the TPMT phenotype test. It addresses the various elements relating to the test, such as the specimen, the method, the reference intervals, application and interpretation. The application is for the identification of patients at risk of potentially fatal myelosuppression from usual doses of thiopurines (including 6-MP), and states: "*All patients* ***should*** *be assessed prior to commencement of the drug, not retrospectively to ascertain the cause of an adverse reaction.*"[94] (emphasis added).

233. Dr Harrison explained that this recommendation is to be interpreted as meaning that it is advisable (not mandatory) to have the result of the TPMT phenotype test before commencing the patient on a thiopurine such as 6-MP (though it could also reasonably be extended to include the TPMT genotype test). In Dr Harrison's experience genotype test results can become known within five working days. He confirmed that this recommendation was in effect as at February 2015.[95]

234. In Dr Harrison's view this RCPA recommendation is developed predominantly for requesting doctors (not pathologists). He agreed that the target audience would be

[93] ts 111 to 112
[94] ts 113; Exhibit 1, tab 41
[95] ts 114 to 115; ts 117

medical practitioners intending to prescribe 6-MP. The recommendation would have had input from immunopathologists, and joint fellows in haematology and genetics.[96]

235. Dr Harrison also agreed that if a substantially lower than usual dose of 6-MP was being considered, that would temper the RCPA recommendation (which is made in connection with the usual dose) and that if a condition meant that a patient needed to start treatment immediately, then it may be reasonable to start treatment but also obtain the test result for this test.[97]

236. Dr Gannon, president of the Australian Medical Association (AMA) informed the court that the AMA fully supports the clinical views expressed by the RCPA as the leading organisation that is responsible for the training and professional development of pathologists, and that the AMA (WA) has written to the WA Department of Health encouraging it to follow the clinical protocols set out by the RCPA.[98]

The treating clinicians' views on TPMT testing

237. As at February 2015, in addition to the RCPA recommendation, there were a number of other international guidelines and protocols regarding the utility of TPMT testing prior to the prescription of 6-MP. This is addressed in the context of the evidence of the clinicians responsible for the deceased's treatment at various points during his first admission to FSH.

238. Dr Chong, as consultant in charge between 4 and 8 February 2016, was the deceased's treating clinician and his name remained on the deceased's medical records even after his handover to Dr Ayonrinde, because the deceased was initially admitted under his care.

239. Dr Chong was not the consultant involved in the decision to prescribe the deceased the 6-MP. His views on TPMT testing were relevant to the inquest given his extensive experience as a consulting gastroenterologist. He first became aware the deceased had been prescribed 6-MP when the deceased was admitted to FSH's ICU on 1 March 2015. In his

[96] ts 116 to 118
[97] ts 117 to 118
[98] Exhibit 1, tab 41

experience, as at February 2015, the results of a blood test for TPMT activity were usually available within two to four weeks, and that period has subsequently contracted to one to two weeks.[99]

240. Dr Chong informed the court that it is not currently his practice to commence patients on 6-MP without TPMT testing. However, he was aware that at FSH in 2015 (and Fremantle Hospital before that), the standard approach was that 6-MP was frequently commenced without TPMT assessment and the potential for side effects was monitored by regular blood tests (full blood count and liver function tests).[100]

241. Whilst it is not Dr Chong's current practice at FSH to commence patients on 6-MP without TPMT testing he still believed it is acceptable to start a patient on 6-MP under the appropriate circumstances before knowing what the TPMT results are. Clearly, had Dr Chong known that the deceased was taking 6-MP and that his TPMT level was very low, as occurs in one in 300 people, he would have asked him to stop the medication. At a general level, depending on the result, another option may be to modify the dose.[101]

242. As at February 2015, Dr Chong was not aware of the RCPA Manual recommending TPMT testing. Whilst his practice is now to regularly test for TPMT, he has not found it to be of great value. He continues his practice of requesting regular full blood counts and liver function tests.[102]

243. Dr Chong informed the court that international guidelines on the question of TPMT testing are mixed:

- The European Crohn's and Colitis Organisation says TPMT testing is not mandatory;
- The Food and Drug Administration in the United States says that it is mandatory;
- A recent meta-analysis for routine testing for TPMT for all patients starting on thiopurines (including 6-MP) questioned the usefulness of routinely testing for TPMT for all such patients.[103]

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[99] Exhibit 7
[100] Exhibit 7
[101] Exhibit 7
[102] Exhibit 7
[103] Exhibit 7; "*Use of thiopurines in inflammatory bowel disease*" World Journal of Gastroenterology, Volume 19, Issue 7, 21 February 2013

244. Information provided to the court by Dr Chong indicates that as at February 2015 6-MP was commonly used as a steroid-sparing agent in chronic autoimmune inflammatory conditions (such as Crohn's disease). In considering the utility of TPMT testing, one of the factors taken into account was that patients receiving 6-MP were required to have full blood counts measured on a regular basis to prevent severe toxicity by early detection.

245. The 6-MP medication had been used successfully for a number of years before TPMT testing was available. Another factor taken into account was that thiopurine related toxicities could also be partially explained by mutations in other enzymes, drug interactions, concurrent infections and immune-mediated drug reactions.[104]

246. In Dr Chong's experience, regular full blood counts and liver function tests are expected for any patient started on 6-MP. In his view a full blood count is the usual way to monitor bone marrow suppression related to 6-MP. He would have expected this to be done weekly to two weekly for the first six to eight weeks after commencement or change of dose, then three monthly thereafter.[105]

247. Dr Ayonrinde took over from Dr Chong as consultant in charge on 9 February 2015. Dr van Rijnsoever arranged for the prescription of the 6-MP to the deceased on that date, with Dr Ayonrinde's agreement. Dr Ayonrinde informed the court that treatment for the deceased with the immunomodulatory drug 6-MP (50 milligrams per day) was initiated as a steroid-sparing agent to facilitate reducing the prednisolone dose as quickly as possible to reduce the potential effect of steroids on the deceased's mood, and for discharge home on 10 February.[106]

248. Dr Ayonrinde referred to potential effects of steroids on the deceased's mood such as disturbed sleep, irritability and altered mood that could be lowered or increased. Being aware that 6-MP was generally slow acting, he hoped that it would gradually achieve the effect of immunosuppression that would allow for reducing steroid dosing. His

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[104] "*Assessment of Thiopurine S-Methyltransferase Activity in Patients Prescribed Thiopurines: A Systemic Review*" Annals of Internal Medicine, Volume 154, Number 12, 21 June 2011

[105] Exhibit 7

[106] Exhibit 5

expectation was that any adverse effects would be monitored by way of full blood count and liver function tests.[107]

249. Dr Ayonrinde pointed to another reason for starting the deceased on 6-MP as soon as possible, which was to shorten the time necessary for him to qualify for Pharmaceutical Benefits Schedule funded biologics treatment with the anti TNF (tumor necrosis factor) drug infliximab, which has strict approval guidelines. The deceased did not qualify for infliximab given his initial non-adverse response to steroids.[108]

250. Dr Ayonrinde does not recall discussing TPMT at the time the deceased was prescribed the 6-MP. I am satisfied it is unlikely that he discussed it because TPMT testing was not part of his routine procedure prior to commencing patients on 6-MP at FSH at that time. As at February 2015, Dr Ayonrinde was not aware of the RCPA Manual recommending TPMT testing. He does not consider it universally accepted or adopted.[109]

251. Dr Ayonrinde did not agree with the RCPA recommendation in an absolute sense because there are instances (as in the case of the deceased) where a clinician may prefer not to wait up to four weeks for the TPMT result when desiring a lead time for 6-MP to take effect on order to enable withdrawal of steroids.[110]

252. In Dr Ayonrinde's experience, clinical practice has been split over the necessity of having TPMT test results available prior to commencing 6-MP. He informed the court of a web-based cross-sectional survey of 175 relevant participants between December 2009 and April 2010. The purpose was to evaluate the extent to which gastroenterologists who are experts in the field of IBD's are utilising thiopurine metabolism in practice. One of the conclusions was that thiopurine testing was relatively underutilised by IBD gastroenterologists.[111]

253. Dr Ayonrinde also pointed to two other studies. One addressed the question of whether pre-treatment

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[107] Exhibit 5
[108] Exhibit 5
[109] Exhibit 5
[110] Exhibit 5
[111] "*Use of Thiopurine Testing in the Management of Inflammatory Bowel Diseases in Clinical practice: A Worldwide Survey of Experts*", Inflammatory Bowel Diseases, Volume 17, Number 12, December 2011.

determination of TPMT enzymatic activity (phenotyping) or TPMT genotype to guide thiopurine therapy in chronic autoimmune disease patients reduces treatment harms. Due to the low number of patients who were homozygous for TPMT variant alleles, there was insufficient evidence regarding the effectiveness of pre-testing.[112]

254. The objective of the other study was to assess the TPMT levels in patients with IBD and to determine how these levels impacted thiopurine dosing and leukopenia over the first six months of therapy. Notably, of the 423 patients, only one had a low TPMT level. It was concluded that normal TPMT levels did not prevent the development of leukopenia, although life threatening leukopenia was rare. It was also considered that physicians are not using TPMT levels to substantially dose thiopurines at the outset, which may limit the speed at which adequate doses are reached to facilitate remission.[113]

255. Dr Ayonrinde understanding was that in February 2015, it was not routine practice or policy to have a TPMT test result prior to commencing a patient on 6-MP at Fremantle Hospital or FSH. This is supported by all of the evidence before me at the inquest.

256. Consistent with Dr Chong, as at February 2015, in Dr Ayonrinde's experience, a patient's full blood count (for example which would show the effect of bone marrow suppression for individual patients) was considered critical regardless of the TPMT result.[114]

257. Dr Ayonrinde also sounded a note of caution about relying on TPMT tests alone in these circumstances. While useful in risk assessment for the effect of 6-MP on bone marrow suppression, in his experience TPMT tests alone can provide a false sense of security about the risk of bone marrow suppression for individual patients.[115]

258. Dr Ayonrinde explained that the purpose of a full blood count is mainly to check the different blood cell counts, particularly the white blood cell count to pre-empt or detect

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[112] "*Assessment of Thiopurine Methyltransferase Activity in Patients Prescribed Azathioprine or Other Thiopurine-based drugs*" University of Ottawa, AHRQ Publication Number 11-E002, December 2010

[113] "*The utility of thiopurine methyltransferase enzyme testing in inflammatory bowel disease*" Canadian Journal of Gastroenetrology, Volume 27, Number 1, January 2013

[114] Exhibit 5

[115] Exhibit 5

excessive bone marrow suppression and 6-MP efficacy. The outcome will assist the relevant clinician in determining whether the 6-MP dose should be reduced or stopped or if there is a need for an unscheduled review of the patient.[116]

259. Dr Ayonrinde considered that the first full blood count should have been done within one or two weeks (that is at least by approximately 24 February 2015) and then repeated within one to two weeks. By performing the first full blood count within the initial time frame, if the patient is starting to have a negative reaction to the 6-MP it would be detected before the patient deteriorates to the point of being severely unwell.[117]

260. Despite the divided views on the utility of TPMT testing and past practices, Dr Ayonrinde confirmed that in accordance with the new FSH Mercaptopurine Policy (addressed later in this finding) he has now adopted TPMT testing prior to prescribing 6-MP, together with initial weekly full blood count testing for four weeks to provide more confidence about reducing the risk of toxicity.[118]

261. Dr van Rijnsoever arranged for the prescription of the 6-MP to the deceased (with Dr Ayonrinde's agreement). He also confirmed his understanding that as at February 2015, the protocol at Fremantle Hospital and FSH was not to perform TPMT testing. He added a note of caution, namely that a normal TPMT test does not mean that 6-MP can be safely taken and the only way to prevent complication is regular blood testing.[119]

262. Dr van Rijnsoever pointed to studies that have shown TPMT not to be a reliable indicator of thiopurine toxicity. In one study, 35 of the 36 patients with thiopurine toxicity had a normal TPMT genotype. Another study found that of IBD patients on thiopurines who experienced bone marrow suppression, only 10% had a homozygous TPMT mutation, 17% were heterozygous and 17% had normal TPMT genotype.[120]

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[116] Exhibit 5
[117] Exhibit 5
[118] Exhibit 5
[119] Exhibit 4
[120] Those studies are, respectively: *"Pharmacogenomics and Metabolite Measurement for 6-Mercaptopurine Therapy in Inflammatory Bowel Disease"* Gastroenterology, Volume 118, Number 4, April 2000, and "*Genotypic Analysis of Thiopurine S-Methyltransferase in Patients with Crohn's Disease and Severe Myelosuppression During Azathioprine Therapy"* Gastroenterology, Volume 118, Number 5, June 2000

263. In Dr van Rijnsoever's experience, for those patients who tolerate 6-MP it is a very effective medication for long term management of IBD. In his view, anti-INF therapy such as infliximab is also an effective injectable therapy for IBD but it would not have been available to the deceased under the Pharmaceutical Benefits Scheme unless he had failed 6-MP treatment over a period of six months. For this reason he considers it beneficial to start patients on 6-MP sooner rather than later, so that in the event they need to progress to anti-INF therapy, treatment is not further delayed.[121]

264. From Dr van Rijnsoever's perspective side effects of 6-MP are detected with close blood test monitoring (full blood counts) and it is the blood testing that is critical.[122]

265. Dr Pearce, who did not have care of the deceased until 1 March 2015, assisted the court with information concerning the accepted practices in respect of TPMT testing. His views on TPMT testing were relevant to the inquest given his extensive experience as a consulting gastroenterologist.

266. In Dr Pearce's experience, there is a 50:50 split between gastroenterologists who would and those who would not request TPMT testing prior to starting 6-MP. He would not do so. Rather, he would start the treatment and then stop if the full blood count showed a problem or if the patient complained of adverse effects. In his experience, of the gastroenterologists who do request TPMT testing prior to commencing 6-MP, some wait for the test result to come back prior to commencing a patient on 6-MP and some do not.[123]

267. Dr Pearce informed the court, consistently with all the other evidence before me, that as at February 2015, it was not the practice at FSH to rely on TPMT testing. He pointed to the undesirability of delaying treatment while awaiting the test results, and he himself was not convinced of its utility for most patients, preferring instead to rely on the full blood count testing.[124]

[121] Exhibit 4
[122] Exhibit 4
[123] Exhibit 8
[124] Exhibit 8

The expert opinions on TPMT testing

268. In addition to the opinions of the deceased's treating clinicians regarding TPMT testing, I also sought the views of independent experts.

269. Dr Connell is a gastroenterologist with a sub-speciality in IBD. He has been the director of IBD services at St Vincent's Hospital in Melbourne for 18 years, and has been a doctor for 34 years. Most of his career has been has been devoted to treating people with IBD. As a clinician he attends to inpatients and outpatients with Crohn's disease and ulcerative colitis. He is very experienced in his area. He prepared a report for the coroner and gave expert evidence at the inquest.[125]

270. On the question of TPMT testing and whether it ought to be undertaken prior to commencing a patient on 6-MP Dr Connell's evidence, considered in the context of all of the other evidence, persuades me that the science behind the medicine in this area has been evolving, particularly given that TPMT enzyme activity and genotype testing became generally available in the mid 2000's. Dr Connell explained the developments apposite to TPMT testing as follows:

> *"….there are other factors apart from one's genotype that can affect the …. impact of thiopurines on bone marrow. Now, genotype is a powerful determinant of bone marrow effects of thiopurines, but it's not the only one. And so what's historically been put in place, what still is essential throughout the treatment of thiopurines is that people have to have regular blood tests measuring what's called the full blood count. So anyone who's assigned the need for this drug, there is a requirement for them to have regular blood monitoring to …. measure the white cell count at periodic intervals, and if there is a reduction in the white cell count from this drug, the dose either needs to be reduced or the drug has to be withdrawn. So in spite of knowing what the genotype is, …. there's still a requirement to perform these regular blood tests throughout the duration of …. treatment with thiopurines. So some people have argued, well, if you're doing the blood tests anyway then there's not much point in doing the enzymes or the phenotype because there is a safeguard against its effects by the – doing the regular blood test. And that's been the contemporary view and one that's been recommended by various international guidelines historically, and one that many practitioners employ.* ***This situation is evolving****, though – it is changing – and I think gradually, in the last few years, there has*

[125] ts 12 – 58; Exhibit 1, tab 18

> *been a much more – an attitude where the enzyme should be done and should be – either the genotype or the phenotype before the drug is used. And I think that's reflected by the – the* ***difference in guidelines that apply nowadays to what even applied five years ago, and .... I think in time most of the guidelines will eventually recommend that the .... enzyme be measured prior to treatment****."*[126] [emphases added]

271. In fact Dr Connell's prediction that most guidelines will eventually recommend TPMT testing prior to commencing a patient on 6-MP has been borne out in FSH's Mercaptopurine Policy addressed later in this finding. Like the other clinicians, Dr Connell pointed to a range of international guidelines operating as at February 2015, that placed different emphases on the utility of TPMT testing and/or the receipt of results prior to commencing a patient on 6-MP.[127]

272. At the inquest Dr Connell sounded a note of caution in the cases where there is clinical urgency to commence 6-MP to alleviate disease severity and suffering, given that in most parts of Australia, in his experience a TPMT test result will take two to four weeks to be known. In the deceased's case, Dr Connell pointed to the profound impact of steroids on a person's psychology.[128]

273. It is to be borne in mind that many of the guidelines referred to contain recommendations. They are not all intended to be interpreted as mandating TPMT tests. Clinicians will assess the individual circumstances. The deceased was commenced on 6-MP at 50 milligrams per day, which was a lower than usual dosage. The normal recommended dosage for a person of his body weight would be in the range of 125 milligrams per day.[129]

274. Dr Connell opined that in the deceased's case it was neither unreasonable nor inappropriate to commence him on 6-MP given the context of his disease severity and the need to quickly introduce a steroid sparing agent. He considers that most other IBD experts would concur with it. He did not suggest that the TPMT test not be done. Rather, he supported the commencement of 6-MP in these

[126] ts 24
[127] ts 27 to 29
[128] ts 24 to 25
[129] ts 30

circumstances, before the results were known, given the acute severe colitis.[130]

275. Dr Connell pointed to the risk of compromising the care of the vast majority of patients with acute, severe colitis if TPMT tests were to be considered mandatory in such circumstances, because those patients would need to await results before the 6-MP becomes available, and in the meantime, the effects of ongoing inflammation may accrue.[131]

276. Dr Connell expressed these opinions on the proviso that "*safeguards*" are implemented. Those were the full blood count tests that ought to have been performed two weeks later, to safeguard against the effects of any potential susceptibility to 6-MP.[132]

277. The requirement for the full blood count testing was addressed verbally with the deceased, and as part of his discharge planning. This is addressed later in this finding.

278. Professor David Joyce is a physician in internal medicine at Sir Charles Gairdner Hospital, director of clinical pharmacology and clinical toxicology at PathWest and professor of pharmacology and medicine at the University of Western Australia. Over half of his time is devoted to clinical work. He is very experienced in his areas. He prepared a report for the coroner and gave expert evidence at the inquest.[133]

279. On the question of TPMT testing, Professor Joyce noted that uptake has been slow partly because the full blood examination testing regimen has provided a time-proven way to detect patients at risk, and TPMT testing can never replace it. That testing regimen, two weeks after starting 6-MP will identify patients who are destined for bone marrow aplasia. The monitoring of full blood examination and liver function tests continues regularly throughout the duration of mercaptopurine therapy.[134]

280. Some published guidelines recommend that full blood examination starts at one week, proceeds at weekly intervals

[130] ts 27 to 28; Exhibit 1, tab 18
[131] ts 28
[132] ts 27; Exhibit 1, tab 18
[133] ts 396 to 424; Exhibit 15.1
[134] ts 410; Exhibit 15.1

for four weeks, and then reduces according to a time frame. However, Professor Joyce considered the one week starting point to be a bit more cautious and reiterated that deferring the first test until two weeks would be defensible.[135]

281. In evidence Professor Joyce postulated that a full blood examination at one week may have shown some early fall in white blood cell count to herald that the deceased was susceptible to the drug. At two weeks, his expectation would be that it would show a low white blood cell count that required revision of treatment intentions.[136]

282. Professor Joyce's views regarding the pre-eminence of the full blood count regimen are consistent with those of the clinicians who treated the deceased, the independent expert Dr Connell, the US Food and Drug Administrations "*label*" for thiopurine and the Australian TGA-approved product information for 6-MP.[137]

283. In Professor Joyce's experience the full blood count regimen is very reliable and has been employed throughout the approximately 60 years in which thiopurines have been used in clinical medicine. Like the other clinicians, he pointed to the varying advice from different professional and regulatory bodies about TPMT testing, which in his view partly reflects the different weights put on the value, timeliness, practice efficiency and cost benefit of testing.[138]

284. Given that TPMT testing in most places cannot provide a timely answer because of slow turnaround on genetic testing, Professor Joyce expressed a caution in that there are patients whose disease is so threatening that delaying treatment poses a greater risk to them than the small chance of genetically slow mercaptopurine elimination.[139]

285. Professor Joyce explained that the deceased's starting dose of 50 milligrams of 6-MP per day was quite a low dose, and in the years before TPMT testing was available, it was the starting dose, to be followed by a full blood examination within one week or one fortnight, to ascertain whether the patient was oversusceptible to it.[140]

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[135] ts 408
[136] ts 408
[137] Exhibit 15.1
[138] ts 411; Exhibit 15.1
[139] Exhibit 15.1
[140] ts 409

286. Professor Joyce pointed to the limitations of TPMT testing, resulting in it complementing the full blood examination regimen over recent times, but not superseding it. Limitations include the fact that TPMT testing is insensitive to all the non-genetic factors that can precipitate marrow failure in a mercaptopurine treated patient. He pointed to drug interactions, other marrow toxic drugs, vitamin deficiencies arising from failure of gut absorption and marrow diseases.[141]

287. In Professor Joyce's experience, TPMT phenotyping tests give incorrectly low results in patients who have had recent blood transfusions and maybe also in patients taking certain drugs for IBD. Genetic testing for TPMT also has no predictive value for other serious adverse effects such as hepatotoxicity and pancreatic toxicity.[142]

288. Professor Joyce considered the proper place of TPMT testing to still be incompletely defined. He outlined the various perspectives, namely that in one argument, full blood counts are a practically foolproof method of protecting people, and on another argument, TPMT testing provides foresight and can therefore potentially identify a patient's susceptibility a little more safely that the traditional method.[143]

289. Professor Joyce also pointed to the different clinical imperatives that are factored into the decision regarding TPMT testing. Like Dr Connell, he expects that within time, clinicians will move towards advance TPMT testing:

> *"The view which prevails amongst the clinicians that are using the drug is that the system works. So why fix it? And they are properly sceptical about the benefits of a new test. Those who don't actually look after the patients and who are not so moved by the imperatives of getting people quickly onto the treatment will then have their minds more heavily weighed by the beauty of actually knowing something very well in advance.... if we're to say how the relative weightings of those things have been moving was progressively moving more towards the practice of testing most people in advance there and the reason it's moving is not because the arguments have changed, it's just because the weightings have changed. So for example, the time taken to get the test is now much less. So it's ....less of an .... interference. That then makes forewarning more valuable there. The cost of the doing the test is now not heavily falling on the patient with –*

[141] ts 410; Exhibit 15.1
[142] Exhibit 15.1
[143] ts 420 to 421

with appropriate subsidies available there. So overall, with the passage of time, they're the same arguments, the weighting is changing and they are ***moving more towards a standard practice of testing in advance****."*[144] [emphasis added]

Conclusions with respect to TPMT test or full blood count

289. The evidence from the treating clinicians and the independent experts reflected that as at February 2015, on the question of whether the potential toxicity of 6-MP was to be ascertained by TMPT testing in advance, there were established, and defensible, approaches that varied. The TPMT test has become commercially available relatively recently and this continues to be an evolving area of medicine, as indicated by the clinicians' evidence, and a number of scholarly articles on the subject.

290. It is clear that, on either approach, the risk of ongoing potential toxicity is monitored by a regime of full blood count testing. That is the primary safeguard. The question of whether TPMT testing in advance of commencing a patient on 6-MP is recommended or desirable can be affected by a range of considerations. They include a balancing of the risk of potentially fatal toxicity in the one in 300 people that are homozygous for TPMT variant alleles, and the risk of delaying potentially vital treatment until the results are known. In the deceased's case, given his mental health condition, there was also a felt need to introduce a steroid sparing agent as soon as was practicable.

291. FSH's Mercaptopurine Policy as of April 2017 provides that TPMT genotype or phenotype testing shall be undertaken prior to 6-MP being administered.

292. Undoubtedly this area of medicine will continue to evolve and it is likely that best practice will change as knowledge develops. It is not my role, as coroner, to make findings on whether or not advance TMPT testing ought to be performed on IBD patients prior to administration of 6-MP. That remains a matter for the experts in the field and the specialised clinicians. On the evidence to date it is clear that advance TPMT testing is becoming a preferred option, and it is equally clear that studies will continue to be undertaken that may impact upon this question in the future.

[144] ts 422

293. My inquiry in this area is undertaken because:

- It is my role to comment on whether there ought to have been a written policy at FSH as at February 2015 to guide clinicians in the safe prescription of 6-MP, that addressed the question of whether or not TPMT testing was to be undertaken, or considered, and/or how, exactly, full blood counts were to be arranged; and

- Given the varied approaches to TPMT testing as at February 2015, it addresses critical questions. It establishes that:

  (a) it was reasonable for Dr Ayonrinde and Dr van Rijnsoever not to have ordered a TPMT test, to have relied on a plan for full blood count monitoring, and not to have expected that a TPMT test had been undertaken; and

  (b) it was reasonable for PathWest to have expected that the TPMT test was being undertaken in advance of commencing the deceased on 6-MP, consistent with the endorsements on the order form and the recommendations in the RCPA manual.

294. The events leading to the deceased's death arose not because of the prescription of the 6-MP, but because the planned safeguard (full blood counts) and the available safeguard (TPMT genotyping) were not followed up. These aspects are addressed in the context of the deceased's discharge arrangements and the follow up with his GP.

Discharge arrangements

The discharge procedure

295. The deceased was discharged from FSH on 10 February 2015 whilst he was still unwell. At the inquest I explored the circumstances of his discharge and whether a re-admission on 10 February 2015 would have been appropriate.

296. On 9 February 2015, Dr Ayonrinde authorised the discharge for the deceased for 10 February 2015, and made it subject to his condition continuing to improve. The plan was that

he be discharged home with his father. Unfortunately, as it transpired, the deceased's condition did not continue to improve, but he was nonetheless discharged from FSH. The details are addressed immediately below.

297. Dr Ayonrinde last saw the deceased during the consultant ward round at approximately 10.30 am on 9 February 2015, the day before his discharge. During that ward round Dr Ayonrinde noted improvements in the deceased's condition and recommended he continue the treatments that he was on. He did not see the deceased again prior to his discharge.[145]

298. Dr van Rijnsoever last saw the deceased the next day, during the ward round at approximately 10.13 am on 10 February 2015, being the day of his discharge. He was the most senior doctor on that ward round. Medical records reflect that the deceased was observed to look comfortable, that his symptoms continued to improve and that he could be discharged that day: "*Improving colitis. For discharge today with weaning prednisolone and 6-MP, plan as below.*" That plan was replicated in his discharge summary.[146]

299. The deceased's discharge plan, outlined in his discharge summary was for review and blood monitoring to be undertaken by his GP in two weeks. This is consistent with the recommendations in the American Guidelines on laboratory monitoring for patients treated with thiopurines:

> *"CBC [complete blood count otherwise known as full blood count - FBC or full blood picture - FBP] and transaminases [liver function test - LFT] should be assessed before onset of treatment and at two, four and eight weeks after initiating therapy, irrespective of TPMT status"*[147]

300. The instructions in the discharge summary dated 10 February 2015 to the Nominated Primary Healthcare Provider provided as follows:

- In the advice to patient section:

  "Please see your GP for blood tests in 2 weeks"

  "Start at a dose of 40mg Prednisolone for one week post discharge, then reduce dose by 5mg per week until ceased"

[145] Exhibit 5
[146] Exhibit 2, tab 3 (R, S); Exhibit 4
[147] Exhibit 4; "*Therapeautic Drug Monitoring in inflammatory bowel disease*" Annals of Gastroenterology, (2014) 27, 304 - 312

- In the advice to GP section:

  "Patient copy of discharge summary provided

  For IBD clinic follow up 4 weeks post discharge

  Please review FBP, U&E, LFT at 2 weeks post discharge

  For psychiatry outpatient clinic follow up"[148]

301. There was no explanation on the face of the discharge summary as to the reasons for undertaking a full blood count two weeks post-discharge. It was not flagged as urgent, nor was it highlighted so as to indicate its critical importance. Nonetheless, it is reasonable to expect that a GP who saw this entry would act to arrange full blood count testing at the two-week period as stipulated. The 6-MP was listed as one of the deceased's new medications on that discharge summary.[149]

302. Dr Ellis completed the deceased's discharge paperwork at FSH, including the discharge summary, being the junior member of the gastroenterology team tasked with this role. The actual discharge decision was made by the senior members of the gastroenterology team. As at 10 February 2015, Dr Ellis had only been working at FSH for approximately two weeks, and this was his first rotation as an intern. He had graduated from the University of Western Australia with a MBBS at the end of 2014. It is clear that he acted on instructions of his senior colleagues.[150]

303. Dr Ellis handed the discharge summary to the deceased, and explained a number of matters to him, including that he needed to see his GP for blood tests in two weeks, and to seek medical attention if he was feeling worse. Dr Ellis formed the view that the deceased appeared to understand these instructions.[151]

304. Whilst the deceased had been waiting in the transit lounge, and before Dr Ellis discussed his discharge summary with him, he had complained of pain to the nursing staff. As a result, nursing staff had contacted Dr Ellis requesting a phone order for pain relief medication. Dr Ellis did not consider this request to be unexpected, because he was

[148] Exhibit 1, tab 15 and Exhibit 4;
[149] Exhibit 1, tab 15
[150] Exhibit 11
[151] Exhibit 11

aware that the deceased had been receiving regular pain medication on the ward and had not been given any in the transit lounge.[152]

305. By the time Dr Ellis was able to provide the deceased with his discharge paperwork, the deceased had been in the transit lounge awaiting discharge for some hours and was upset about that. Dr Ellis was empathetic and he also suggested that the deceased express his concerns to FSH so that the hospital can look at what needs improving.[153]

306. Prior to this request, the deceased's last dose of buprenorphine was at 5.30 pm on 9 February 2015, and of tramadol at 6.00 am on 10 February 2015. As a result of Dr Ellis' phone order the deceased was given tramadol at 4.40 pm and then buprenorphine at 6.00 pm on 10 February 2015.[154]

307. When Dr Ellis later saw the deceased to discuss his discharge summary with him, the deceased did not appear unwell to him, though he indicated he still had some pain. Whilst the deceased was waiting in the discharge lounge, the results of his final routine blood sample for the day, taken at 11.25 am that morning, became available. Dr Ellis received them as he was recording the details on his discharge summary. He inputted the CRP at discharge as 100, based upon those results. He did not have a role in assessing the clinical implications of that CRP.[155]

308. The deceased left FSH's transit lounge at 6.48 pm on 10 February 2015, and was accompanied home by his father. By the time of his departure, the deceased had been awaiting discharge in the transit lounge for approximately seven and a half hours. At the inquest Dr Mark, FSH's executive director, readily agreed that this amount of time was wholly undesirable, and patients would not normally stay in the transit lounge awaiting discharge for anywhere near that period of time. He noted that in the deceased's case, there were some delays at the pharmacy.[156]

309. The FSH nursing note made shortly afterward the deceased's departure, at 7.22 pm on 10 February 2015 records that he

[152] Exhibit 11
[153] Exhibit 11
[154] Exhibit 11
[155] Exhibit 11
[156] ts 317 to 319

was in significant pain during his time in the transit lounge: "*Patient still complaining of pain post Tramadol. Pain score 9/10, groaning* +++". It is recorded that by the time the deceased left the transit lounge, his pain had decreased to 7/10.[157]

310. The deceased had no further contact with FSH until after his collapse on 1 March 2015.

311. At the inquest, Dr Mark was questioned about FSH's discharge procedures in the transit lounge, specifically in light of the evidence that emerged concerning the views of his treating clinicians, to the effect that, with the benefit of hindsight, he ought not to have been discharged. Dr Mark noted that whilst the deceased's pain score had gone up, his recorded observations did not indicate that there was a reason for Dr Ellis to have escalated the case to his registrar.[158]

312. Dr Mark did not consider the pattern of the deceased's illness to have changed whilst he was in the transit lounge and noted that the analgesics that he was given were similar to the medications that he was being sent home with.[159]

313. However, the gastroenterology consultants presented a different perspective, and this is outlined below.

The clinicians' views on the discharge

314. Dr Chong was no longer the rostered consultant when the deceased was discharged 10 February 2015. After the deceased's collapse on 1 March 2015, Dr Chong was informed that the deceased's CRP (a marker of inflammation) had risen to 100 on the day of his discharge. The CRP had been 33 the day before.[160]

315. Based on his experience, in his report to the coroner Dr Chong postulated that the deceased's raised CRP at discharge could have been interpreted as an indicator of the deceased requiring ongoing high dose steroids, or less likely an indicator of infection. The deceased's intravenous steroids had been substituted with lower doses of oral steroids. Dr Chong suggested that the deceased's raised

[157] Exhibit 2, tab 3 (U, V); Exhibit 11
[158] ts 317 to 318
[159] ts 317 to 318
[160] Exhibit 7

CRP might have indicated that he required a higher dose of steroids prior to discharge.[161]

316. At the inquest Dr Chong was also informed that at discharge, the deceased had a pain score of seven out of ten. This was the first time Dr Chong became aware of this fact. Having regard to the new information about not only the raised CRP, but also the pain score Dr Chong testified: *"It's much easier in hindsight, I would say, but if I knew that someone had abdominal pain and a CRP which was rising, in my practice I would not discharge a patient like that."*[162]

317. In Dr Chong's experience, the usual practice is for one of the nurses in the transit lounge to alert a doctor in the team that a patient to be discharged still had pain. Dr Chong suggested that if the deceased had remained in hospital instead of being discharged, with the raised CRP and pain score, he would likely have had an x-ray to exclude complications, and if there were no complications and no infection, he may have been put back on a higher dose of intravenous steroids. He qualified his response by noting that he was not there at the time.[163]

318. Dr Ayonrinde was the rostered consultant in charge when the deceased was discharged on 10 February 2015, but he last saw the deceased the day before. On that previous day Dr Ayonrinde had assessed the deceased and formed the view that his condition was improving and that he was doing well, and so the decision was made to fulfil his discharge the following day.[164]

319. The gastroenterology team arranged the deceased's discharge, and as I have outlined above, the deceased spent over seven hours in the transit lounge awaiting his discharge. Unfortunately Dr Ayonrinde was not informed of the deceased's raised CRP or pain score prior to the deceased's discharge (or at any time prior to the deceased's collapse on 1 March 2015).[165]

320. In his report to the coroner Dr Ayonrinde postulated that the deceased's higher CRP and white blood cell count as at 10 February 2015 would have raised the possibility of

[161] Exhibit 7
[162] ts 133
[163] ts 133 to 134
[164] ts 239; Exhibit 1, tab 5
[165] Exhibit 1, tab 5

inadequate oral steroid control of his acute colonic inflammation as compared with intravenous steroids. In his experience this would normally result in delaying discharge, because a CRP that is trending up reflects persisting or increasing inflammation. He outlined a number of reasons for a rising CRP (including but not limited to colonic inflammation) that would require further investigation.[166]

321. At the inquest Dr Ayonrinde testified that had he known that the deceased's CRP had risen to 100, and that he had a pain score of seven out of ten, he would have had him reviewed again and it is likely that the deceased would not have been discharged that day, and he outlined a range of further investigations: *"....with that description I would be keeping him in hospital."*[167]

322. In Dr Ayonrinde's experience, with the dual factors of raised CRP and pain, the usual practice is that the junior doctor would advise the registrar (with or without involving him) and the registrar would unilaterally reverse the decision for discharge. Given those changes, then the situation would normally be reassessed.[168]

323. Dr Ayonrinde hypothesised that reassessment would have included a review of the discharge plan, thereby keeping the deceased in hospital for clinical review (gastroenterology and perhaps also surgical), possibly a CT scan of his abdomen, reversion back to IV steroids and possibly antibiotics and formalised involvement of an IBD colleague if he was required to stay in hospital.[169]

324. In Dr Ayonrinde's opinion, it is unlikely that the inflammation reflected by the deceased's raised CRP was related to his death. He explained that inflammation and pancytopenia (from bone marrow suppression) are two independent processes. He believed the raised CRP would have reflected acute colonic inflammation or an infection unrelated to pancytopenia.[170]

325. Whilst consultant gastroenterologist Dr Pearce was not involved in the deceased's care until after his collapse on 1 March 2015, given his level of expertise, he was able to

[166] Exhibit 1, tab 5
[167] ts 242 to 243
[168] ts 242 to 243
[169] Exhibit 1, tab 5
[170] Exhibit 1, tab 5

provide relevantly helpful information to the court concerning the discharge practices. In Dr Pearce's experience, CRP results are not a valid indication of the effectiveness of IV steroid application compared to oral steroids.[171]

326. From Dr Pearce's perspective, being in hospital is a dangerous place for someone on immunosuppression. If he had known of the deceased's CRP results on the day of his intended discharge, he would have provided a considered opinion on the appropriateness of discharge, taking into account the reviews of the surgical and psychiatric teams.[172]

327. I am satisfied that discharge processes in FSH's transit lounge were insufficient to allow for a satisfactory discharge, given that the deceased's pain score had increased to seven out of ten, and his CRP had risen to 100. It was not Dr Ellis' role to make the clinical decision as to the deceased's re-admission. It ought not have been left to Dr Ellis to see the deceased alone in the discharge lounge without any guidance or process for the deceased being re-admitted, or the escalation process for pain management.[173]

328. There were cogent reasons for re-admitting the deceased. It cannot now be known what the results of further testing would have shown if the deceased had been re-admitted on 10 February 2015.

329. I am not satisfied that the evidence establishes that a re-admission on 10 February 2015 would have been likely to avert the toxicity that the deceased subsequently experienced as a result of taking 6-MP. On the evidence of the treating clinicians, that I accept, it would more likely have focussed on the ascertainment of reasons for his pain, and its management, including a possible reversion back to IV steroids.

The communication of the discharge arrangements

330. The deceased did not have his follow up blood tests within two weeks of his discharge from FSH, or at any time prior to his collapse. The intent was for him to have seen his GP for those tests. Unfortunately, his GP, Dr Jan Ravet did not

[171] Exhibit 8
[172] Exhibit 8
[173] ts 326 to 327

receive the discharge summary prepared by FSH. It was addressed to Bull Creek Medical Centre, with a street address and marked for the attention of: "*Attending Doctor of Bull Creek Medical Centre (Nominated Primary Healthcare Provider Person).*" It did not name Dr Ravet.[174]

331. At the inquest, a question arose as to the adequacy of FSH's procedures for providing a discharge summary to a patient's GP. It was particularly relevant because the follow up blood tests by the GP were the consultant's intended safeguard to detect and avert the possibility of 6-MP toxicity.

332. Dr Mark explained that there were a number of ways in which notifications occurred at FSH:

- First, every patient is given a copy of the discharge summary; and

- Secondly, the ward clerk mails a copy of the discharge summary to the GP by ordinary mail, places a copy on the patient's file and scans a copy into the patient's medical record.[175]

333. Whilst if a GP practice had "*opted in*" to the electronic messaging system, some information may have been sent electronically, a discharge summary was considered to be too confidential to send by email. At the inquest, Dr Mark was confident that the ward clerk would have mailed the discharge summary to the Bull Creek Medical Centre in accordance with FSH's procedures.[176]

334. Due to FSH having been operational for approximately one to two weeks, Dr Mark believed that it was unlikely that the address details of the Bull Creek Medical Centre on the discharge summary were entered by FSH staff; rather, they were more likely entered by the hospital he previously attended, based upon that medical centre's entry in the global health provider register.[177]

335. The deceased's GP, Dr Jan Ravet, testified that he did not receive a copy of the discharge summary at the material time. He was shown a copy at the inquest and he confirmed it cited the correct address for Bull Creek Medical Centre. In

[174] Exhibit 1, tab 15
[175] ts 315 to 316
[176] ts 315 to 316
[177] ts 315 to 316

his experience, all mail received by the surgery gets sorted. He did not consider it a probable scenario that the discharge summary reached the surgery, but did not reach him. FSH did not keep a separate record of mail sent, nor did it generally track the progress of correspondence sent through ordinary mail.[178]

336. At the inquest, Dr Ayonrinde, who approved the prescription of 6-MP to the deceased, stated that he was worried to hear that the deceased's discharge letter was not immediately available to his GP. Whilst a copy was routinely provided to the patient as a safeguard, Dr Ayonrinde agreed that FSH placed great reliance on the GP getting that information concerning post-discharge care through the discharge summary, and that this (i.e. mailing it) was the usual method of transmitting that information. Dr Ayonrinde explained that the clinical team was accustomed to this method, and consequently did not check with each recipient to see they received what, in practice, was automatically being mailed out by FSH.[179]

337. At the inquest Dr Mark explained that the deceased had been referred to the outpatient IBD clinic four weeks post-discharge. A purpose of an IBD clinic is to assist patients to transition into the community. Dr Mark testified that while nursing staff were available to assist in the management of the clinic, at that time they were not available to go chasing up blood tests of patients who had recently been discharged.[180]

338. Dr Mark considered it entirely satisfactory to refer a patient back to a GP for what he referred to as "*common*" blood tests. He pointed to resourcing and the fact that as at the time of the deceased's discharge, FSH had advertised twice for a clinical nurse specialist but unfortunately had not been able to make an appointment to that position in the IBD clinic. That appointment was made shortly after the deceased's death, on 23 March 2015.[181]

339. Dr Mark explained that FSH now has IBD nurses following up on blood tests, a service consistent with practice at Fremantle and Royal Perth. At the inquest he agreed that this improves the quality of care for patients, but

[178] Exhibit 6; ts 100 to 103; ts 315
[179] ts 261; ts 266
[180] ts 301
[181] ts 301

maintained that it does not mean it was unsafe not to have this service at the time of the deceased's death.[182]

340. I am satisfied that in the context of the crucial importance of the full blood count two weeks-post discharge, and the complexities surrounding the treatment of the deceased's condition, FSH's processes for communicating with external parties about a patient's discharge situation were not sufficient to support Dr Ravet or the deceased.

The expert opinion on the discharge arrangements

341. The expert gastroenterologist Dr Connell provided his opinion on two aspects of the deceased's care, being his discharge from FSH in circumstances where his condition appeared to have deteriorated in the transit lounge, and his post-discharge care plan, which he believed was not implemented despite intentions to do so. These two aspects are addressed immediately below.

342. Turning first to the deceased's discharge on 10 February 2015, at the inquest Dr Connell opined that the care the deceased received in hospital at FSH was very good considering the complexity of his situation, but he considered that something seemingly went wrong on the afternoon of his discharge that may not have been fully appreciated or recognised. Those concerns related to the deterioration in the deceased's condition in the transit lounge whilst he awaited his discharge prescriptions to become available.[183]

343. Dr Connell took account of the increase in the deceased's pain score (at one stage it was recorded as nine out of ten). He noted that the deceased's CRP (inflammatory marker) had decreased from over 200 upon admission, to 33 on the day before his discharge, but on the day of discharge there was a "*sharp increase*" to 100. In his view the logical conclusion was that the deceased's condition had become reactivated and this may have warranted a review of his discharge arrangements.[184]

344. Essentially, Dr Connell formed the view that the deceased was discharged when he was physically unwell with ongoing severe colitis, and therefore exposed to the consequences of

[182] ts 302
[183] ts 35
[184] ts 35

severe colonic inflammation (which has a high mortality if not treated effectively). From the medical records, Dr Connell also understood the deceased to be psychologically very depressed, a condition possibly aggravated by the steroids he was given. Put together with the lack of implementation of the follow up blood test (addressed below) Dr Connell considered there was a deficient component in the deceased's post-discharge care, despite every intention to do it properly.[185]

345. The second aspect concerned the delegation of the deceased's post-discharge care to his GP. In his report to the coroner Dr Connell had outlined his review of the deceased's post-discharge care and expressed the opinion that it highlighted a deficiency, having regard to its coordination, responsibility and the way in which clinical information and pathology results were communicated and collated.[186]

346. Whilst the intended follow up arrangements for the deceased were in keeping with a basic model of care currently available in Australia, with assigns a responsibility for patients to keep appointments as directed, Dr Connell was concerned as to whether this model is sufficiently patient centred and reliable especially in vulnerable or high risk individuals. Dr Connell underscored this concern by reference to patients with complex multi-system disease on potentially strong medication. At the inquest he opined that it was not a particularly good model of care for the deceased who was vulnerable by reason of his physical health and his psychological issues.[187]

347. Dr Connell questioned whether it was reasonable to delegate the role for monitoring treatment in such a case to an unidentified GP, and whether this handover was communicated effectively. He explained that he would have thought a GP assigned with responsibility to take on the particular task on the crucial full blood count for the deceased would need to know as much information as possible.[188]

348. Specifically Dr Connell testified that most GP's do not commence a patient on 6-MP and are not particularly

[185] ts 40
[186] ts 36; Exhibit 1, tab 18
[187] Exhibit 1, tab 18
[188] ts 36; Exhibit 1, tab 18

familiar with its effects: *"And so if someone else has started the drug then – and the GP is required to …. then adopt the follow-up arrangements, then it's necessary for that GP to be informed about the …. need for the blood test."*[189]

349. Dr Connell considered it would have been ideal for someone from FSH to have contacted Dr Ravet by telephone to advise of the need for the blood test, and that whilst the deceased was told on possibly two occasions that he needed to have this follow-up blood test, it is not a foolproof mechanism in a vulnerable person.[190]

350. Dr Connell also considered it surprising that a follow-up appointment in the FSH IBD clinic was not planned until a period of four weeks after discharge. In his experience follow-up with an IBD clinic can be dependent on a clinic's capacity, but in light of the deceased's condition and co-morbidities, including his CRP of 100 upon discharge, he would have thought it would have been more prudent to arrange a review with the IBD clinic within two weeks of discharge (as opposed to the four weeks as planned for the deceased).[191]

351. At the inquest Dr Connell explained that IBD clinics are an emerging area of practice that extend a service to a patient beyond that traditionally provided by the outpatient clinics. The IBD clinic is a multidisciplinary clinic that allows a patient access to specialist services throughout the working week, with a nurse coordinating and integrating the care. It will likely be able to draw on the expertise of physicians, surgeons, nurses, dieticians and psychologists and whilst this mode is not shared universally Dr Connell foreshadows that IBD clinics are the right way of proceeding.[192]

352. In his report to the coroner Dr Connell explained that for the purposes of post-discharge care, most major IBD services in Australia now employ specialist nurses to coordinate that care for complex disease:

> *"Their role is to follow-up patients discharged on strong medication by phone, monitor drug therapy (including the results of blood tests), provide a point of contact for patients or family members who have concerns, and to integrate care among various health practitioners, including GP's. In this way, the IBD*

[189] ts 37
[190] ts 37; ts 40
[191] ts 39
[192] ts 39

nurse has become indispensible in optimising risk management and delivering person-centred care for patients treated by public hospital IBD services"[193]

353. In practical terms Dr Connell explained that one of the key functions of a coordinating nurse is to identify and exercise a greater deal of attention to vulnerable patients, to coordinate patient care through the various health providers involved in the management of a patient's condition, to ensure they: "*don't fall through the cracks.*"[194]

354. In Dr Connell's opinion while FSH's discharge plans were in keeping with the accepted model of care in Australia, sadly they were not implemented and they did not succeed: *"There are no easy answers to these questions, but as hospitals discharge patients as quickly as possible, the quality and detail of post discharge care assumes increasing importance."*[195]

355. Dr Connell's evidence highlighted the importance of transitional care after discharge, to avoid a similar situation recurring. Dr Connell observed that it was unfortunate that the services of an IBD nurse coordinator were unavailable in this case. The availability of an IBD nurse coordinator would likely have prevented the system breakdown whereby reliance was placed on the discharge summary, sent by the ordinary post, not marked for the attention of a particular doctor at the Bull Creek practice: "*to hopefully arrive at the doctor's practice.*"[196]

356. I accept the evidence of Dr Connell together with that of Dr Mark and am satisfied that post-discharge care processes at FSH did not adequately support the FSH clinicians in their delivery of care to the deceased.[197]

357. I have had regard to Dr Mark's evidence to the effect that FSH had been unable to recruit an IBD clinical nurse specialist at the material time. That was rectified after the deceased's death by FSH increasing the staffing at its IBD clinic. This is addressed later in this finding in the context of improvements since the deceased's death. At the inquest,

[193] Exhibit 1, tab 18
[194] ts 40
[195] ts 40; Exhibit 1, tab 18
[196] ts 40; Exhibit 1, tab 18
[197] ts 40; ts 325 to 326

Dr Mark described the IBD nurses as an added asset and as being invaluable.[198]

Follow up with GP

358. Dr Ravet of the Bull Creek Medical Centre had been the deceased's GP since 2011. The deceased had attended for intermittent consultations since 2012. It is clear that Dr Ravet had built up a good rapport with the deceased over a number of years, and he retained positive memories of him as a person.[199]

359. In addition to Dr Ravet, the deceased had also been seen by doctors at Parkwood Medical Centre (intermittently since 1980) and AM & PM Doctors Rostrata (intermittently since 2012). Many of those consults since at least 2011 were in connection with the deceased's reported anxiety and depression. After the deceased's discharge from FSH on 10 February 2015, records reflect that he only saw Dr Ravet.

360. Most of the deceased's visits to Dr Ravet related to the treatment of his anxiety and depression, and medication to assist with sleep. Whilst the topic of suicidal ideation had arisen on more than one occasion during his visits to Dr Ravet, the deceased denied having any plan or intention to take such action.[200]

361. The deceased had complained of abdominal pain intermittently since 2012 and had been hospitalised for treatment on some occasions. In 2012 Dr Ravet had referred the deceased to a gastroenterologist, along with associated medical tests, but it appears the deceased elected not to proceed with this.[201]

362. In early January 2015 the deceased saw Dr Ravet for recurrent abdominal pain and associated symptoms. Some tests were conducted which failed to demonstrate an infective aetiology. By late January 2015, the deceased reported to Dr Ravet on more than one occasion that he was feeling better and specifically on 28 January 2015 that his abdominal symptoms had resolved. However, as at that

[198] ts 302
[199] ts 60 to 61; Exhibit 1, tab 17.1
[200] Exhibit 1, tab 17.1
[201] ts 62 to 63; Exhibit 1, tab 17.1

date he also reported feeling low, with flat affect. Dr Ravet was continuing to treat the deceased's mental health concerns.[202]

363. Dr Ravet had no specialty in gastroenterology. He had treated approximately three to four patents with IBD over a number of years, but none specifically with Crohn's disease.[203]

364. After the deceased was discharged from FSH on 10 February 2015, he next saw Dr Ravet on 13 February 2015. During this consultation, they discussed the deceased's admission to FSH and the fact that he was being treated with 6-MP and prednisolone for Crohn's disease. The deceased informed Dr Ravet that he was to be reviewed as an outpatient in four weeks' time.[204]

365. This would have presented an opportunity for Dr Ravet to ascertain that the FSH clinicians had instructed that full blood count testing be done at two weeks post-discharge on the deceased's discharge summary dated 10 February 2017. Unfortunately however, at the material time Dr Ravet did not become aware of that instruction. I have accepted Dr Ravet's evidence to the effect that at the material time he did not see the discharge summary that FSH mailed to Bull Creek Medical Centre. It cannot now be known whether it arrived at the medical centre at all.[205]

366. The deceased did not show Dr Ravet his own copy of his discharge summary on 13 February 2015, nor tell him that he needed follow-up blood tests.[206]

367. At the consult on 13 February 2015, the deceased informed Dr Ravet of a number of developments including that he had been in FSH in connection with his abdominal pain, that he had been prescribed 6-MP and that certain changes had been made to his medication regime in connection with his pain management and his mental health condition. Dr Ravet had some concerns about the changes to the deceased's medication regime, particularly in connection with the interactions with the anti-depressants and the analgesia, and the consult focussed on those aspects.[207]

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[202] Exhibit 1, tab 17.1
[203] ts 60
[204] Exhibit 1, tab 17
[205] ts 72 to 74
[206] ts 72 to 74
[207] ts 70 to 71

368. Dr Ravet accepted that the deceased's health requirements were complex. As at that time, he had only seen 6-MP used by oncologists to treat patients, and he had not previously encountered a patient taking 6-MP. At the inquest he was questioned as to why he did not contact anyone at FSH to find out what was wrong with the deceased. Dr Ravet agreed this would have been a good option, but he elected to rely upon the information communicated by the deceased, who he described as a "*good historian.*"[208]

369. In Dr Ravet's experience, past attempts to ring hospitals in order to ascertain facts and/or obtain copies of discharge summaries had resulted in interactions with records departments, with the result that access to the desired information was not generally available while the patient was with him.[209]

370. At the consult on 13 February 2015, the deceased had informed Dr Ravet that FSH was waiting on the results of a "*very clever blood test*", and that those results would be available to Dr Ravet. This would appear to be a reference to the TPMT testing, but not in those terms. After the deceased's death, on provision of information from his father, Dr Ravet apprehended that that was probably the test the deceased had been referring to. At the inquest, Dr Ravet agreed it would have been better or best practice for him to have made some further inquiries about the test that the deceased was talking about at the material time.[210]

371. At the consult on 13 February 2015, Dr Ravet issued the deceased with a prescription for 6-MP. At the inquest Dr Ravet was questioned on the reasons for this. Dr Ravet had no specific recollection of intending to prescribe 6-MP to the deceased. He did not know why the 6-MP script printed out after the tramadol script, but when they all came out he signed the 6-MP script along with the others without taking critical note of it.[211]

372. Dr Ravet posited that it may have printed out because he entered the 6-MP in the deceased's medication list on the computer and the software assumed he was trying to prescribe it. In his experience if he ticked the box "*not to be*

[208] ts 71 to 72
[209] ts 73; ts 93
[210] ts 74
[211] ts 89

printed" it would come off the medication list, and this would require another set of actions.[212]

373. At the inquest Dr Ravet conceded that he should have taken critical note of the 6-MP script. Speaking of the 6-MP script he testified as follows:

> "*I don't know why that got printed out, but I imagine that we have the Tramal queued and the mercaptopurine might've come out because everything else was queued. I don't think I did it with particular intent to supply him with more, but my feeling was that this had been issued by the specialists, they were happy with it, they would be – they would normally be responsible for the monitoring of it.*"[213]

374. At the inquest Dr Ravet agreed that it would have been very desirable to have spoken with someone at FSH about his concerns with the possible drug interactions, and about the 6-MP. He also agreed it would have been better practice for him to have informed himself about 6-MP. With the benefit of hindsight Dr Ravet believed that he should have ordered a full blood count test for the deceased on 13 February 2015, and done the same probably one week later, and one week after that.[214]

375. Dr Ravet also saw the deceased on 20 and 25 February 2015. Because he was unaware of the requirement for the deceased to have a full blood count test two weeks post-discharge, these represent further missed opportunities for ascertaining the requirement and/or ordering those tests.[215]

376. Dr Ravet recalled urging the deceased to return to the ED of FSH on each of the occasions that he saw him after discharge (being 13, 20 and 25 February 2015) but that the deceased appeared to him to be, in effect, reluctant to complain and felt that his pain was not bad enough to warrant his return to hospital.[216]

377. At the inquest Professor Joyce explained that a GP would not start a patient on 6-MP, but that it would be quite common for a GP to take over the monitoring of a patient taking 6-MP, rather than having the patient repeatedly return to a specialist for the checking of the blood tests.

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[212] ts 89
[213] ts 88
[214] ts 73 to 74; ts 87 to 88
[215] ts 76; ts 87 to 88
[216] ts 80; ts 97

However, Professor Joyce also added that in these circumstances, there would normally be telephone conversation between the prescribing specialist and the GP to make sure the GP was comfortable taking over the role.[217]

378. Specifically, in Professor Joyce's opinion, the GP would need to know factors influencing safety in connection with the medication. This would include dosage, monitoring schedule, and information regarding criteria for stopping the drug and referring back to the specialist: "*The person who has got primary responsibility can't hand it on without making sure the responsibility has been accepted by the general practitioner.*"[218]

379. I am satisfied that Dr Ravet's explanation for signing the 6-MP script was unsatisfactory in that a doctor must properly check a script before signing. Further, Dr Ravet signed such a script without being sufficiently informed of the possible side effects and requisite monitoring for toxicity. Through his counsel Dr Ravet accepts that he should have taken steps to better inform himself prior to prescribing 6-MP to the deceased. Fortuitously the medication was not dispensed pursuant to that script.

380. However, I am also satisfied that Dr Ravet was not provided with sufficient information by FSH to apprehend the severe nature of the deceased's condition and the requirements of his treatment plan. In particular Dr Ravet received no clear advice or instructions from FSH to the effect that the deceased required follow up blood tests to safeguard against 6-MP toxicity on or before 24 February 2015. The mailing out of a discharge summary in these circumstances was inadequate notification to Dr Ravet. As it transpired that document did not reach him.

CAUSE AND MANNER OF DEATH

381. Regrettably, as a result of an apparent miscommunication or misunderstanding the deceased's death was not reported to the coroner. As a consequence, there was no opportunity for the coroner to consider and direct a forensic pathologist to perform a post mortem examination on the body of the deceased pursuant to s 34(1) of the Coroners Act. There was no opportunity for a forensic pathologist to remove any

[217] ts 411
[218] ts 411 to 412

tissue from the body of the deceased pursuant to s 34(2) of the Coroners Act, in order to assist with the investigation of his death.

382. The importance of the post mortem examination cannot be underestimated. The forensic pathologist's opinion on the cause of the death is of material assistance to the coroner investigating the death. The coroner has a duty to find, if possible, how death occurred and the cause of the deceased's death, pursuant to s 25(1) of the Coroners Act.

383. There was no opportunity for the coroner's investigators to attend immediately after death, and no opportunity for those investigators to commence their inquiries and to obtain the information to assist the coroner as close as possible to the time of the events leading to the death.

384. The deceased's death was drawn to the attention of the coroner by his father. From an initial outline of the circumstances it was readily apparent that it was a reportable death within the meaning of s 3 of the Coroners Act. At the inquest I received and heard evidence about the events giving rise to the issue by FSH of a medical certificate of cause of death on 5 March 2015 (which has been voided) and evidence from a toxicologist and a forensic pathologist to assist me with making my finding on the cause of the deceased's death.

Why a medical certificate was issued

385. On 5 March 2015 FSH purported to issue a medical certificate of cause of death (the medical certificate) for the deceased. The disease or condition directly leading to death was specified to be (a) septic shock. The antecedent causes were specified to be (b) *Klebsiella pneumonia* septicaemia, due to (c) aplastic anaemia, due to (d) 6 Mercaptopurine, due to (e) Crohn's colitis.[219]

386. The medical certificate was filled out by Dr Aileen Fenelon, a junior doctor who was then a resident medical officer, having commenced with the ICU at FSH in January 2015. Dr Fenelon was acting under the guidance of the ICU consultant in charge, and had been instructed to contact the

[219] ts 222; Exhibit 1, tab 33

coronial investigation squad as the deceased's death was potentially medication related.[220]

387. Dr Fenelon first had contact with the deceased as an intubated patient at ICU on 3 March 2015. She attended a number of ward rounds with the treating team between 3 and 4 March 2015, and made a number of entries in the deceased's digital medical record. Dr Fenelon recalled that in the deceased's case, the ICU consultant was extensively involved in his care and often made his own entries. She also recalled that the deceased was critically unwell and not expected to live.[221]

388. When Dr Fenelon commenced her shift at 8.00 am on 5 March 2015, she was informed that the deceased had died earlier that morning, at 6.40 am. As a result of completing the necessary paperwork Dr Fenelon herself also identified that it may have been a reportable death, due to it appearing to be unexpected or unnatural. Specifically, on the Death in Hospital Form, guiding reporting to the coroner by a series of "*yes/no*" answers, Dr Fenelon marked "*yes*" to the question as to whether the death was as a result of: "*Complications following administration of a medication….*"[222]

389. As instructed, Dr Fenelon telephoned the coronial investigation squad telephone number. Contemporaneous medical records created by Dr Fenelon at 11.12 am and 1.44 pm on 5 March 2015 reflect that she made the arrangements to record the deceased's death, and that she discussed the matter with the police with a view to ascertaining whether the deceased's death was a reportable death: "*I have also contacted the coroner's office and discussed case with Craig Robertson who advised me that patient would not be a coroner's case.*"[223]

390. At the inquest Dr Fenelon testified that she spoke over the telephone to a police officer who identified himself as Craig Robertson. Whilst Dr Fenelon could not recall the exact words of the conversation, she remembered what was discussed. Dr Fenelon recalled that she outlined the background, and what she proposed to put on the medical

[220] ts 219 to 222; Exhibit 1, tab 33
[221] Exhibit 1, tab 33
[222] Exhibit 3, tab 4
[223] ts 219 to 222; Exhibit 1, tabs 4.2 and 33; Exhibit 1, tab 4.2

certificate, and that the police officer did not request it to be a coronial investigation.[224]

391. Dr Fenelon also recalled that when she informed the ICU consultant that she was advised by the police officer that the death was not a reportable death, he appeared surprised and instructed her to document the conversation. Dr Mark, FSH's A/executive director informed the court that it was known, throughout the deceased's second admission to FSH, that there was a likely relationship between his sepsis and 6-MP.[225]

392. Senior Constable Craig Robertson of the coronial investigation squad informed the court that he was indeed on duty as the medical liaison officer between 7.00 am and 3.00 pm on 5 March 2015 but that he did not recall any conversation with Dr Fenelon and there are no concomitant records concerning a report of the deceased's death, or any telephone conversation with Dr Fenelon.[226]

393. It is no longer possible for me to ascertain exactly what exchange of information led to an understanding on Dr Fenelon's part that the deceased's death was not a reportable death. The most likely explanation is that the complexity of the medical issues obscured the rather more obvious fact that the deceased's death appeared to be unnatural and unexpected, in that it appeared to arise as a result of complications following the administration of medication. An additional factor mandating reporting at that stage was the apparent ingestion of numerous tablet-like bodies that were seen on an abdominal CT examination on 1 March 2015, meaning that at that stage, the death may also have appeared to have resulted from self-harm.

394. I cannot be satisfied that all of the factors giving rise to these considerations were outlined to the named medical liaison officer, or indeed any other officer at the coronial investigation squad. Equally, given her junior role at the material time, I cannot be satisfied that Dr Fenelon herself was even fully apprised of all of these factors.

395. The import of the ICU consultant appearing surprised when Dr Fenelon reverted back to him, telling him that she was informed the death was not reportable is not to be ignored.

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[224] ts 223
[225] ts 223; Exhibit 6
[226] Exhibit 1, tab 4.2

ICU consultants are undeniably busy, and that exchange possibly reflects his more detailed understanding of the circumstances. I accept Dr Fenelon's evidence to the effect that she contacted the coronial investigation squad. There is insufficient evidence before me to ascertain the reasons for the outcome.

396. As outlined above in this finding, on 31 March 2015 the deceased's father wrote to the coroner to inform of the deceased's death. Upon inquiry it was found to be a reportable death within the meaning of s 3 of the Coroners Act.

The evidence on cause of death

397. There was no post mortem examination performed on the body of the deceased, consequently no post mortem samples were taken. At the inquest I heard evidence from a number of experts to assist me in making my finding on the deceased's cause of death.

398. In the opinion of clinical pharmacologist and toxicologist Professor Joyce the conclusion that the deceased's bone marrow aplasia was a result of the 6-MP toxicity occurring in the context of failed metabolic clearance through TPMT can be accepted. He noted the association is circumstantial, but it is an acknowledged situation of high risk and in his opinion there is no credible alternative diagnosis.[227]

399. At the inquest Professor Joyce explained that it has been known for more than 60 years that if you give too much 6-MP the suppression of white blood cell production is so severe that there will not be enough white blood cells produced to handle infections. In the deceased's case, he did not have a functioning copy of the TPMT gene on either of his chromosomes, meaning that he was not able to waste the toxic effects away. He is also aware that this condition affects about one in 300 people.[228]

400. As a result of the bone marrow aplasia, the deceased's bone marrow was not working to produce blood cells, most pertinently resulting in an abnormally low white blood cell count, and also a low platelet count. Consequently, the

[227] Exhibit 15.1
[228] ts 400

deceased was not able to fight off the normal microorganisms that are usually dealt with by the white blood cells. One such organism that is frequently encountered is *Klebsiella pneumoniae*. When that infection is present throughout the body, the condition is termed sepsis, which is a particularly severe form of infection.[229]

401. Professor Joyce considered the cause of the deceased's death to be *Klebsiella pneumoniae* sepsis. As a result of the immune disturbances, the functioning of the deceased's liver, lungs and kidneys was impaired. The failure of those organs, and the failure of the circulation resulted in death.[230]

402. Whilst the deceased might have had a level of susceptibility to infection from the Crohn's disease itself and the prednisolone therapy, in terms of the hierarchy of responsibility, Professor Joyce opined that the low white cell count from the 6-MP would have to be the most important. The other factors would not be likely to introduce a risk of a sepsis syndrome except in the most extraordinary cases.[231]

403. At the inquest, independent expert gastroenterologist Dr Connell reviewed the cause of death and antecedent causes that had been entered by the FSH clinician on the medical certificate. Whilst he agreed with the general terms of the medical certificate, he suggested that the severity of the Crohn's colitis was perhaps underestimated, and he would have included the adjective "*fulminant*" to describe the Crohn's colitis. This is because in his view, one of the reasons as to why the deceased could not be saved was because his Crohn's colitis was so bad. It is a reference to very severe Crohn's colitis.[232]

404. Forensic pathologist Dr Jodi White's opinion was sought on the deceased's cause of death, having regard to relevant medical records pertaining to the deceased, and the reports and/or evidence of Professor Joyce and Dr Connell and Dr Pearce. Dr White prepared a report for the coroner and gave evidence at the inquest.[233]

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[229] ts 401
[230] ts 401 to 404
[231] ts 404
[232] ts 46
[233] ts 425 to 433; Exhibit 17.1

405. Dr White noted that the deceased was diagnosed clinically, radiologically and on biopsy as having severe acute colitis, that bacterial aetiology was excluded and that he was considered to have a fulminant type of inflammatory bowel disease, most likely Crohn's colitis.[234]

406. Having regard to the deceased's medical records, Dr White opined that the 6-MP's toxicity appears to have been compounded by his homozygous genotype for TPMT. Dr White confirmed the deceased subsequently developed a severe infection (bacterium *Klebsiella pneumoniae*) and due to his immunosuppressed state, this has taken hold, and progressed rapidly leading to overwhelming septic shock with cardiovascular collapse and multi organ failure. He also had severe and ongoing colitis with bleeding from his bowel contributing to his death.[235]

407. At the inquest Dr White was asked about her level of confidence in attributing 6-MP as a contributor to the deceased's death and she answered as follows:

> *"Yes, I am confident because of his known genotype. He was more susceptible and at a greater risk, so the drug dose he was on was more potent because of his genotype, and therefore he was also – as a result of that he was more prone to the toxic effects due to his accumulation."*[236]

408. Dr White also had regard to the medical certificate and in all of the circumstances, provided her own opinion on cause of death, which is addressed in my conclusions on cause of death, below. At the inquest Dr White explained that as a forensic pathologist her opinion on cause of death is more narrative, as opposed to a medical certificate on cause of death. Dr White agreed that her opinion is very much similar to the medical certificate, except that she also added the TPMT deficiency as a contributing factor.[237]

The tablet-like bodies on the CT scan

409. A further question that needed to be explored at the inquest concerned the outcome of an abdominal CT examination performed on the deceased on 1 March 2015 that showed the presence of tablet profiles. Specifically it showed

[234] Exhibit 17.1
[235] Exhibit 17.1
[236] ts 427
[237] ts 428

multiple dense tablet-like bodies, at least 20 in number, in the lumen of the large bowel. It raised the question of intentional ingestion of excessive 6-MP tablets. In his report to the coroner and in evidence at the inquest Professor Joyce outlined his reasons for forming the opinion that these tablet-like bodies were not 6-MP.[238]

410. Professor Joyce observed that most of the tablet-like bodies seen on the abdominal CT examination appear elongated and large, so do not have the dimensions of 6-MP Puri-Nethol tablets. Such tablets, at a dosage of 50 milligrams appear as 7 millimetres in diameter, round, biconvex discs having a maximum thickness of around 2.5 millimetres. They are formulated to release their active drug quickly after ingestion.[239]

411. Professor Joyce undertook a dispersion study, that I accept, which showed that Puri-Nethol would completely disintegrate into powder over a period of between 12 to 18 minutes. The outcome showed that 6-MP tablets would not remain intact in the gut for more than a few minutes, even if there were obstruction or sequestration.[240]

412. Professor Joyce also testified that the tablet-like substances were the wrong size and shape for oral prednisolone, and that they were not iron tablets for similar reasons. He posited that it would probably be fairly likely that they were tablets purchased over the counter by the deceased, because such medications are sometimes fairly roughly formulated and may not dissolve up quickly in the gut. Dr White had noted that paracetamol toxicity was excluded.[241]

413. On the material before him, Dr Joyce could not identify the tablet-like substances, and whilst he could not exclude the possibility of a contribution to the deceased's death, he opined that there is a sufficient explanation for everything that happened just in the 6-MP.[242]

414. At the inquest Dr Connell considered it a little unusual that the tablets had reached the colon without being absorbed. To him it indicated that either the small bowel was terribly diseased and not capable of even absorbing the tablets, or

[238] Exhibit 15.1
[239] ts 405 to 406; Exhibit 15.1
[240] ts 406; Exhibit 15.1
[241] ts 407; Exhibit 17.1
[242] ts 407

that a number of tablets were taken at once and overwhelmed the capacity of the small bowel to absorb them.[243]

415. In Dr Connell's experience, severe colitis may, paradoxically, cause gut motility to become slower than normal, resulting in a state of stasis. Whilst he considered it an exceptionally uncommon event for the tablets to have accumulated simply because the gut was not working, in his view it could not be discounted.[244]

416. I am satisfied that the tablets seen on the abdominal CT scan cannot be 6-MP, and I accept Professor Joyce's opinion to the effect that even if the tablet-like substances cannot be identified, there is sufficient evidence to attribute the deceased's death to the 6-MP.

Conclusion on cause of death

417. At the inquest Dr White, having regard to the medical records and on the basis of her experience as a forensic pathologist for approximately 12 years, outlined her reasons for her opinion on the deceased's cause of death, as follows:

- The deceased developed fulminant sepsis; fulminant refers to a severe and overwhelming infection;
- Sepsis refers to a generalised infection, so as well as being in a primary source such as the lung, bowel or urinary tract, it has travelled to the bloodstream and infected other organs;
- The organism that caused the fulminant sepsis is *Klebsiella pneumoniae*, which was identified on several tests done while the deceased was an inpatient;
- The deceased's body reached a point where it could not maintain blood pressure, pulse rate and breathing so as to get oxygen into the blood; his system was overwhelmed by the infection, resulting in multi-organ failure;
- The deceased's lungs, kidney and heart began to cease functioning properly, resulting in a very fast heart rate and very low blood pressure;
- He developed pancytopenia;

[243] ts 44
[244] ts 44

- This was as a result of the administration of 6-MP, a cytotoxic and immunosuppressant drug which affects the bone marrow;
- Severe ongoing colitis was also a contributing factor because this chronic severe and debilitating illness weakened him and his ability to fight off infection was much less, he had ongoing blood loss as a result of his severe colitis, making him more anaemic, and more prone to hypoxia and subsequent damage to organs, and it may also have resulted in nutritional disturbances from not being able to eat and absorb food over a number of days or weeks;
- Finally, the TPMT deficiency put the deceased at greater risk and made him more vulnerable and susceptible to the cytotoxic effects of 6-MP.[245]

418. The medical certificate referred to the deceased having Crohn's colitis, as one of the antecedent causes of his death.[246]

419. At the inquest Dr White was questioned regarding Dr Connell's opinion to the effect that the medical certificate perhaps underestimated the severity of the deceased's Crohn's colitis and that he would have included the words "*fulminant Crohn's colitis*" to give some insight into how bad the Crohn's colitis was.[247]

420. In her report Dr White had also considered the medical certificate and she referred to the deceased having "*acute severe colitis (Crohn's*)." At the inquest, having regard to the evidence and in consideration of it being a chronic condition, Dr White formed the view that the deceased had suffered an acute severe exacerbation of chronic colitis (Chron's).[248]

421. At the end of her evidence Dr White formed the following opinion on the deceased's cause of death:

- Fulminant sepsis (*Klebsiella pneumoniae*) with multi-organ failure complicating severe pancytopenia following the administration of 6-Mercaptopurine in a man with acute severe exacerbation of chronic colitis (Crohn's) and TPMT deficiency.[249]

[245] ts 426 to 427
[246] Exhibit 1, tab 33
[247] ts 46
[248] ts 424; Exhibit 17.1
[249] ts 429; Exhibit 17.1

422. I accept and adopt Dr White's opinion on cause of death.

Conclusion on manner of death

423. In his report to the coroner Dr Connell opined that, although the cause of the deceased's eventual death was multifactorial, it is clear that the use of 6-MP in the context of his inherited TPMT deficiency of the TPMT enzyme contributed to his bone marrow aplasia. In his experience the suppression is dose dependent and usually occurs gradually over several weeks of treatment.[250]

424. At the inquest Dr Connell testified that "*undoubtedly*" the 6-MP to some extent played a role in the deceased's death. Professor Joyce's evidence was to the effect that there is no credible alternative diagnosis, Dr White was confident of it being a contributor and Dr Mark, FSH's A/executive director, opined that the 6-MP made a very major contribution to the deceased's death.[251]

425. Dr Ayonrinde, who approved the prescription of 6-MP to the deceased testified as to his belief that this medication had a major effect on his bone marrow, resulting in pancytopenia, which made him vulnerable to the sepsis.[252]

426. I am satisfied that the deceased was suffering from a serious health condition, but prior to the administration of the 6-MP, this condition did not immediately threaten his life. He underwent treatment with 6-MP that unexpectedly took a turn leading to his death. The evidence overwhelmingly establishes that the treatment of the deceased with 6-MP significantly contributed to, and ultimately resulted in, his death.

427. I find that the manner of the deceased's death was by way of misadventure.

WAS THE DECEASED'S DEATH PREVENTABLE?

Withdrawal of 6-MP after TPMT results

428. Having regard to the manner of the deceased's death, being by way of misadventure, it was necessary to explore whether

[250] Exhibit 1, tab 18
[251] ts 44; ts 303; ts 427
[252] ts 252

his death could have been prevented. At the inquest I heard evidence about whether the deceased's death could have been prevented if, hypothetically, the 6-MP had been withdrawn after the TPMT results.

429. There was general agreement by the clinicians that had a clinician responsible for the deceased's care become aware of the TPMT test results (phenotype and/or genotyping), direction would have been given for the deceased to cease taking 6-MP urgently.[253]

430. The product information for 50-milligram tablets of 6-MP, under the trade name Puri Nethol states that it is an active cytotoxic agent for use only under the supervision of physicians experienced in the administration of such agents. Bone marrow suppression is a known side effect, and is reversible if 6-MP is withdrawn early enough. In the deceased's case, this side effect was magnified due to this profoundly low TPMT activity.[254]

431. Dr Ayonrinde, who was responsible for approving Dr van Rijnsoever's plan to prescribe 6-MP to the deceased, only became aware of the deceased's TPMT results after his re-admission in March 2015, when his case was discussed at a gastroenterology morbidity meeting.[255]

432. Dr Ayonrinde's evidence was that if he had known of the TPMT test prior to then, he would have immediately instructed that the deceased stop taking 6-MP, left him on a higher effective dose of steroids, and expedited earlier review in the IBD clinic for assessment of his progress. He would have wanted a consideration of access to a biologic agent such as infliximab to treat the deceased.[256]

433. On 12 February 2015 the deceased's initial phenotype result showing a TPMT activity of 0.04 nmol/gHb/min became available at PathWest Laboratories, but as outlined earlier in this finding PathWest's policy was to repeat phenotype results below the threshold of 0.57 in the next run of testing, and for genotype testing to also be conducted. While this was being done, at that time the policy was that

[253] ts 26; ts 199; ts 232 to 234
[254] Exhibit 1, tab 34
[255] Exhibit 5
[256] Exhibit 5; ts 253

phenotype results were not released, because they were not sufficiently reliable.[257]

434. At the inquest Dr Ayonrinde testified that if he had known that the deceased's phenotype test result had come back at 0.04, then whether the deceased was still in hospital or outside of hospital, he would have instructed that he be contacted for the purpose of having him immediately stop the 6-MP. Knowledge of the phenotype test alone would have been enough for him to initially act on it.[258]

435. On 19 February 2015 the deceased's genotype results, incorporating his DNA sequencing results first became available at PathWest and they became electronically available to FSH that same date. The genotyping identified a homozygous *3A genotype. This showed that the deceased had a substantially impaired capacity for clearance of thiopurines. Unfortunately, as is known, no FSH clinician became aware of this result until after the deceased's collapse and re-admission on 1 March 2015.[259]

436. At the inquest Dr Connell noted that the deceased was commenced on a lower dose of 50 milligrams of 6-MP per day, in the context of where the usual dose having regard to his body weight would have been about 125 milligrams per day. In his opinion, the deceased's phenotype result was profoundly low and most clinicians would stop the 6-MP treatment, as opposed to further reducing the dose to 5% of its normal level.[260]

437. In Dr Connell's experience, such a profoundly abnormal phenotype as the deceased had could only be purely due to a genetic cause, and would signal an urgent need to stop the 6-MP. Whilst other factors may partially affect the enzyme level, he believed it would not result in such a low level as found in the deceased.[261]

438. At the inquest Dr Connell testified that if the 6-MP had been withdrawn on or about 12 February 2015 (when the phenotype results became available at PathWest) he was sure that the deceased would not have developed bone marrow toxicity and the consequences of the 6-MP would

[257] Exhibit 16.1
[258] ts 244; ts 253 to 254
[259] Exhibit 1, tab 31; Exhibit 15.1
[260] ts 29 to 30
[261] ts 26

have been averted. He explained that bone marrow toxicity develops gradually over a period of weeks.[262]

439. However, Professor Joyce did not consider that the TPMT phenotype result of 0.04 nm/gHb/hr on 12 February 2015 could be shared with FSH. In the case of TPMT phenotyping, Professor Joyce considered that the "*gold standard*" validation is through genotyping. He referred to the need to balance the consequences of releasing a test that is probably right (phenotyping) as against releasing a test that is certainly right (genotyping). In his opinion, the first moment that the laboratory could be perfectly sure of the predictive value of the phenotype was on 19 February, when the genotype was in hand.[263]

440. At the inquest Dr Connell testified that even if the 6-MP had been withdrawn on 19 February 2015 (when the genotype results were released to FSH) it still would have averted the consequence of irreversible bone marrow toxicity. In his experience that toxicity could have been averted by medical treatment with modern techniques.[264]

441. At the inquest Professor Joyce considered that if, hypothetically, the 6-MP had been withdrawn on 12 February 2015, the outcome for the deceased may have been different, meaning that his death may have been prevented. Had the 6-MP been withdrawn on 19 February 2015, Professor Joyce suspected that the deceased may have been prevented from developing severe bone marrow failure and sepsis, but qualified his answer by explaining that his depth of experience relates to the effects of 6-MP after one week, based upon there being a full blood count test at that stage.[265]

442. At the inquest Dr Ayonrinde opined that the deceased would have been much less likely to have died if the 6-MP had been withdrawn on 12 February 2015 (when the phenotype test results became available to PathWest) or 19 February 2015 (when the genotype results were released to FSH).[266]

443. I am satisfied that, given the procedures regarding the release of TPMT results as at February 2015, there was a

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[262] ts 30 to 31
[263] Exhibit 15.1
[264] ts 30 to 31
[265] ts 419
[266] ts 253 to 254

clear missed opportunity at FSH to treat the deceased when the TPMT test results were made available by PathWest to FSH on 19 February 2015. If on or about that date the FSH clinicians had instructed the deceased to cease taking the 6-MP and followed up with medical care, it is likely that his death could have been prevented.

Withdrawal of 6-MP after full blood count

444. The evidence at the inquest established that whilst the TPMT testing would likely show whether 6-MP is contraindicated, the time-honoured and primary safeguard as at February 2015 had been to perform a full blood count within one or two weeks after the commencement of 6-MP. In Dr Connell's experience the commonly accepted view is that there is a requirement for the full blood count to be conducted intensively in the weeks after the 6-MP is commenced. Professor Joyce described this safeguard as a practically foolproof method of protecting people.[267]

445. The deceased was supposed to have his full blood count test on or about 24 February 2015, and for the reasons outlined earlier in this finding this did not occur. In Dr Connell's opinion there may have been evidence of bone marrow impairment at that stage. If hypothetically the 6-MP had been withdrawn at this point, Dr Connell believed it would not have been at an irreversible stage. Whilst Dr Connell could not be certain, somewhere late in February 2015 (being clearly after 24 February 2015) the threshold would have been reached for the deceased to have developed irreversible bone marrow toxicity.[268]

446. At the inquest Professor Joyce testified that after the prescription of 6-MP a patient would need a very high level of surveillance to protect them from falling white cell counts, and emphasised the importance of a full blood count after the introduction of 6-MP:

> *"There was nearly half a century of experience with the drug where full blood picture monitoring was the only thing available and it did provide protection. So the answer is yes. The blood*

[267] ts 31 to 32; ts 421
[268] ts 31

monitoring, we can anticipate, would have identified his susceptibility."[269]

447. Professor Joyce addressed the recommended full blood count testing sequence starting at one week, proceeding at weekly intervals for four weeks, then reducing by steps to two weekly, then once a month and sometimes even less frequently. However he also considered that deferring the first full blood count test until two weeks would be defensible.[270]

448. At the inquest Professor Joyce opined that hypothetically, if a full blood count had been taken one week after commencing the deceased on 6-MP there may have been some early fall in white blood cell count to herald that the deceased was susceptible to the drug, but he did not know whether such an early fall would have caused anyone to immediately take the deceased off the 6-MP.[271]

449. At the inquest Professor Joyce also opined that hypothetically, if a full blood count had been taken two weeks after commencing the deceased on 6-MP, it would be expected to show a low white blood cell count that required a revision of treatment intentions. In his view it is not a given that the 6-MP would have been withdrawn at that point. Depending on the severity of the fallen white blood cell count, the 6-MP may have been withdrawn to allow the marrow to recover and reintroduced in a lower dose, or alternatively simply reduced.[272]

450. Whilst a starting dose of 50 milligrams of 6-MP a day was low, Professor Joyce confirmed that if the deceased's genotyping had been known, he would not have been prescribed that dosage.[273]

451. Professor Joyce was aware of recommendations to the effect that in persons who are genetically unable to remove 6-MP, the drug may still be administered but in very much attenuated dosages, such as 5 milligrams per day. If such patients have very severe Crohn's disease that is very difficult to bring under control, but are experiencing an undeniable prospective benefit from 6-MP, then treatment may appropriately continue at very much reduced dosages

[269] ts 410
[270] ts 408
[271] ts 408
[272] ts 409
[273] ts 409

(with ongoing full blood screening). Each case would need to be individually considered and Professor Joyce suggested that different gastroenterologists would probably address that question differently.[274]

452. At the inquest Dr Ayonrinde, who approved the prescription of 6-MP to the deceased, testified to the effect that if, hypothetically, the blood monitoring had been done and available, they might have at least been alerted to whether, in addition to needing to stop the 6-MP, there was a need to seek that the deceased urgently see his GP or come back to FSH, even via the ED, for an informed review.[275]

453. Given that the full blood count testing was ordered for two weeks after discharge, being by 25 February 2015 at the latest, Dr Ayonrinde, as the deceased's treating consultant gastroenterologist was asked for his opinion as to whether the outcome would have changed for the deceased had this been done. Dr Ayonrinde outlined that prior blood tests for the deceased had already shown a significant depression in his blood counts. Had the tests that were ordered post-discharge been done, in his opinion they would have most likely shown significant side effects and the 6-MP would have been stopped.[276]

454. In Dr Ayonrinde's estimation, hypothetically, had the 6-MP been stopped on or about 25 February 2015, and if the degree of suppression of bone marrow was severe at that point then the deceased would have been asked to return to FSH. There would have been a better opportunity to have intervened to treat the deceased on or about 25 February 2015 as opposed to one week afterwards when he was re-admitted after his collapse. Such treatment would have involved efforts to boost his white blood cell count.[277]

455. I am satisfied that, had the communication of the deceased's discharge plan been executed by FSH, and his full blood count undertaken by his GP as intended by 24 or 25 February 2015, the results would most likely have shown significant side effects, namely a low white blood cell count militating further inquiry, and a review of his treatment plan.

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[274] ts 409
[275] ts 253
[276] ts 254
[277] ts 255

456. If on or about 24 or 25 February 2015 the GP or the FSH clinicians had instructed the deceased to cease taking the 6-MP and followed up with medical care, it is likely that his death could have been prevented. The failure by FSH to implement sufficient processes for notifying external parties of the deceased's discharge situation led to another clear missed opportunity to treat the deceased.

QUALITY OF THE DECEASED'S CARE

457. As is the norm, the clinicians at FSH worked on a roster system. The ward consultant gastroenterologist at FSH changed each week. Each such consultant was on duty for seven days, accepting care of gastroenterology and hepatology in-patients between 8.00 am and 5.00 pm, and then there was a consultant on call from 5.00 pm Friday to 8.00 am Monday.[278]

458. There was also a different consultant on call after hours during the week, overnight (between 5.00 pm and 8.00 am Monday to Thursday). Consultant ward rounds were held on three days during the week (generally Monday, Wednesday and Friday, or as required).[279]

459. The ward consultants changed each week in order for FSH's ward team to have a single consultant responsible for all or most patients as a single point of contact. The intent was that continuity of care be maintained via a formal handover between the duty consultants when the previous weekly shift ended and the next one began. No consultant gastroenterologist worked full-time at FSH, most were employed at 0.5 full-time equivalent (FTE).[280]

The treating team

460. In the deceased's case, he was in the care of consultant gastroenterologists Dr Chong between 4 and 8 February 2015, and Dr Ayonrinde between 9 and 10 February 2015. However, the deceased's electronic medical records over the entire period retained Dr Chong's name because he was the admitting consultant. At the inquest FSH's A/executive director Dr Mark explained that if the consultant's name is altered in the electronic records when the care is handed

[278] Exhibit 8
[279] Exhibits 5 and 8
[280] Exhibits 5 and 7

over, it will give the appearance of there having been a discharge and re-admission.[281]

461. For this reason the deceased's discharge summary dated 10 February 2015 cites Dr Chong as the consultant, whereas on this date and for this discharge, Dr Ayonrinde was the responsible consultant and decision-maker. I am satisfied that Dr Chong did not have a role in the prescription of the 6-MP, nor in the deceased's discharge and follow-up planning.[282]

462. From the period spanning the plan for the prescription of the 6-MP until his discharge was completed at FSH the deceased was in the care of the gastroenterology team comprising Dr Ayonrinde as consultant in charge, Dr van Rijnsoever (advanced gastroenterology trainee), Dr Shah (resident medical officer) and Dr Ellis (intern). Support to this team was provided by Dr Gan, (registrar and hepatology fellow).

463. I am satisfied that the deceased's individual clinicians at FSH provided an appropriate level of care to the deceased during the periods of his first and his second admissions.

464. However, with respect to his post-discharge care after his first admission, by reason of a lack of policies and processes at FSH to address the safe prescription of 6-MP, follow up for test results and follow up care to address potential toxicity, there were missed opportunities to treat the deceased. These missed opportunities arise as a consequence of these systemic failures, and are addressed below.

Missed opportunities

465. Dr Gan instructed Dr Shah to order the TPMT test, without being aware that at that time FSH did not have a practice of ordering a TPMT test prior to the prescription of 6-MP in such circumstances. Unbeknown to him, as at February 2015, FSH elected instead to rely on the safeguard of full blood count testing within two weeks of the commencement of 6-MP.

[281] ts 325
[282] Exhibit 1, tab 15

466. Dr Shah duly executed Dr Gan's instruction to order the TPMT test. Dr Shah was not familiar with this test, nor was it his role to familiarise himself with the nature of and/or reasons for the test. When Dr Shah ordered the TPMT test, for reasons already outlined, on FSH's electronic system it was ordered under Dr Ellis' name. Dr Ellis did not know the TPMT test had been ordered, consequently was not awaiting a result. When PathWest electronically released the deceased's TPMT results to FSH on 19 February 2015, no clinician became aware of the result.

467. Expert gastroenterologist Dr Connell explained that thiopurines (such as 6-MP) are frequently started before the TPMT test results are known if there is a clinical imperative to do so, as long as a full blood count is performed at either weekly or fortnightly intervals for the first two to three months after its commencement: "*In this way, the early development of myelosuppression can be recognised before it becomes severe, and the drug stopped or its dose reduced if necessary*."[283]

468. It is submitted to me that it was the failure to follow through with the full blood count testing within two weeks of the commencement of the 6-MP that is the critical factor giving rise to the deceased's death.

469. Whilst I accept the evidence concerning the primary importance of the follow up blood count testing, the fact remains that a TPMT test was done by FSH and a result was received by FSH on 19 February 2015 that ought to have caused the deceased's clinicians to have him immediately contacted to instruct him to cease the 6-MP and seek an urgent medical review.

470. Although it is not a certainty, as outlined above in this finding, I am satisfied that this it is likely that this could have prevented his death. The failure to act upon the TPMT test result received on 19 February 2015 is the first of the missed opportunities to treat the deceased.

471. The next missed opportunity to treat the deceased occurred as a result of a failure to follow through with the deceased's discharge planning, specifically, his full blood count testing within two weeks of discharge. Again, although it is not a certainty, and also as outlined above in this finding, I am

[283] Exhibit 1, tab 18

satisfied that it is likely that this could have prevented his death.

472. For reasons outlined previously, in February 2015 FSH's IBD clinic, which had opened on 19 January 2015, had been unable to recruit a clinical nurse specialist, and therefore FSH relied on the deceased's GP for the follow up blood test to establish whether the deceased was experiencing toxicity from the 6-MP. At the time, for the Bull Creek Medical Practice this was done by administratively mailing the discharge summary to the patient's GP.

473. I am satisfied that given the critical importance of this blood test, FSH's reliance on the discharge summary marked for the attention of the unnamed "*Attending Doctor of Bull Creek Medical Centre*" reaching the deceased's GP by ordinary mail with no further follow up was unacceptable. It is clear that by about 25 February 2015, blood tests would have shown anomalies such as to cause the GP to have concerns, and to cause FSH's clinicians to question 6-MP toxicity and review the deceased. Even by this stage, there existed a real and not insubstantial potential to save the deceased's life.

474. Whilst it is submitted to me that the importance of the follow up blood tests was explained to the deceased and he was handed a copy of the discharge summary, it is unacceptable to expect the deceased to arrange his own follow-up blood tests. It cannot reasonably be assumed that a patient in the deceased's position will apprehend the critical importance of the follow-up blood tests and act accordingly. Bearing in mind the deceased's vulnerability by reason of his mental health issues, the problems with reliance on a patient initiated follow-up are magnified.

475. At the inquest, FSH's A/executive director Dr Mark agreed that Dr Ayondrinde would have been better supported in his delivery of care to the deceased if there had been a clinical nurse specialist available in FSH's IBD clinic. Such a clinician would have been able to effectively follow up on the blood tests. Being attached to FSH, the clinical nurse specialist would be reasonably expected to maintain contact with the gastroenterology team. For example a clinical nurse specialist and would have been able to ensure that results were duly conveyed to the team and would have been able to alert the team in the event of a non-attendance.

Delay in the transit lounge

476. Whilst the delays in the deceased's actual discharge process on 10 February 2015 were unacceptable, and FSH regrets the amount of time he spent in the transit lounge (some seven and a half hours), I am not satisfied on the evidence that a re-admission of the deceased on that date would have been likely to cause the clinicians to question the potential toxicity of the 6-MP.

477. Nonetheless, the processes in the discharge lounge on 10 February 2015 were insufficient to allow for a satisfactory discharge, given that over this extended period, the deceased's pain scores had increased to seven out of ten, and it became known that his CRP had risen to 100. All of the clinicians who were provided with the details of his pain score and change to his CRP, and who were asked whether they would have discharged him, had they known of those indicators, gave evidence to the effect that they would have considered readmitting him and conducting further tests.[284]

478. The deceased's treating team ought to have been provided with information concerning the change in circumstances so that readmission could have been considered. The deceased was seen in the transit lounge by a recent medical graduate who was on his first rotation as an intern, and was only some weeks into his medical career. He was acting on instructions from senior colleagues and was not tasked with deciding whether the patient was fit for discharge.[285]

479. At the inquest, FSH's A/executive director, Dr Mark accepted that it would have been better if the deceased had been attended to by somebody more experienced. He explained that there was a registered medical officer and an intern on that unit and they generally work opposite shifts.[286]

480. I am satisfied that as of 10 February 2015, with the deceased having taken two dosages of 6-MP medication, it is likely that the further tests that may have been ordered if he was readmitted would have been addressed to his pain, and not the potential toxicity of 6-MP. The toxicity was intended to be addressed by the full blood count two weeks post discharge, and could also have been addressed if the TPMT

[284] ts 132 to 133; ts 160; ts 182; ts 243
[285] Exhibit 11
[286] ts 326

test results had been ascertained on or about 19 February 2015. I accept FSH's submission, through its lawyers, to the effect that patients are not kept in hospital to monitor the effects of 6-MP, as this would have taken some weeks.

Conclusion on quality of care

481. Unfortunately, despite both national and state-wide guidelines requiring that there be policies be in place regarding the prescription of medications such as 6-MP, and accepting that FSH was required to comply with the WA High Risk Medication Policy, it is entirely regrettable that at the materials time FSH did not have a written policy, to assist the responsible clinicians, regarding the safe prescription of 6-MP.

482. I accept the evidence at the inquest, consistently given by the clinicians, and accepted by FSH though its lawyers, to the effect that had the deceased stopped taking the 6-MP on or about the following critical dates, his bone marrow impairment would likely have been reversible:

- 12 February 2015, when the phenotype TPMT test was produced;
- 19 February 2015 when the TPMT genotype test was produced; or
- 24 February 2015 when the full blood count was intended to have been performed.

483. On all of the evidence before me, and in particular by reason of a lack of systems within FSH to guide the clinicians in the safe prescription of 6-MP, and a lack of systems to ensure effective follow up on critical safeguards, the deceased's care at FSH was deficient, and fell below the standards that should ordinarily be expected of a public hospital.

484. Since the deceased's tragic death, there have been a number of improvements at FSH with the aim of avoiding a death in similar circumstances and these are outlined below.

IMPROVEMENTS SINCE THE DECEASED'S DEATH

FSH's Mercaptopurine Policy

485. The evidence at the inquest established that at the material time FSH did not have a policy regarding the safe

prescription of 6-MP, despite the national NSQHS Standards and the WA High Risk Medication Policy requiring procedures and policies to be in place for FSH staff involved in providing chemotherapy and targeted therapy (such as 6-MP).

486. After the deceased's death, in compliance with national and state-wide guidelines, in December 2015 FSH developed and published the Inflammatory Bowel Disease Patients commencing on Mercaptopurine or Azathioprine Policy and Procedure (FSH's Mercaptopurine Policy).[287]

487. Various versions of FSH's Mercaptopurine Policy have been published, and updated as part of a continual review and improvement. The copies provided to the court on 19 April 2017, showing changes made to prior versions were received as Exhibits 18.1 and 18.2. One such change included the delegation of blood monitoring to the IBD fellow instead of nursing staff.[288]

488. FSH's Mercaptopurine Policy as at April 2017 gives guidance to clinicians on a range of factors (and is not limited to guidance on 6-MP). In the context of the inquest the material developments are as follows:

Regarding the safe prescription of 6-MP

- It is outlined that 6-MP exerts a steroid sparing effect in patients with steroid dependent and steroid refractory IBD but the use is limited by concerns of toxicity.
- Patients are to be informed of the risk associated with 6-MP treatment and the need for regular blood monitoring.
- Close monitoring is required for patients on 6-MP due to risk of serious, potentially life threatening adverse effects (these are outlined).
- Blood monitoring is considered the standard of care.
- Bone marrow suppression or hepatic toxicity may be sudden in onset (protective measures are outlined).
- TPMT phenotyping and genotyping testing shall be undertaken and results obtained prior to 6-MP being commenced, including the following: "*Acutely unwell IBD patients on the ward that have no TPMT result are to be reviewed 7 – 10 days after discharge at outpatient*

[287] Exhibit 1, tab 38
[288] Exhibit 18

clinic for the specific purpose of confirming the TPMT result and commencing a thiopurine. The early proactive initiation of a thiopurine will enable a patient to become eligible for biologics in the PBS."

- The IBD fellow is to be informed of all patients being considered for 6-MP.
- All patients prescribed 6-MP shall have full blood count and liver function test monitoring (a schedule for monitoring frequency is set out, beginning with every week for the first four weeks after therapy and with additional safeguards).
- Dosing guidelines for 6-MP are outlined, including the commencing dose, which must be prescribed by the treating consultant; dosage increases are guided by the treating consultant.
- A detailed flow diagram for the initiation of 6-MP, including prior TPMT testing, and the subsequent monitoring appears at Appendix 1.
- Close follow-up communication is specified with the patient and between the IBD clinical nurse specialist, IBD fellow and treating consultant.
- The IBD fellow must personally add the patient's name to FSH's iCM system, perform the weekly monitoring, review and update the patient list on a weekly basis, acknowledge the blood tests results, titrate the dosages, and review uncompleted tasks.
- PathWest is to notify the IBD clinical nurse specialist for any urgent results including severe neutropenia.
- Guidance regarding dosages is outlined in respect of patients with normal TPMT activity and low TPMT activity.
- The GP and patient are advised by the clinical nurse specialist if there is non-attendance for blood monitoring.
- Procedures are set out for addressing adverse reactions and/or non-compliance.

<u>Regarding consent to treatment with 6-MP</u>

- Following the explanation concerning the role and risks of 6-MP, the patient will be given a "*consent to treatment with immunosuppressant*" form to sign, which will also be signed by the treating consultant. A pro forma appears at Appendix 2, which includes the following:

- "*I understand why I am starting this medication*";
- "*I agree to have regular blood tests to monitor for side effects as described in the patient information sheet and by my IBD doctor*"

- The IBD clinical nurse specialist is to provide patients with information sheets, counselling and education.

Regarding GP follow-up

- The GP follow-up commences after the patient has been on a stable dose of 6-MP and three monthly blood monitoring. The patient is to nominate a GP who will continue the three monthly blood monitoring and prescription of 6-MP. A pro forma letter to the nominated GP outlining roles and responsibilities in the shared care arrangement appears at Appendix 3. The letter outlines some critical information concerning the parameters to check for in the blood tests. Provision is made in case the GP does not agree to be part of the arrangement.

Regarding non-compliance

- In the event that a patient fails to attend for the agreed blood test monitoring, provision is made for a procedure that includes the cessation of treatment with 6-MP under certain circumstances. A pro forma letter to the patient recommending attendance at FSH or PathWest for a blood test appears at Appendix 4. If the blood test is not received within a fortnight, the letter goes on to state: "*We will no longer prescribe you this medication as it is dangerous to do so without the blood test results.*"

489. Treatment with thiopurines including 6-MP is an evolving area of medicine and undoubtedly, changes to FSH's Mercaptopurine Policy will be made as developments ensue. Those changes are entirely a matter for the clinicians.

490. In respect of my functions under section 25(2) of the Coroners Act, I am satisfied that, following the deceased's death, there is in existence a policy for FSH staff involved in providing chemotherapy and targeted therapy (such as 6-MP) as contemplated by the national NSQHS Standards and the WA High Risk Medication Policy. The policy also addresses informed consent.

491. For this reason, there is no need for me to make any recommendation regarding guidance for the safe prescription of 6-MP at FSH, and consent to treatment.

Staffing at IBD Clinic

492. The evidence at the inquest established that at the material time FSH had endeavoured, but not been able, to recruit a clinical nurse specialist at its IBD clinic to assist with coordinating the management of outpatients, including their follow up blood tests.

493. Dr van Rijnsoever explained that prior to the transfer to FSH, previously at Fremantle Hospital and Health Service there were IBD clinic nurses who performed a number of roles including monitoring blood test results and providing a help-line service for thousands of IBD patients in the South Metropolitan Health Service. The new model of care for IBD patients at FSH was for them to see their GP for blood tests in between clinic visits and to contact their GP or the IBD clinic if they develop any problems.[289]

494. FSH's IBD clinic opened on 19 January 2015, a matter of weeks prior to the deceased's first admission. FSH's IBD clinic is a component of its broader IBD unit and its function is to coordinate the management of outpatients with IBD. At the material time, the IBD unit treated inpatients and outpatients who attended the IBD clinic and patients requiring post-admission blood tests were referred back to their GP.

495. On his discharge summary, the deceased was due to attend at the IBD clinic for follow up four weeks post discharge. Tragically he collapsed 19 days after discharge and died four days later on 5 March 2015.

496. Shortly after the deceased's death, on 23 March 2015 FSH recruited an IBD clinic clinical nurse specialist (CNS IBD) for its IBD clinic, and an additional clinical nurse commenced on 7 April 2015. Together with the services of an administrative assistant, these staff members have been able to provide the additional assistance with following up IBD patients, including following up on full blood count tests.

[289] Exhibit 4

497. The services at the FSH's IBD clinic are now more expansive than they were in February 2015, and there is now more staff as outlined above. Services now provided at the IBD clinic include those detailed in FSH's Mercaptopurine Policy and in practical terms are expressed as follows:

- Outpatients will be followed up with regular phone calls by the CNS IBD and are subsequently reviewed at the IBD outpatient clinic at 4 weeks;
- The CNS IBD provides patient information sheets to the patient;
- They will add the patients name to the TPMT list in iCM;
- And will review this list regularly;
- After receiving the TPMT result, the consultants will determine whether 6-MP treatment is to be commenced and if so the CNS IBD will communicate with the GP;
- The CNS IBD will add the patient's name to the azathioprine/mercaptopurine list in in iCM and to the azathioprine/mercaptopurine database;
- The CNS IBD shall review blood monitoring lists regularly;
- The CNS IBD will contact the patient by phone and provide written information advising them of the frequency of blood monitoring required;
- If a patient fails to attend for required blood monitoring they will attempt to contact the patient and supply correspondence to the patient's GP; and
- If the patient has an adverse reaction to treatment the CNS IBD will forward correspondence to the patient's GP (with a copy to the patient) advising them to cease treatment; in addition they will contact the patient by phone.[290]

498. I am satisfied that this comprehensive system incorporating the IBD clinic's services represents a significant improvement on the safeguards for patients commenced on 6-MP.

499. For this reason, there is no need for me to make any recommendation regarding guidance for the follow-up of patients prescribed 6-MP at FSH.

[290] Exhibit 6

Transit Lounge procedures

500. The evidence at the inquest established that the deceased experienced an unacceptable delay in the provision of his discharge medications and suffered an exacerbation of pain whilst in the transit lounge. He was in the transit lounge awaiting discharge approximately seven and a half hours.[291]

501. As outlined above in this finding Dr Mark, FSH's A/executive director, accepts that the delays in the discharge process were unacceptable and that FSH regrets them. Dr Mark explained that these delays mostly reflected the first week of the hospital operating at high occupancy with new staff and systems, and that delays of this nature are now very uncommon.[292]

502. My comments concerning the deceased's discharge are also outlined above in this finding. I accept that there has been an improvement since the opening of FSH and in the circumstances, there is no need for me to make any recommendation concerning FSH's transit lounge procedures.

PathWest's Biochemistry Phone Limits procedure

503. The evidence at the inquest established that the deceased's abnormal TPMT activity test was available at PathWest on 12 February 2015. His initial phenotype result showed a TPMT activity of 0.04 nmol/gHb/min, which was abnormally low.[293]

504. At that time, PathWest's written policy was that phenotype test results below the threshold of 0.57 nmol/gHb/min were repeated in the next run of testing, and for genotype testing to also be conducted before releasing the results to the hospital. Broadly speaking it involved confirming and validating the results.

505. At the inquest, Professor Joyce explained the rationale for confirming and validating such results, based upon wanting to avoid the unnecessary and inappropriate cessation of thiopurine treatment, which might for example be used as a child's anti-leukaemia therapy. He outlined a range of

[291] ts 319; Exhibit 6
[292] Exhibit 6
[293] Exhibit 16.1

reasons for very low TPMT phenotype activity, and factors that may impact upon treatment decisions:

> *"....in reality, the phenotyping is poorly predictive often enough so that one might anticipate that for every case that stopped on good reason, there would be quite a few that were stopped on insufficient reason and then restarted, because a lot of the low phenotype results will be low for various reasons."*[294]

506. Dr Ee Mun Lim, head of Biochemistry Department at PathWest QEII informed the court of relevant changes implemented since the deceased's death. PathWest had, and still has, a biochemistry phone limits document, with a list that mandated the ringing of abnormal and critical results through to the requesting clinician/team. In February 2015, TPMT was not part of that list.[295]

507. Accordingly, when the deceased's genotype results did become available for release on 19 February 2015, they were sent by PathWest electronically to FSH, with no phone call, as it was not mandated. As is known, no clinician at FSH became aware of the results until after the deceased's collapse, for reasons outlined above in this finding.[296]

508. Dr Lim and Dr Joseph (scientist in charge of Special Chemistry) explained that after the deceased's death changes were made to the PathWest's procedures regarding the ringing through of abnormal TPMT results. This occurred at a general level, and also at a specific level in respect of FSH, at the hospital's request.

509. Details concerning TPMT test results were added to PathWest's biochemistry phone limits document, meaning that certain results would be conveyed by PathWest both electronically, and by telephone call, to the clinician. The laboratory's special chemistry chromatography methods manual was updated on 15 March 2015, shortly after the deceased's death, to reflect these changes.[297]

510. The outcome of such changes is that all phenotype results are now uploaded onto iCM on the day after the test is run, with the caveat that "*low*" and "*low normal*" results are reported as "*preliminary pending verification and genotyping.*" Any TPMT test results under the

[294] ts 417
[295] Exhibit 1, tab 31
[296] Exhibit 1, tab 31
[297] ts 387 to 390; Exhibit 1, tab 31; Exhibit 16.1

0.4 nmol/gHb/min cut-off are now also phoned through by PathWest to the requesting clinician/team.[298]

511. FSH has requested a further procedure that PathWest has acceded to. For FSH specifically, TPMT test results above 0.4 nmol/gHb/min, but below 0.57 nmol/gHb/min (which would not normally mandate a telephone call) are also required to be phoned through by PathWest to the requesting doctors (and copied to the IBD clinical nurse specialist) including interim results that have not been validated.[299]

512. In practical terms, Mr Joseph testified that if, now, an initial phenotype result of 0.04 nmol/gHb/min was returned, such as the one that was returned for the deceased, the following would occur:

> *"We would print out the request form, write the result on there and get our registrars to bring it to the attention of the treating team or the requesting clinician with the proviso that this result needs to be validated a second time, but just bear in mind that on first pass this is what we have obtained. And that it has also been sent for genotyping for confirmation. So those two points are brought to their attention."*[300]

513. This approach is supported by Professor Joyce and Dr Connell. Dr Connell referred to the importance of "*closing the loop*" in terms of getting abnormal pathology results notified. He described it as a major challenge, and this is addressed further in the context of my recommendations, below.[301]

514. Since the deceased's death, PathWest has been allocated additional resources to run phenotype TPMT tests twice weekly (instead of weekly). Whilst in February 2015 TPMT test results usually took two to four weeks to return, now they usually take one to two weeks.[302]

515. I am satisfied that the changes to PathWest's system, specifically those requiring that there be a discussion with the requesting clinician/team represent a significant improvement and a safeguard against certain critical

[298] Exhibit 1, tab 31; Exhibit 16.1
[299] Exhibit 1, tab 31;
[300] ts 394
[301] Exhibit 1, tab 18.2
[302] ts 269; Exhibits 5 to 8

information being overlooked by reason of it being conveyed electronically.

516. For this reason, there is no need for me to make any recommendation regarding the conveyance of critical information concerning TPMT test results by PathWest.

COMMENTS ON PUBLIC HEALTH OR SAFETY

517. Pursuant to section 25(2) of the Coroners Act, I may comment on any matter connected with the deceased's death including public health or safety or the administration of justice. The comments that I make below concern the importance of hospitals having systems and safeguards in place to ensure that patients' test results are received, noted and understood by the appropriate treating clinicians.

518. At the inquest, Dr van Rijnsoever outlined the risks involved in the increasing reliance upon electronic communications, within the context of incoming test results for patients:

> *"The difficulty with the system currently in Western Australia, that there's no way of getting results back to you. There's a way where you can flag that you've got – acknowledged it. But in order to get to that screen you must know your unit number, go down and find within the whole range of tests, your own test result as such. Previously there was also a back-up system in place where all results would get printed out and put into the pigeon hole of either yourself or the consultant, but that system was not put in place at Fiona Stanley Hospital, and there were no paper copies sent."*[303]

519. The difficulty outlined by Dr van Rijnsoever is compounded by the fact that doctors, who work in team environments and on rotation, may not consider it their obligation to go back and retrieve a test result that they ordered. Dr Shah ordered the deceased's TPMT test on Dr Gan's instruction, but Dr Shah did not consider it his role to go back and retrieve the results in due course. This is correct; it was not his assigned role. He was executing Dr Gan's instruction, but Dr Gan, believing it was usual procedure for FSH gastroenterologists to order a TPMT test in such circumstances, finished his rotation and assumed a result would be provided to the treating team.

[303] ts 179

520. In the meantime, the TPMT test was ordered in Dr Ellis' name, who knew nothing about the ordering of such a test, so he would not know to go looking for it. No doctor became aware of the TPMT test results. That knowledge could likely have saved the deceased, as outlined above in my finding.

521. At the inquest Dr Mark, FSH's A/executive director, explained that at the material time, there was no alert system on the iCM regarding receipt by FSH of pathology test results for TPMT:

> *"– it just goes back into the – into the computer system – the iCM computer system. Unfortunately, there is no alert. There is no email to warn people that a result has come back. The problem is you have got to remember that you have done the test and go back and check it, and that is the problem with results that come back some time. You know, when the patient is on the ward you have got the patient in front of you. If you have got 10 patients, you know you're going to go and look up 10 patients' results. But when the patient has gone home, you have another 10 patients on your ward, you have got to remember to look up the previous results."*[304]

522. FSH through its lawyers refers me to the "*weakness*" in the State-wide iCM system, in that when patients are not seen (for example when the patient is already discharged and before they attend their next clinic appointment) there is no prompt within the iCM system to inform doctors that a test has been produced.

523. The court is informed that in December 2015 FSH established a Results Acknowledgement Steering Committee. A document outlining the draft terms of reference for the Steering Committee was supplied to the court. It is due for revision in December 2017. The court is further informed that the iCM system is a State-wide system that is not under the management or control of FSH. It is submitted to me that modification, upgrade or replacement of iCM is a matter for the WA health system broadly.[305]

524. However, the salient issue within the context of the inquest is not addressed to whether iCM is to be modified. Rather, it is addressed to the steps that ought to be taken by a hospital, when it is known that test results for discharged patients will not go into a particular doctors' inbox

[304] ts 310
[305] Exhibit 6

(electronic or otherwise), but into a pool of results that must be searched.

525. Whilst FSH had a policy on "*Following up results of Clinical Investigations – Pathology*" as at December 2014, requiring that each treating team put in place systems for tracking lists of patients in iCM for whom tests have been ordered, it is clear that the gastroenterology team had not implemented a system that covered the type of tracking that was needed for a test such as the TPMT test, at that time. Further, I am not satisfied that this responsibility ought to have been passed onto individual specialities within FSH.[306]

526. Expert gastroenterologist Dr Connell highlighted the problem to be addressed. In his opinion, and self-evidently, it is not an isolated event concerning TPMT test results. He considers it a far broader risk issue that impacts upon general patient care in most public hospitals. He described it as "*closing the loop*" of getting abnormal pathology tests notified, and considered it a major challenge, particularly in hospitals where junior staff frequently rotate through different parts, and reliance is placed upon doctors to chase up the results themselves:

> "*In private practice most clinicians have an electronic medical system where results of tests ordered by an individual are automatically sent to a doctor's inbox. In contrast, few public hospitals have equivalent systems for collating results, and rely on a doctor to chase the result up himself or herself.*"[307]

527. FSH through its lawyers submits to me that it would not be appropriate to criticise FSH's systems if I accept that FSH placed no reliance on TPMT testing and that this approach was reasonable medical practice. The issue however is that a TPMT test was done, results were received by FSH. They were in possession of FSH, but not acted upon. I have no adverse comment in respect of any of the individual clinicians involved. This was a systemic issue.

528. The combination of the absence of a policy addressing the safe prescription of 6-MP, and the absence of an adequate system in place for tracking lists of patients in iCM for whom tests have been ordered, were systemic failures at

[306] Exhibit 6
[307] Exhibit 1, tab 18.2

FSH, with tragic consequences for the deceased and his family.

529. As a result I make the following recommendations, in the hope that they may avoid deaths in similar circumstances. The recommendations are addressed to the implementation of systems that proactively bring test results to the attention of the relevant clinicians, as opposed to requiring those clinicians to chase up the results.

RECOMMENDATIONS

Recommendation No. 1

That FSH put in place its own internal robust systems for tracking lists of patients in iCM for whom tests have been ordered and received, including for patients that have been discharged, that those systems facilitate the conveyance of test results to the attention of the clinician who ordered the test and the consultant in charge of the patient's treatment, and that those systems highlight urgent and/or abnormal test results.

Recommendation No. 2

That the Department of Health consider whether an operational directive or instruction is required to support governance within public hospitals regarding the implementation of systems for tracking test results, particularly where patients have been discharged. Such operational directive or instruction would include an alert to public hospitals regarding the need for robust systems to be in place to facilitate the conveyance of an abnormal laboratory result to the attention of the clinician who ordered the test and the consultant in charge of the patient's treatment.

CONCLUSION

530. The deceased was treated for Crohn's colitis with the immunosuppressant medication 6-MP, a cytotoxic drug. He was unable to metabolise it because he had two non-functioning copies of the TPMT gene. This led to 6-MP toxicity and profound bone marrow suppression, ultimately resulting in his death.

531. FSH missed a number opportunities to detect and avert the possibility of 6-MP toxicity in the deceased.

532. The inquest highlighted the risks for patients when too much reliance is placed on electronic communications in an environment where clinicians routinely work on rotation and in team environments. For the deceased this risk crystallised, with tragic consequences, when a series of events led to significantly abnormal test results being received electronically at FSH, with no clinician becoming aware of them.

533. It is profoundly disturbing for the deceased's father to have to bear the knowledge that the information that could likely have saved his son's life was available at FSH, on its computer system, but with no adequate system or process for conveying those abnormal test results to the attention of his treating clinicians.

534. The inquest also highlighted the risks for patients when critical post-discharge care arrangements with GP's are planned, but with no adequate system in place to check on whether the GP has become aware of his or her function. The final opportunity to save the deceased's life rested upon the attending doctor of a medical practice receiving a critical document (a discharge summary) from FSH after processing by a ward clerk and placement in the ordinary mail. There was no follow up telephone call or other communication to ascertain whether the GP received the discharge summary and to confirm he understood and accepted his role in the post-discharge care.

535. After the deceased's death FSH and PathWest developed a number of procedures in support of improved communication, and the avoidance of a fragmented system of care, that I have outlined in this finding. They have included the imperative for health professionals to speak with each other in certain cases to ensure that vital information has been passed on, that it has been received, noted and understood, that appointments are kept, that patients are contacted, and that the chain of clinicians involved in a patient's care operates in a more integrated fashion.

536. The issue regarding the proactive conveyance of abnormal test results to the attention of the appropriate treating clinicians, those with the seniority to make the important decisions, remains a concern. Hence my two recommendations.

537. In closing the loop it ought to be expected that discussions are vital part. The conveyance of critical information by electronic communication only cannot replace the more traditional discussions between clinicians, which are so important for the delivery of safe and integrated care for patients. In addition to imparting information, such discussions also operate as a cross checking mechanism, to ensure information is received or understood.

R V C FOGLIANI
State Coroner
26 September 2017