Coroners Act 1996
[Section 26(1)]

Coroner's Court of Western Australia

RECORD OF INVESTIGATION INTO DEATH

Ref: 37/19

I, Rosalinda Vincenza Clorinda FOGLIANI, State Coroner, having investigated the death of ***Stephen Michael KELL*** *with an inquest held at the* ***Perth Coroner's Court, Court 85, CLC Building, 501 Hay Street, Perth*** *on* ***21*** *and* ***22 August 2019*** *find that the identity of the deceased person was* ***Stephen Michael KELL*** *and that death occurred on* ***26 April 2015*** *at* ***Graylands Hospital, Ellis Ward, Brockway Road, Mount Claremont*** *as a result of* ***acute vomit aspiration in a man with acute large intestine obstruction (severe megacolon) and clozapine-induced intestinal hypomotility*** *in the following circumstances:*

Counsel Appearing:

Mr Toby Bishop assisting the State Coroner.

Mr Joshua Berson, with Mr Benjamin Tomasi (State Solicitor's Office) appearing on behalf of the North Metropolitan Health Service and the Department of Health.

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INTRODUCTION

1. Stephen Michael KELL (Mr Kell) was a 35 year old man who tragically died at Graylands Hospital on 26 April 2015 from the complications of an acute large intestine obstruction (that are described in detail in this finding). Immediately before death, Mr Kell was subject to an Involuntary Patient Order made under the *Mental Health Act* 1996 (Mental Health Act). Accordingly, under the *Coroners Act* 1996 (Coroners Act) Mr Kell was a "*person held in care*" and by reason of s 22(1)(a) of the Coroners Act, an inquest into his death was mandated.

2. Mr Kell had a history of chronic paranoid schizophrenia first diagnosed in 2001 when he was 22 years old. However, he had reportedly displayed symptoms of his illness since he was 18 years old. His mental illness unfortunately responded poorly to clinical treatments and it was exacerbated by his ongoing abuse of illicit substances. When unwell, he could become aggressive.

3. Mr Kell had numerous admissions to various hospitals for the treatment of his mental illness over the years, commencing from 2002. Immediately prior to his death, he had been a long term involuntary patient at Graylands Hospital, due to the difficulties of managing his mental illness in the community.

4. One of the medications that had been prescribed to Mr Kell over the years to treat his mental illness was the antipsychotic medication clozapine. Upon his June 2012 admission to Graylands Hospital it was noted that his clozapine had been ceased due to a low white blood cell count (a known side-effect that is monitored). However, his mental health deteriorated from the time of cessation.

5. Following consultations with him and his family, and compliance with the manufacturer's processes, Mr Kell was recommenced on clozapine in May 2013, with medication to boost his white blood cell count. An improvement in his mental state was subsequently noted. He did however continue to experience some ongoing psychotic symptoms and he displayed difficult behaviours which included physical altercations with other patients.

6. Mr Kell's involuntary patient status was last reviewed in March 2015, and it was continued for a further three months. In the month leading up to his death his behaviour and mental state were noted to fluctuate, and he appeared to be responding to unseen stimuli (apparent hallucinations). Clinicians posited that his behaviour was consistent with varying levels of psychosis, possibly as a result of substance abuse. He was restricted to escorted ground access only due to these concerns.

7. On 24 April 2015, two days before his death Mr Kell was granted a day's leave in the company of his father, and they spent the day together in Perth and Subiaco, socialising. His father returned him to Graylands Hospital on the afternoon of that date. Later that evening a psychiatric

review was done. Mr Kell appeared drowsy and he was not able to speak coherently. He denied using drugs.

8. The next day, 25 April 2015, Mr Kell was recorded as displaying bizarre behaviour and it was posited amongst his clinicians that he had smoked synthetic cannabis. He settled, but later that evening when approached for his medications, he was unable to communicate, he had a tremor and an elevated heart rate. His tremor and heart rate subsequently settled, but later that night his condition rapidly deteriorated. He became unresponsive, and despite resuscitation attempts he remained in asystole and died in the early hours of 26 April 2015.

9. Mr Kell's death was unexpected and of an unknown cause, and it was therefore a "*reportable death*" within the meaning of s 3 of the Coroners Act.

10. The death was reported to the coroner as required under s 17 of the Coroners Act and subsequent post mortem examination reflected that the cause of death was related to acute vomit aspiration in the context of an acute large intestine obstruction (severe megacolon). Subsequent investigations reflected that clozapine-induced hypomotility also potentially contributed to Mr Kell's death.

11. Prior to his death some of Mr Kell's clinicians suspected that his abnormal mental state may have been due to synthetic cannabis use. Also in the days leading up to his death, records reflect that Mr Kell had not reported abdominal pain, constipation or vomiting. His clinicians considered that there were no signs to suggest he was developing a bowel obstruction in the days leading up to his death.

12. My primary function is to investigate the 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 death occurred and the cause of the death. Pursuant to s 25(2) of the Coroners Act, in this finding I may comment on any matter connected with the death including public health, safety or the administration of justice. This is the ancillary function.

13. By reason of s 25(3) of the Coroners Act, I am required to comment on the quality of the supervision, treatment and care of Mr Kell (because he was a person held in care).

14. 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.

15. I held an inquest at Perth on 21 to 22 August 2019. I heard from eight witnesses and received three volumes of exhibits into evidence, containing a total of 57 tabs (Exhibits 1 to 3).

16. Further exhibits were tendered into evidence during the inquest (Exhibits 4 to 6).

17. The focus of the inquest was upon:

a) the supervision, treatment and care of Mr Kell prior to his death, including whether he showed clinical signs of a bowel obstruction in the days prior to his death; and

b) the possible causes of the bowel obstruction, specifically whether Mr Kell experienced a mechanical obstruction, and/or whether the antipsychotic medication clozapine impaired his gut motility, thereby contributing to the overall clinical picture.

18. In September 2019 the court received submissions from the counsel for the SSO, directed towards potential recommendations.

19. Between September 2019 and January 2020, the court received additional documentary information directed towards potential recommendations (Exhibits 7 to 11).

20. In making my findings I have applied the standard of proof as set out in *Briginshaw v Briginshaw* (1938) 60 CLR 336 per Dixon J at 361 - 362 which requires a consideration of the nature and gravity of the conduct when deciding whether a matter has been proved on the balance of probabilities.

21. My findings appear below.

PSYCHIATRIC ADMISSIONS

22. Mr Kell had a history of chronic treatment resistant schizophrenia. His mental illness was characterised by poor response to medication, with ongoing psychotic symptoms including persecutory and referential delusions and auditory hallucinations. He had little insight into his illness and his management was complicated by substance abuse.[1]

23. Mr Kell had a history of aggressive behaviour. He had a forensic history for multiple offences that included charges relating to drugs, offensive behaviour and assault occasioning bodily harm. There were breaches of Intensive Community Service Orders due to his failure to attend appointments or being found in possession of drugs.[2]

24. Mr Kell was unable to work. The severity of his symptoms impacted upon his level of functioning and required long term hospitalisations, at times as an involuntary patient. Unfortunately, even within the structure of the hospitals, his schizophrenia and substance abuse were

[1] Exhibit 1, tab 15; Exhibit 2.
[2] Ibid.

difficult to manage. He received a disability support pension and his affairs were under the administration of the Public Trustee.[3]

25. An overview of Mr Kell's psychiatric admissions appears below. When Mr Kell was not hospitalised, crisis accommodation was sometimes able to be secured for him, but he continued to struggle with substance abuse. Numerous placements failed due to his drug taking and poor compliance with medication, leading to deterioration in his mental state and aggressive behaviour.[4]

26. Between 2001 and 2004 he had four admissions to Graylands Hospital, ranging from a few weeks, to up to approximately six months, where he was diagnosed and treated for schizophrenia. His history of substance abuse, inappropriate behaviour and aggression were noted in his medical records.[5]

27. Between January and November 2004 Mr Kell was detained in the secure Frankland Unit of the Graylands Hospital on a Hospital Order, then released into Graylands Hospital until the latter part of 2007. Over this period he had been commenced on clozapine. It was noted he suffered seizures. It was posited, but not established, that these seizures were as a result of taking clozapine. Subsequent medical investigations indicated epilepsy. In August 2007 he was discharged on clozapine (600 milligrams per day), as well as other medications.[6]

28. In June 2010 Mr Kell was admitted to Bentley Hospital having suffered a psychotic relapse with auditory hallucinations and impaired judgement, and it was also noted that his clozapine dosage had been reduced in the preceding months. There were concerns about his compliance with the medication. His diagnosis was undifferentiated schizophrenia, treatment resistant with prominent cognitive symptoms. A lack of insight into his condition, and cannabis abuse were also noted. He was recommenced on clozapine and his symptoms settled. He was discharged in July 2010 on clozapine (again 600 milligrams per day) and medication for seizures, and released on a Community Treatment Order.[7]

29. Between late 2010 and early 2011 he was admitted to Swan Hospital, following non-compliance with clozapine. The medication was reinstated and he was discharged.[8]

30. Between January to June 2012 Mr Kell was admitted to Swan Hospital following difficulties with his placements in psychiatric hostels and crisis services due to his history of substance abuse and aggression. From there, he was transferred to the Hospital Extended Care Service at Graylands Hospital on 13 June 2012.[9]

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[3] Exhibit 1, tab 15.
[4] Exhibit 1, tab 15; Exhibit 2.
[5] Exhibit 1, tab 13; Exhibit 2.
[6] Ibid.
[7] Ibid.
[8] Ibid.
[9] Ibid.

31. Mr Kell had initially been admitted to Graylands Hospital on 13 June 2012 as a voluntary patient on an open ward, but he was detained as an involuntary patient 9 August 2012 following two assaults on patients (thought to be psychotically driven), reports of inappropriate behaviour in public and refusal of medication. He remained at Graylands Hospital until his death on 26 April 2015.[10]

TREATMENT OF MR KELL WITH CLOZAPINE

32. Clozapine is a novel antipsychotic reserved for use in treatment resistant schizophrenia. The North Metropolitan Health Service, Mental Health Clozapine Prescribing Policy (Prescribing Policy) at the material time noted that clozapine is indicated for the treatment of schizophrenia where the patient is non-responsive to, or intolerant of, other antipsychotics. Guidance is given in the Prescribing Policy on the thresholds for such non-responsiveness and intolerance.[11]

33. The inquest examined the effect of the clozapine on Mr Kell's gastrointestinal motility, and whether clozapine-induced gastrointestinal hypomotility contributed to his death. Gastrointestinal hypomotility refers to the delayed transit through the gastrointestinal tract, also known as "*slow gut*".

34. Clozapine-induced gastrointestinal hypomotility was not a well-known side effect of this medication in 2015 when Mr Kell was being treated. This condition is to be distinguished from constipation (a known side effect of this medication in 2015).

35. Treatment with Clozapine can be life changing for individuals with schizophrenia, but the medication has been controversial due to its side effect profile. At the time that Mr Kell was being treated, the two main side effects, for which there was proscribed monitoring, were considered to be:

a) agranulocytosis (lowered white blood cell count); and

b) myocarditis (inflammation of the heart muscle).[12]

36. Mr Kell's clinicians had formed the view that he seemed to only experience symptomatic relief with clozapine. He had some problems with this medication, and it remains unclear as to whether it contributed to his seizures. Previous attempts at reducing the dosage were observed to have resulted in him relapsing, with his mental state deteriorating. His usual dosage of clozapine was between 575 to 600 milligrams at night-time.[13]

[10] Ibid.
[11] Exhibit 1, tab 13; Exhibit 3.
[12] Exhibit 3.
[13] Exhibit 1, tab 13, Exhibit 2.

37. Throughout his treatments, Mr Kell was on a range of medications (in addition to periods of being medicated with clozapine). These included medications to treat other side effects of clozapine (to reduce hyper-salivation and constipation), medications for seizures, a mood stabiliser, an anxiolytic, and medication for hypothyroidism and hypertension.[14]

38. Medical records reflect that Mr Kell had a total of three trials with clozapine. He first commenced clozapine in early 2002 but stopped a couple of months later in April 2002 due to non-adherence. The reasons for the non-adherence are not recorded. On this first trial he had been commenced on an initial dosage of 25 milligrams per day, gradually increased to 400 milligrams per day, in accordance with the recommended protocol.[15]

39. Mr Kell was recommenced on clozapine in August 2004, and the dose titrated to 500 milligrams per day, and then increased to 600 milligrams per day. In 2020, Mr Kell's dosage was reduced at his request, but he suffered a relapse and the dosage was again increased to 600 milligrams per day, before being reduced to 500 milligrams per day in March 2011.[16]

40. Mr Kell remained on clozapine until October 2011, when it was ceased due to him experiencing the recognised side effect of a low white cell count (agranulocytosis). The drug company that manufactures clozapine issues strict guidelines on the monitoring of agranulocytosis and myocarditis.[17]

41. Therefore as outlined previously, in June 2012 when Mr Kell was transferred to Graylands Hospital, his clozapine had been ceased. After transfer to Graylands Hospital, it was thought that the cessation of his clozapine had again contributed to a decline in his mental state. He displayed behaviours that were more paranoid, aggressive and inappropriate, and he refused medication. His status was changed to involuntary on 9 August 2012.[18]

42. A December 2012 request to the manufacturer's haematologist to rechallenge Mr Kell with clozapine (following the previous agranulocytosis) was declined, with the strong recommendation that all other atypical antipsychotics be tried first.[19]

43. Over the early part of 2013, after consultation with Mr Kell, family members and a nominated patient advocate, and with a second medical opinion in support, clinicians sought and on this occasion received approval from the manufacturer's haematologist to recommence Mr Kell on clozapine. Account was taken of the fact that Mr Kell had been in Graylands Hospital for 17 months, the treating team had tried all other

[14] Ibid.
[15] Exhibit 3.
[16] Ibid.
[17] Exhibit 1, tab 13; Exhibit 2.
[18] Ibid.
[19] Exhibit 3.

antipsychotics, he remained mentally unwell, and steps would be taken to increase his neutrophil count.[20]

44. Therefore after almost one year off this medication, Mr Kell was recommenced on clozapine on 27 May 2013, and his clinicians observed his mental state to improve significantly, with no further incidents of aggression or inappropriate behaviour. Approximately two months later, on 27 July 2013, Mr Kell suffered another seizure, and on his admission to hospital, his medications were adjusted, and this included a decrease in his dosage of clozapine.[21]

45. The decrease in Mr Kell's clozapine dosage was followed by a significant deterioration in his mental state, and he was transferred to the secure ward to contain and manage his aggression. Medications to control his seizures continued to require adjustment.[22]

46. Mr Kell remained on clozapine until his death, the dose at that stage being 600 milligrams per day. This was within the accepted recommended dose range in accordance with the Therapeutic Guidelines and the Australian Medicine Handbook (between 200 to 600 milligrams per day, and up to a maximum dose of 900 milligrams per day).[23]

47. Records reflect that Mr Kell's clozapine dose had been withheld in the days before his death, on 24 and 25 April 2015, though it would still have been exerting some of its therapeutic sedating effect.

EVENTS LEADING TO DEATH

48. In the month before his death Mr Kell's behaviour and mental state were noted to fluctuate, he was intermittently unsettled, and was sometimes thought to be responding to unseen stimuli. He occasionally displayed aggression towards others. Clinicians attributed his behaviour to varying levels of psychosis and considered also whether it could possibly be as a result of substance abuse.[24]

49. From 10 March 2016, Mr Kell was on daily physical observations, and his pulse rate was consistently noted as being elevated. He had regular blood testing in accordance with the clozapine protocol.[25]

50. Between 23 and 27 March 2015, Mr Kell was reviewed medically and psychiatrically. Mr Kell's involuntary status was reviewed on 27 March 2015. This more formal mental state examination found him to be psychotic, with grandiose, referential and persecutory delusions. His clinicians remained concerned about access to illicit drugs, and he was reluctant to engage with them. On 27 March 2015 Mr Kell was ordered

[20] Exhibit 1, tab 13; Exhibit 2.
[21] Ibid.
[22] Ibid.
[23] Exhibit 3.
[24] Exhibit 1, tab 13; Exhibit 2.
[25] Ibid.

to be detained under the Mental Health Act for a further three months, with a restriction to escorted ground access only.

51. On 10 April 2015 Mr Kell went on an outing with his father for several hours, off the hospital grounds. When Mr Kell returned to the hospital his behaviour was observed to be strange. Security personnel conducted a search and found a small amount of a substance that had the appearance of baking herbs, which was believed to be intended for smoking. It was not known if he had consumed any portion.[26]

52. On 21 April 2015 Mr Kell was involved in an unprovoked attack on another patient. It appeared that this was in response to psychotic symptoms.[27]

53. On 24 April 2015, Mr Kell's last formal psychiatric review took place. He was questioned about the attack, but did not take responsibility for it, describing it as trivial and unimportant. Overall, his clinicians assessed him as being psychotic, with delusions of reference and persecution.[28]

54. During that last psychiatric review Mr Kell had expressed frustration at his ongoing lack of unescorted ground access. On that same date he was granted community access in the company of his father, who collected him from Graylands at 11.00 am on 24 April 2015, and together they spent time socialising in Subiaco and Perth.[29]

55. Although Mr Kell senior had seen his son recently, during their time together on 24 April 2015 he felt his son looked drawn and thinner. He noticed his son was responding to unseen stimuli more than on other occasions. He was gentle with his son and did not want to exacerbate his agitation by questioning him about weight loss. He returned his son to Graylands Hospital at approximately 2.30 pm on 24 April 2015, and that sadly was the last occasion upon which he saw him.[30]

56. Upon his return to Graylands Hospital on 24 April 2015, Mr Kell appeared drowsy to his clinicians, and it was suspected he had smoked synthetic cannabis. Mr Kell denied this when questioned. With his consent, Mr Kell's personal belongings were searched, and nothing untoward was found.[31]

57. Mr Kell senior had some awareness of his son's long term cannabis use, and he knew that it exacerbated his mental health condition. He confirmed that he did not observe his son take, get or use any cannabis on any occasion when he was with him.[32]

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[26] Ibid.
[27] Ibid.
[28] Ibid.
[29] Exhibit 1, tabs 8 and 13; Exhibit 2.
[30] Ibid.
[31] Ibid.
[32] Ibid.

58. Mr Kell was reviewed by the doctor later on the evening of 24 April 2015 and medical records reflect that he appeared drowsy, and he was hyper-salivating. A urine drug screen was ordered, escorted ground access was suspended, and a decision made to withhold his clozapine dose. On this occasion, his heart rate was observed to be 100 beats per minute.[33]

59. Medical records reflect that on the morning of the next day, 25 April 2015, Mr Kell displayed behaviour described as being bizarre, but that he subsequently settled. It was still thought to be possibly related to him smoking synthetic cannabis. In the early evening on that same date when Mr Kell was approached for the usual administration of his medications, he was noted to be confused and uncommunicative, with evidence of a coarse jerky tremor. He did not show signs of distress. By reason of his elevated pulse rate (119 beats per minute), hospital policy required that Mr Kell have a medical review.[34]

60. The hospital's Duty Medical Officer was duly contacted, but this clinician was at that point tasked with reviewing another patient for admission, and he advised that he would attend to review Mr Kell when able. The Duty Medical Officer further advised that if he was not able to attend within the next 60 minutes, repeat observations of Mr Kell were to be taken.[35]

61. Medical records reflect that less than one hour later, at approximately 9.00 pm, Mr Kell was reviewed by a registered nurse and his pulse rate was observed to be within normal limits, though it is noted he had vomited, and this was attended to. At this stage, Mr Kell was observed to be coherent and his jerky movements had stopped. He also appeared calm, however expressed displeasure at the intrusion of having his observations taken.[36]

62. An hour afterwards, at approximately 10.00 pm the registered nurse timed Mr Kell's respirations through the observation window, so as not to disturb him, and found them to be within normal limits. At approximately 11.00 pm further clinical observations recorded a respiratory rate within normal limits.[37]

63. However, shortly afterwards, at around the time of the nursing shift handover, being between 11.00 pm and 11.30 pm, Mr Kell was found to have vomited extensively and been incontinent of a faeces. He was confused and incoherent. Nursing staff assisted him to the bathroom, and while there, being attended to, his clinical state deteriorated rapidly and he became unresponsive.[38]

[33] Exhibit 1, tab 13; Exhibit 2.
[34] Exhibit 1, tabs 13 and 18; Exhibit 2.
[35] Ibid.
[36] Ibid.
[37] Ibid.
[38] Ibid.

64. Records reflect that shortly after midnight, in the early minutes of 26 April 2015, a Code Blue (Medical Emergency Team) was activated, and the Duty Medical Officer was alerted. The Medical Emergency Team promptly attended and commenced resuscitation.[39]

65. Records reflect that St John Ambulance received a Priority One call at 12.12 am and that they promptly departed arriving at the scene at 12.16 am on 26 April. The paramedics took over the resuscitation efforts. Mr Kell's airway was suctioned, but the deployment of successive suction units was unable to keep up with the volume of vomit. Intubation was attempted, but the airway was unable to be secured. Successive attempts to gain intravenous and interosseous access were unsuccessful.[40]

66. Resuscitation attempts continued for 20 minutes, but Mr Kell remained in asystole. At 12.39 am on 26 April 2015, the paramedic pronounced Mr Kell to be deceased.[41]

CAUSE OF DEATH

Post Mortem Examination and investigations

67. On 29 April 2015 the forensic pathologist Dr Gerard A. Cadden (Dr Cadden) made a post mortem examination at the State Mortuary on the body of Mr Kell and on that date formed the opinion that the cause of his death was acute vomit aspiration in a man with acute large intestine obstruction (severe megacolon). At post mortem examination Dr Cadden noted that severe bowel obstruction was evident, with marked dilatation of the large bowel secondary to this obstruction.[42]

68. In considering the size of the distended segments of the large bowel, Dr Cadden estimated the diameter to be in the order of 150 – 200 millimetres. The area of obstruction was noted to be in the sigmoid colon (in the vicinity of the junction of the descending colon and sigmoid colon), with a band like area of adhesion. It was in the order of approximately 300 to 400 millimetres from the rectum.[43]

69. Dr Cadden noted that extensive inhalation of vomit had occurred. The vomit aspiration was widely distributed within the major airways and bronchial tree. This stopped Mr Kell's breathing, resulting in his death.[44]

70. Toxicological analysis was ordered and reports became available in May and August 2015. Neuropathology analysis was ordered and became available in June 2015. Following further analysis, in July 2016 Dr Cadden reported that the medication clozapine was approximated in

[39] Ibid.
[40] Exhibit 1, tabs 16 and 17.
[41] Exhibit 1, tab 2.
[42] Exhibit 1, tab 4.
[43] Ibid.
[44] Ibid.

blood (aorta preserved) at therapeutic levels. Alcohol was not detected in blood (mortuary admission preserved) while amphetamines, benzodiazepines, cannabinoids and opiates were reported as negative by immunoassay in respect to the same blood sample.[45]

71. Relevantly, in July 2016 Dr Cadden also noted that toxicological analysis reported that the synthetic cannabinoid AB-CHMINACA was detected in Mr Kell's blood. There was little to no scientific literature available regarding the toxicity and/or pharmacology of this synthetic cannabinoid. It is known that synthetic cannabinoids are metabolised in the liver, and at post mortem it was noted that Mr Kell had advanced liver disease (cirrhosis of the liver). It is possible, though not established, that Mr Kell may have been unable to metabolise cannabinoids normally.[46]

72. The Neuropathology analysis reported that Mr Kell's brain showed no significant abnormalities. After reviewing these additional investigations, in July 2016, the forensic pathologist reported that his opinion on cause of death remained unchanged.[47]

73. In July 2018 the expert opinion of specialist general and colorectal surgeon Dr Michael Levitt (Dr Levitt) was sought in connection with the obstruction in Mr Kell's large bowel, including an opinion sought as to the expected general symptoms of a person suffering from an acute large bowel obstruction, and whether Mr Kell was displaying such symptoms. I have referred to this under the section headed: *QUALITY OF SUPERVISION, TREATMENT AND CARE*, below.[48]

74. For the purpose of my analysis of the cause of death, it suffices at this point that I record that in August 2018 Dr Levitt provided his report to the coroner, stating that:

a) he did not believe that Mr Kell suffered an acute large bowel obstruction; and

b) a far more plausible explanation of Mr Kell's death is that he encountered adverse effects of self-administered drugs with diarrhoea and vomiting presenting pre-agonal features rather than reflecting an underlying gastrointestinal pathology.[49]

75. As a consequence, in October 2018, the court sought the opinion of Clinical Pharmacologist and Toxicologist Professor David Joyce (Professor Joyce) in connection with whether any of the substances recorded as being detected in Mr Kell's blood (including the synthetic cannabinoid AB-CHMINACA) caused or contributed to his death.[50]

[45] Exhibit 1, tabs 4 and 5.
[46] Exhibit 1, tabs 4 and 5; ts 132.
[47] Exhibit 1, tabs 4 and 5.
[48] Exhibit 1, tabs 4, 5 and 11.
[49] Exhibit 1, tab 11.
[50] Exhibit 1, tab 10.

76. In December 2018 Professor Joyce provided his report to the coroner, addressing the toxicology of synthetic cannabinoids, and also raising the toxicology of clozapine, and the contribution of clozapine-induced intestinal hypomotility to the pathology found in Mr Kell's gut at post mortem examination.[51]

77. The various expert opinions were considered at the inquest. The evidence given by Professor Joyce, Dr Levitt and Dr Cadden assisted me in formulating my findings on the cause of Mr Kell's death. Relevant aspects of this evidence are outlined below.

Professor Joyce's evidence

78. In his report to the coroner Professor Joyce noted that toxicity relationships in connection with the synthetic cannabinoid AB-CHMINACA are not well understood. Detection confirms exposure to AB-CHMINACA, but does not establish that the drug is responsible for any clinical manifestation. Professor Joyce referred to one other case in Perth (in the same year that Mr Kell died) where AB-CHMINACA was established as the cause.[52]

79. In his report Professor Joyce had concluded that in the circumstances of Mr Kell's case, attempts to quantitate AB-CHMINACA would probably not give a better insight into its contribution to death in this case, noting that the actual measured blood concentrations of synthetic cannabinoids have only an indistinct relationship to their lethal potential.[53]

80. At the inquest Professor Joyce outlined some of the known and serious effects of intoxication with AB-CHMINACA, including disturbances of consciousness (including severe disturbance of brain function and seizures), a propensity towards hallucinations, and hyperpyrexia (excessively high and uncontrollable body temperature which may lead to irreversible brain damage and disturbance to heart function leading to death).[54]

81. Professor Joyce's opinion was that prior to death Mr Kell showed some signs consistent with cannabinoid exposure, such as episodic disturbances in gait, behaviour, speech and alertness.[55]

82. However, in the Professor's opinion, Mr Kell did not have a clinical course that otherwise aligned with experience of lethal synthetic cannabinoid toxicity, which typically evolves over hours with progressive failures of organ systems. In contrast, Mr Kell's terminal deterioration began within an hour of death, and became abrupt, going

[51] Ibid.
[52] Ibid.
[53] Ibid.
[54] ts 149.
[55] Exhibit 1, tab 10.

from a state of being able to walk to the bathroom with assistance, to unconsciousness apparently within the space of minutes.[56]

83. In his report Professor Joyce noted that AB-CHMINACA may provoke reflex vomiting, and it is also a sedating drug. He explained at the inquest that it may have accounted for Mr Kell's sedated appearance on 24 and 25 April 2015. However, he does not know it to have any direct effect on bowel function, has not seen any connection in literature reviews, nor encountered such in clinical cases.[57]

84. I accept Professor Joyce's opinions and am satisfied that the synthetic cannabinoid AB-CHMINACA did not cause or contribute to the pathology found in Mr Kell's gut at post mortem. I am also satisfied that Mr Kell did not experience synthetic cannabinoid toxicity at lethal levels. He did not die by reason of having taken a lethal quantity of a synthetic cannabinoid.

85. I turn now to the likelihood of the contribution of clozapine to Mr Kell's death, a matter that Professor Joyce considered. The benefits of clozapine for patients with treatment resistant schizophrenia are well known, but they come with a substantial risk of adverse events, that I analyse in more detail under the heading: *CONTRIBUTION OF CLOZAPINE TO DEATH*, below. The Professor outlined that adverse gastrointestinal effects of clozapine are very common.[58]

86. For the purpose of my analysis of the cause of death, it is sufficient that at this point that I record that Professor Joyce referred to the term "*clozapine-induced intestinal hypomotility*" that covers a range of clinical events that follow clozapine's interference with the normal physiological control of intestinal motility. The Professor noted that while there are no cases of clozapine induced hypomotility in the post mortem literature to date, the clozapine therapy is very likely to have been a contributor to the pathology found in Mr Kell's gut at post mortem.[59]

87. That in turn provides a plausible explanation as to why Mr Kell had a dysmotile stomach with a large residual content in it, and by chain of logic, it potentially explains the availability of so much stomach content that it allowed for a lethal aspiration by Mr Kell when he vomited.[60]

88. At the inquest Professor Joyce's opinion was also sought in respect of the other medications that had been prescribed to Mr Kell as reflected in the Graylands Hospital dispensing charts, as to whether they had a bearing on Mr Kell's death, including in particular whether these may have contributed to gastrointestinal hypomotility.[61]

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[56] Ibid.
[57] ts 149 to 151; ts 156 to 157.
[58] Exhibit 1, tab 10.
[59] Ibid.
[60] ts 144 to 147; ts 151 to 153.
[61] ts 150 to 151.

89. Professor Joyce's opinion was that the following medications that had been prescribed for Mr Kell did not have any contribution: lithium carbonate, clonazepam, levetiracetam, perindopril, and thyroxine.[62]

90. Professor Joyce's opinion was that the following medications that had been prescribed for Mr Kell do reduce motility of the gut, but the amounts were small, therefore the contribution comparatively small: hyoscine bromide and atropine drops.[63]

91. Professor Joyce's report and evidence at the inquest persuades me that there is a condition known as clozapine-induced gastrointestinal hypomotility. Whilst one cannot detect it with absolute certainty in Mr Kell's case, nor establish the chain of events with absolute certainty, applying the legal standard of proof outlined in *Briginshaw's* case (referred to at the outset) I am satisfied that the clozapine therapy is highly likely to have been a contributor to the pathology found in Mr Kell's gut at post mortem, and that contributed to his death.

Dr Levitt's evidence

92. At the inquest specialist general and colorectal surgeon Dr Levitt was asked to elaborate on some of the opinions expressed in his report to the coroner, and in particular the question of whether Mr Kell had a large bowel obstruction in the area of the sigmoid colon (or otherwise). In his report Dr Levitt had opined that the sequence of clinical events for Mr Kell did not suggest a large bowel obstruction.[64]

93. Dr Levitt has extensive clinical and surgical experience in the areas concerning adhesions, obstructions and motility of the bowel. Until Dr Levitt was asked to review Mr Kell's case, he had not been referred any patient with clozapine-related constipation.[65]

94. At the inquest Dr Levitt was asked to explain the characteristic symptoms of a patient with a mechanical large bowel obstruction, and of a patient with a hypomotility disorder. Notably, there are no clinical records of Mr Kell having referred to feeling any pain prior to his death.

95. In Dr Levitt's experience, the characteristic symptoms for a person with a mechanical large bowel obstruction are colicky abdominal pain and abdominal distension. There would be no passage of flatus or stool. An bowel obstruction is an insistent pain. Generally such a patient would present at an emergency department, and would require opiate painkillers, such as morphine or fentanyl, and there would be a prospect of surgery being required.[66]

[62] Exhibit 1, tab 10; ts 150 to 151.
[63] Ibid.
[64] Exhibit 1, tab 11.
[65] ts 113 to 142.
[66] ts 120 to 121.

96. With hypomotility (or underactivity), as opposed to a mechanical obstruction, distention is the main problem, and pain is less prominent (though some persons with motility disorders do feel pain).[67]

97. At the inquest Dr Levitt was also asked about vomiting as a symptom associated with gastrointestinal conditions (it was noted that Mr Kell was not suffering from a gastrointestinal infection, so this aspect is not traversed in the finding).

98. In respect to symptoms of vomiting, at the inquest Dr Levitt outlined the following:

a) A person may vomit as a reflex to pain, especially at the onset of severe pain;

b) In approximately 20% of the population, the ileocecal valve is incompetent, and in such cases, if there is an obstruction in the colon, then large bowel content can decompress into the small bowel and retrogradely spread all the way back up into the stomach, resulting in vomiting; this may occur over a matter of hours from the time of the obstruction (it is to be noted however that at post mortem examination there was nothing to suggest that Mr Kell's ileocecal valve had malfunctioned); and

c) Whilst vomiting is not a manifestation of a hypomotility disorder, in the lead up to the period where a person has an intense, distressing physical event, such as a cardiorespiratory arrest, to vomit and to be incontinent of faeces is not unexpected, they are agonal events (namely terminal events just prior to death).[68]

99. A primary focus of Dr Levitt's evidence was related to the issue of whether Mr Kell had a large bowel obstruction. In his report Dr Levitt had noted that Mr Kell had not complained of any abdominal pain, making it unlikely that his vomiting was a reflex to pain. There is no report of Mr Kell having complained of abdominal distension, nor was such clinically noted. Dr Levitt reasoned that the reports of the large volume of faecal incontinence were inconsistent with a mechanical obstruction at the level of the distal sigmoid colon.[69]

100. Dr Levitt had regard to Mr Kell's clinical notes at the material time, and the results of the post mortem examination in concluding that there was no indication of a mechanical large bowel obstruction being clinically evident. He noted that the post mortem examination showed a global dilatation of the colon. A congenital adhesion was noted at the junction of the descending colon and the sigmoid colon, but relevantly he noted that there was distension above and below that.[70]

[67] ts 124.
[68] ts 121 to 122.
[69] Exhibit 1, tab 11.
[70] ts 126 to 127.

101. Dr Levitt explained that, if there had been dilatation down to the point of the adhesion, and a completely collapsed bowel beyond, that was empty, that would indicate a mechanical obstruction: "*upstream [proximal] would be dilated; downstream [distal] would be collapsed.*" He mentioned that it would be unusual, though conceivable, that an adhesion would operate as a mechanical obstruction. Dr Levitt has not ever seen a large bowel occluded by an adhesion in a patient.[71]

102. At the inquest Dr Levitt, having reviewed the evidential material, including relevant photographs from the post mortem examination, opined that the dilatation of Mr Kell's bowel was consistent with hypomotility.[72]

103. When asked to consider this is light of there having been some distention of the small bowel (though not a marked distension), Dr Levitt opined that if there was a mechanical large bowel obstruction, then the process by which that would translate into vomiting would be by retrograde distension of the small bowel. Therefore, where the large bowel is dilated, and the small bowel only mildly dilated, he would not conclude that the vomiting was connected to a large bowel obstruction, or a motility disorder.[73]

104. Dr Levitt explained that persons do not die by reason of constipation or faecal impaction. Death occurs by reason of complications arising from such conditions. He pointed to examples such as ulceration, serosal tearing, perforation, abscess, and peritonitis, noting that none of these were evident in Mr Kell's case. There was no likelihood of bacterial translocation given that the post mortem showed that all of the intestine was viable.[74]

105. Therefore Dr Levitt was unable to see any reason for that degree of obstruction, or its consequences, to cause death. If obstruction was present at all, he considered it to be at an early, mild and moderate stage.[75]

106. Dr Levitt's view was that Mr Kell's clozapine-related motility disorder and constipation were conditions that were coincidental to his death, and that the vomiting and diarrhoea, (observed clinically prior to his death), were agonal events that are similarly not connected to those conditions. It is clear however that as a result of the vomiting, Mr Kell aspirated, and this resulted in his death.[76]

107. In his experience, Dr Levitt has not ever seen a non-obstructed segment of a colon reach a dilatation of 20 centimetres, and at such point it would invariably perforate, because it is too much distension for a colon to tolerate.[77]

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[71] ts 127.
[72] ts 131.
[73] ts 133.
[74] ts 134 to 135.
[75] ts 142.
[76] ts 136.
[77] ts 139.

108. Dr Levitt considered that the relevant post mortem photographs do not show a distension of the colon in the range of 15 to 20 centimetres, and posited that this measurement was taken of the opened colon at post mortem examination, and therefore represents the circumference of the distended colon, and not the diameter. In the circumstances (and by reference to the photographs), Dr Levitt describes the degree of distension as "*moderate*". However, the post mortem examination refers to this measurement as being the diameter of the colon (in which case Dr Levitt would describe the distension as "*massive*").[78]

109. Dr Levitt also posited that whilst the degree of distension he saw in the photographs could be comfortably reached within an hour in the case of a mechanical obstruction, it was also possible that Mr Kell's bowel had been quite dilated and distended for months or years.[79]

110. Dr Levitt's evidence therefore raised a question as to whether Mr Kell had a large bowel obstruction, and the forensic pathologist Dr Cadden was able to hear and consider this evidence before testifying as to his opinion on the cause of Mr Kell's death.

Dr Cadden's evidence

111. At the inquest Dr Cadden reiterated that the distension of the colon, in the range of 15 to 20 centimetres, that he measured at post mortem examination, was of the diameter of the colon at the largest point of distension, and not (as Dr Levitt earlier posited) the circumference. This is important in the context of the severity of Mr Kell's clozapine-induced gastrointestinal hypomotility.[80]

112. The main focus of Dr Cadden's post mortem examination was in respect of the entirety of the large bowel, which he described as remarkably distended, severely so. He confirmed that he observed no evidence of peritonitis or localised infection, no perforations or rupture. The bowel wall was not necrotic or breaking down. He observed no obvious obstruction in the ileocecal region.[81]

113. On the other hand, Dr Cadden's observations of the small bowel were that it was not markedly distended. It was noted that the major contents were in the distended large bowel, which appeared to be under significant pressure, with liquid material. He did not observe Mr Kell to have been suffering from constipation.[82]

114. The band-like area of adhesion that Dr Cadden thought had potentially caused the obstruction and dilatation was towards the bottom end of the sigmoid colon. On his assessment, it was the only area that he could find that potentially would provide a mechanical obstruction, and

[78] Exhibit 1, tab 4; ts 139 to 140.
[79] ts 141.
[80] ts 163; ts 166.
[81] ts 163 to 166; Exhibit 6.1 and 6.2.
[82] ts 167.

therefore explain the dilatation. The distension of the large bowel was predominantly (but not solely) above the band-like area of adhesion. At the site of the band-like adhesion, the bowel wall had a haemorrhagic appearance, although it was viable. He did not ascertain that there was a complete obstruction, he found liquid material above and below the band-like area of adhesion.[83]

115. In connection with the vomiting and evacuation of the bowels shortly before death, described by Dr Levitt as agonal events, Dr Cadden noted that they are so described because they occurred at and around the time that Mr Kell collapsed and died. Dr Cadden described these agonal events as being in close temporal time to Mr Kell's death, and he attributed them to the distension of the large bowel, and around having an obstruction.[84]

116. On 29 April 2015 (the date of the post mortem examination) Dr Cadden had formulated his initial opinion on the cause of death for Mr Kell, being: "*acute vomit aspiration in a man with acute large intestine obstruction (severe megacolon).*"[85]

117. Afterwards, the possibility of clozapine-induced gastrointestinal hypomotility was introduced, as a result of further investigations. Specifically, Dr Cadden was provided with Professor Joyce's report to the coroner, dated 13 December 2018, that addressed the potentiality for clozapine-induced hypomotility (in the context of addressing the toxicology of clozapine).

118. In a subsequent report to the coroner, Dr Cadden outlined the matters he took into account from the material provided by Professor Joyce, and his advice that clozapine therapy is very likely to have been a contributor to the pathology found in the gut at post mortem examination:

> "*I do not think that the paucity of pathology literature in regards to clozapine hypomotility detracts from this drug therapy potentially having been a contributing factor. Forensic pathologists encounter numerous conditions that never reach post mortem literature. In Mr Kell's case I think there are good grounds to add to the cause of death "and potential clozapine-induced intestinal hypomotility."*[86]

119. On 15 February 2019 Dr Cadden, having reviewed the new information, amended his opinion to the effect that the cause of death for Mr Kell was: "*acute vomit aspiration in a man with acute large intestine obstruction (severe megacolon) and potential clozapine-induced intestinal hypomotility.*"[87]

120. At the inquest Dr Cadden elaborated on his opinion as follows:

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[83] Exhibit 5; ts 169 to 172.
[84] ts 176 to 177.
[85] Exhibit 1, tab 4.
[86] Exhibit 1, tab 4.
[87] Exhibit 1, tabs 4 and 10; ts 178 to 179.

a) The acute large intestine obstruction resulted in the severe megacolon;

b) There had been suggestions expressed to the effect that Mr Kell died as a result of taking synthetic cannabinoids, and it was necessary to carefully examine the toxicological effects of the drugs detected in the post mortem samples;

c) Having considered Professor Joyce's report, he added the potential clozapine-induced intestinal hypomotility to his opinion on cause of death, as it provided another avenue for explaining the post mortem findings.[88]

121. At the inquest, counsel for North Metropolitan Health Service confirmed that it is not disputed that clozapine is a contributor to Mr Kell's cause of death.[89]

Conclusion on Cause of Death

122. I have taken account of Dr Cadden's opinion on the cause of death, and the evidence of the experts, referred to above. I have carefully considered the question of whether Mr Kell had suffered an acute large intestine obstruction. On balance having regard to Dr Cadden's role and his direct observations at post mortem examination, I am satisfied that Mr Kell had a mechanical obstruction, that was not necessarily a complete obstruction, and that explains the dilatation. That obstruction was around the band-like area of adhesion towards the bottom end of the sigmoid colon.

123. I have noted Dr Cadden's reference to the "*potential*" role of clozapine-induced intestinal hypomotility in his opinion on Mr Kell's cause of death. For the reasons outlined below under the heading: *CONTRIBUTION OF CLOZAPINE TO DEATH*, and taking account of the appropriate standard of proof, I am satisfied that clozapine had a role in Mr Kell's death, and that it was more than a potential role.

124. I find that the cause of Mr Kell's death was acute vomit aspiration in a man with acute large intestine obstruction (severe megacolon) and clozapine-induced intestinal hypomotility.

CONTRIBUTION OF CLOZAPINE TO DEATH

125. Clozapine is marketed under the brand name Clopine by Pfizer Australia Pty Ltd and has been used by North Metropolitan Health Service for many years. Clozapine is also marketed under the brand name Clozaril

[88] Ibid.
[89] ts 180.

by Mylan Australia, but this brand has not been used by North Metropolitan Health Service within the last ten years.[90]

126. Ms Anna Courtney is the senior pharmacist with the North Metropolitan Health Service. As the pharmacist at Graylands Hospital she had a role in assessing patients' medications, that included compliance with the general policies for that medication (monitoring regimes, side effects, adverse reactions, and medication interactions). Ms Courtney reported that clozapine is known to commonly cause constipation as an adverse effect. However, it can also cause gastrointestinal hypomotility, which is the slowing down of the gut peristalsis which may result in severe constipation, ileus (cessation of peristalsis), bowel obstruction and death.[91]

127. Ms Courtney reported that as at 2015, the adverse effect spectrum attributed to gastrointestinal hypomotility was speculative as transit times had not been measured. She referred to a 2016 published study comparing transit times of clozapine with other antipsychotics, that showed a median large bowel transit time of 104.5 hours compared with 23 hours in patients on other antipsychotics (the Clozapine Study).[92]

128. At the inquest Ms Courtney confirmed that:

> *"In 2015 I knew that clozapine commonly caused constipation. It was a common side effect. I knew that there had been cases of fatalities. Very, very, rarely fatalities had occurred. I had never known of anyone who had – who had had the side effect….we knew constipation is a problem. But certainly I had never heard of the term "clozapine-induced gastrointestinal hypomotility". This is something that I learnt since Mr Kell's passing."*[93]

129. In 2017 there was another study (the largest to date) that reviewed all reports of serious cases of clozapine-induced gastrointestinal hypomotility submitted to the Therapeutic Goods Administration in Australia and the New Zealand Pharmacovigilance Centre between 1992 and 2013 (the 22 Year Study). This study reported an incidence of gastrointestinal hypomotility of 37/10,000 (which Ms Courtney considers likely to be an underestimation) and with a case fatality rate of 18%.[94]

130. Professor Joyce reported that efforts to develop a drug with clozapine's efficacy, but without its toxicity, have not yet succeeded, and he also referred to the Clozapine Study. In noting that gastrointestinal adverse effects of clozapine are very common, he explained that clinically this is

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[90] Exhibit 3.
[91] ts 47; Exhibit 3.
[92] Exhibit 1, tab 10; Exhibit 3; "*Clozapine treated patients have marked gastrointestinal hypomotility, the probable basis of life threatening gastrointestinal complications: a cross sectional study*", Every-Palmer et al, EBio Medicine 6 (2016) 125 to 134.
[93] ts 48.
[94] Exhibit 3; "*Clozapine-induced gastrointestinal hypomotility: a 22 year bi-national pharmacovigilance study of serious or fatal "slow gut" reactions, and comparison with international drug safety advice*" Every-Palmer and Ellis, CNS Drugs (2017) 31:699 – 709.

just treated as a propensity to constipation. He notes cases whose clinical course and gastrointestinal manifestations match Mr Kell's case.[95]

131. In his report to the coroner, Professor Joyce explained that clozapine-induced hypomotility reportedly affects the entire intraabdominal gut, and that one recognised pathway to death is the aspiration of gastric contents, as occurred in Mr Kell's case. He explained that in Mr Kell's case, there was no a clinically convincing picture of complete bowel obstruction, but there were pathological findings of grossly impaired bowel transit.[96]

132. At the inquest Professor Joyce drew attention to factors, ascertained in the course of the post mortem examination, that alerted him to the possibility that clozapine-induced disturbances of the bowel went beyond the slowing down of the bowel through constipation. These factors were as follows:

a) The contents of the bowel were not those of constipation; instead there was a lot of fluid, implying that the real problem was not hard stool stopping passage, but that there was something wrong with the bowel wall preventing the large bowel from moving things along;

b) There was also an effect on the small bowel, referred to as being mildly distended;

c) The changes to the large and small bowel may have been pervasive so as to involve the stomach, thereby endowing the stomach with a dilated character and the capacity to hold a larger amount of material; and

d) The reported vomiting had been so extensive as to imply that there was a great deal of upper gastrointestinal content; further, at post mortem examination there was still content remaining in the stomach despite the extensive reports of vomiting.[97]

133. This led Professor Joyce to consider a disorder that was pervasive throughout the gastrointestinal tract, not simply affecting the motility of the large bowel, and perhaps including as a consequence, a dysmotile stomach with a large residual content in it.[98]

134. Whilst distension of the large bowel appears to be a consistent feature of the clozapine-induced intestinal hypomotility in life, Professor Joyce found no case series for comparison with observed post mortem findings of this nature.[99]

[95] Exhibit 1, tab 10.
[96] Ibid.
[97] ts 144; ts 147.
[98] Exhibit 1, tab 10; ts 145.
[99] Exhibit 1, tab 10.

135. In Professor Joyce's view, it is most likely that clozapine can cause a chronic disorder to the gastrointestinal tract or bowel, that affects it throughout its length and is something additional to its constipating effect. However, he does not consider the evidence to go as far as showing that anatomically at post mortem, or to demonstrate the disturbed physiology. In these circumstances, the Professor cannot hold any conviction that this extended condition actually exists, but he noted that it does serve to fairly well explain the clinical observations.[100]

136. On the question of whether clozapine had an essential role in Mr Kell's death, Professor Joyce confined the role through its effects on Mr Kell's bowel. The Professor referred to a chain of logic that links the findings of the post mortem examination with the literature and the events in Mr Kell's final hours, but that certainty is not established in his opinion.[101]

137. At the inquest Professor Joyce further explained that the clozapine potentially explains the availability of so much stomach content that it allowed for a lethal aspiration by Mr Kell, even after he had substantially emptied his stomach with previous vomiting. Where the small gut is not transiting well, that will mean that an already weakened stomach will empty itself less efficiently.[102]

138. Professor Joyce considered the sequence of events that led to Mr Kell's death in terms of probabilities, as follows:

> "*….a plausible explanation for the death that Mr Kell had a background clozapine-induced hypomotility syndrome which went beyond the simple constipation that is well recognised for it, that part of that dysmotility syndrome included involvement of small bowel and stomach, which then meant that – normally, by his nature, he would normally have a high stomach content there. It's then credible that he found himself in a situation where he [was] sedated and cerebrally impaired by intoxication with the AB-CHMINACA so that when vomiting occurred, he was unable to protect his airways*".[103]

139. However Professor Joyce qualified that opinion on the following bases:

a) There is no direct proof of stomach involvement or high gastric content; and

b) There is no explanation as to why Mr Kell vomited (though it was noted that a sudden and substantial drop in blood pressure can result in a reflex that includes emptying bowels as well as vomiting).[104]

[100] ts 145.
[101] ts 146 to 147.
[102] ts 151.
[103] ts 153.
[104] Ibid.

140. Professor Joyce's opinion was also sought on the question of whether administration of the laxative Movicol in the period before Mr Kell's death may have been beneficial or changed the outcome. It is known that Mr Kell had refused his doses of Movicol in the weeks prior to death. In explaining that giving Mr Kell doses of Movicol in the days before his death would not have changed the outcome, the Professor noted that the post mortem findings were not of constipation. Rather, the contents of Mr Kell's gut were largely fluid (placing him outside the conventional understanding of a patient suffering constipation from clozapine):

> "*As such, Mr Kell, as an individual, would not seem to have any opportunity to draw benefit from a laxative whose purpose was to draw more fluid into the gut. That wasn't the problem in his case. The problem was that his gut was not expelling the fluid.*"[105]

141. It would appear that the sigmoid adhesion located at post mortem examination in Mr Kell's case contributed only because it further impeded transit through an already pathologically impaired colon. It did not cause a complete bowel obstruction. It was also noted that whist the medication administered to Mr Kell to limit the hyper salivation that clozapine causes can increase the adverse effects of gut motility, they were given in low doses only, and did not make an important contribution to the gut disorder.[106]

142. Having considered the evidence regarding the contribution of clozapine, I am satisfied that Mr Kell had a background clozapine-induced hypomotility, which together with a partial obstruction, resulted in him having a high stomach content. When he vomited, for reasons that cannot be known, he was unable to protect his airways.

143. As noted above, at the inquest the North Metropolitan Health Service confirmed that it is not disputed that clozapine is a contributor to Mr Kell's cause of death.[107]

MANNER OF DEATH

144. I am satisfied that Mr Kell's treatment with clozapine contributed to his death. This is not to imply fault. It is not possible to reach a conclusion as to the degree of that contribution. The acute large intestine obstruction had a significant role, that cannot be quantified nor separated from the effects of the clozapine-induced gastrointestinal hypomotility. Also, there will likely have been a sedative effect from the synthetic cannabinoid, that might have impaired Mr Kell's ability to protect his airways when he began to vomit.

145. Regard is to be had to what was known about clozapine in 2015. For the reasons outlined in this finding, it was not generally known in the

[105] ts 148.
[106] Exhibit 1, tab 10.
[107] ts 180.

medical profession that treatment with clozapine could contribute to gastrointestinal hypomotility.

146. A lawful intentional human act, namely the treatment of Mr Kell with clozapine, has unexpectedly contributed to his death.

147. I am satisfied that Mr Kell's death arose by way of misadventure.

QUALITY OF SUPERVISION, TREATMENT AND CARE

Clinicians' evidence

148. At the inquest one of Mr Kell's treating psychiatrists at Graylands Hospital, Consultant Psychiatrist Dr Russell Date (Dr Date), described his chronic paranoid schizophrenia as being extremely severe: "*His illness was recurrent, resistant to treatment, had been associated with prolonged and repeated hospitalisations, difficulties with the law and significant loss of function.*"[108]

149. Dr Date had taken over Mr Kell's care in December 2014. He had never seen Mr Kell during a period when he was not on clozapine. Dr Date opined that clozapine would have been considered a "*gold standard treatment*" for a patient with an illness of Mr Kell's severity. This is a matter that is recognised in studies, including the 22 Year Study referred to earlier in this finding. The superior benefits of clozapine are reported to be well established in terms of mental health outcomes, quality of life and life expectancy.[109]

150. Dr Date had been prescribing clozapine over a period of approximately 20 years, to approximately 20 to 25 patients. He is aware of the range of adverse effects from clozapine, including the common side effect of constipation, that had the potential to be acute and life threatening. To address this risk, Mr Kell had been prescribed a laxative, namely Movicol (one of the recommended treatments), as a way of assisting and hopefully preventing that problem from developing.[110]

151. In his experience, over approximately 20 years of prescribing clozapine, Dr Date had seen one other instance of a patient developing gastrointestinal hypomotility or constipation, some five or ten years prior to the case of Mr Kell.[111]

152. In the weeks prior to his death, medical records reflect that Mr Kell refused his daily dose of the laxative Movicol. It appears Mr Kell commenced refusing it from at least 2 April 2015. Dr Date explained that it would not have been possible to compel Mr Kell to take his Movicol (taken orally), and given his mental state, it was difficult to

[108] ts 8.
[109] Exhibit 2; ts 9.
[110] Exhibit 3; ts 14; ts 28 to 29.
[111] ts 31.

monitor his bowel movements, or obtain an accurate report from him about this matter. The only other realistic course would have been to perform an enema, but this would likely have been even less palatable for Mr Kell.[112]

153. I have had regard to Professor Joyce's opinion and am satisfied that, in light of Mr Kell's bowel content being largely fluids, a laxative (for the purpose of drawing more fluid into the bowel) would not have changed the outcome. The management of Mr Kell's refusal to take Movicol is therefore not a matter that bears upon the events leading to his death.

154. At the inquest, Dr Date was questioned about the clinical observations of Mr Kell up to approximately 9.00 pm on 25 April 2015, and whether anything recorded in his medical notes would have indicated to him that more of an urgent clinical response was needed. Dr Date referred to Mr Kell's history of fluctuating levels of interaction and alertness, such that Mr Kell's demeanour and presentation at that stage was not unexpected. Further, he added that clinical staff had increased their monitoring of him and endeavoured to make him comfortable.[113]

155. Dr Date's views were specifically sought in connection with the Duty Medical Officer being unavailable when Mr Kell's heart rate was found to be 119 beats per minute, and also in connection with the rate afterwards falling to 110 beats per minute. Dr Date noted that for some patients, this might still have required a formal medical review, but it depends on the individual circumstances. Generally, Mr Kell's baseline pulse rate tended to be at the higher levels of the normal range.[114]

156. The Duty Medical Officer Dr Prabha Krishnan informed the court that his role at Graylands Hospital involved being the medical officer in charge of all admissions. On 25 and 26 April 2015, Dr Krishnan was on night shift, from 9.00 pm to the following morning until 9.00 am. In addition to the admissions, his role also comprised attending to all requests and emergencies from the wards as and when required throughout the night.[115]

157. When Dr Krishnan arrived at 8.50 pm on 25 April 2015 for his handover, the day shift doctor informed him that he had previously received a call from the nurse on the Ellis Ward requesting a review of Mr Kell because his pulse was elevated. The day shift doctor had not been able to attend when requested, due to attending to another patient, but provided parameters for calling him immediately if Mr Kell's pulse went into a certain range. The day shift doctor informed Dr Krishnan that Mr Kell's pulse at that stage was in a range that did not require immediate review, and that his pulse rate had subsequently gone down.[116]

[112] ts 15; ts 29 to 30; ts 67.
[113] ts 18.
[114] Ibid.
[115] Exhibit 1, tab 25.
[116] Ibid.

158. The day shift doctor also informed Dr Krishnan that Mr Kell had been seen by the Nurse Manager and that should there be any further issues, the nurse would contact him. Dr Krishnan commenced his shift and carried out his duties at the hospital. The communication from the day shift doctor about Mr Kell upon handover was understood by Dr Krishnan to be to the effect that: "*Everything is okay, and there's nothing to be worried.*"[117]

159. However, at approximately midnight Dr Krishnan was called by the nurse to urgently attend to Mr Kell, and on his way to the Ellis Ward, he received the Code Blue page. Upon arrival he became involved in the resuscitation attempts, pending the arrival of the paramedics, who then took over resuscitation attempts. Tragically Mr Kell remained unresponsive.[118]

160. Mr Kell's rapid decline and sudden death was unexpected by the clinicians, and at the material time, they did not know what had led to his death. It was readily apparent that he had vomited, copiously, and stopped breathing. It was not known why this had occurred.

161. Given the subsequent post mortem observations of Mr Kell's severely distended bowel, the question arose as to whether Mr Kell had experienced pain in the days leading to his death. Dr Date reviewed the medical records and confirmed that he was not aware of any reports of pain, and there was no record of him being offered, prescribed, or having declined painkillers (analgesia) over that period.[119]

162. Dr Date did not consider that Mr Kell's psychosis would have "*masked*" his pain, though if he had consumed a synthetic cannabinoid, it could have had an analgesic effect. When asked to comment upon the appropriate response after nursing staff located Mr Kell in bed, incoherent and having opened his bowels, Dr Date's attention was drawn to the actions of the nurses in taking him to shower instead of taking observations.[120]

163. In Dr Date's assessment, the appropriateness would depend on Mr Kell's state of consciousness at that time, and records reflect that he was conscious, though somewhat drowsy or sedated. Dr Date opined that the Code Blue was called at the appropriate time.[121]

164. At the inquest Dr Krishnan was asked whether clinicians that night had formed the view that Mr Kell's deteriorating condition was in fact related to their suspicion that he had taken illicit drugs. Dr Krishnan did confirm that shortly after Mr Kell's death, a clinician made a comment to the effect that Mr Kell had taken synthetic cannabinoid.[122]

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[117] ts 44 to 45.
[118] Exhibit 1, tab 25; ts 33 to 36.
[119] ts 18 to 19.
[120] Ibid.
[121] ts 20 to 22.
[122] ts 43 to 44.

165. I have considered whether the suspicion that Mr Kell had taken illicit drugs adversely impacted upon his medical treatment earlier that night, and whether his reported incoherence may have been hastily or wrongly attributed to the effect of illicit drugs.

166. It is clear that one or more clinicians held that suspicion, but there is no evidence of it having impacted adversely upon clinical decision making. This is a matter that was raised with the independent expert, within the context of whether there was a clinical need for urgent attendance upon him and is addressed below.

167. Mr Kell's clinicians provided clear and cogent information about the circumstances leading to his death, as observed directly, or by review of his medical notes. Having regard to my obligations under s 25(3) of Coroners Act, it is also appropriate that the opinion of an independent expert be sought.

Independent experts' evidence

168. Mr Kell's supervision, treatment and care was reviewed by the independent expert Consultant Psychiatrist Dr Adam Brett. Dr Brett prepared a report for the coroner and he gave evidence at the inquest. Consistent with the comment made by Mr Kell's treating psychiatrist Dr Date, Dr Brett also referred to clozapine as the "*gold standard*" for persons with treatment resistant schizophrenia.[123]

169. In Dr Brett's experience clozapine is one of the few medications which can stop the hallucinations and delusions associated with schizophrenia. He has seen good evidence to show it can reduce violence associated with psychosis. He has prescribed it frequently.[124]

170. Having reviewed Mr Kell's medical records, Dr Brett opined that clozapine was the only medication that gave him any peace from his symptoms. Dr Brett also noted that there were times when Mr Kell's symptoms became much worse, and they were when he used illicit drugs. On such occasions he would become "*floridly psychotic*", and unfortunately there was a history of him being violent to his caregivers.[125]

171. At the inquest Dr Brett made the following remarks in connection with the quality of Mr Kell's supervision, treatment and care while he was in Graylands Hospital:

> *"My understanding was that his treatment was – was very good. He – he was difficult to manage, but they managed him appropriately. He was having supervised leave. I think there was concern about substance use, but that was – they – they tried to*

[123] ts 70 to 71; Exhibit 1, tab 13.
[124] ts 88.
[125] ts 72.

manage that as best they could. He was being monitored reasonably well. He was being referred to other services to have further investigations. I think he had a neurological appointment. So no. I thought his care was good."[126]

172. Dr Brett's attention was drawn to the hospital's concerns, in the last months of Mr Kell's life, about his potential use of synthetic cannabinoids. Dr Brett confirmed that it is very difficult to manage substance use in hospitals and referred to the principles of the least restrictive care possible, and the desirability of allowing as much access to family and the community as is reasonable.[127]

173. Consistent with Dr Date, Dr Brett's evidence was also to the effect that at the material time, in 2015, the focuses of the risks associated with clozapine treatment were agranulocytosis and myocarditis, for which there were well-established monitoring processes. Dr Brett was aware that as of 2015 constipation was known as a common side effect, but it was not highlighted as a serious side effect. He became aware of the hypomotility issues in the course of writing his report to the coroner.[128]

174. At the inquest, Dr Brett was questioned on the issue of whether there was any record or indication of Mr Kell having expressed pain in the period leading to his death. Consistent with Dr Date, Dr Brett found none, and did not consider there to be anything within Mr Kell's medical records to indicate that he was suffering from an abdominal issue that was not identified by his treating clinicians.[129]

175. Dr Brett was asked for his opinion on Mr Kell's treatment when his elevated pulse rate was identified (119 beats per minute) on the evening of 25 April 2015. Dr Brett was aware that hospital policy required that Mr Kell have a further review, but he also noted that such review was not critical especially if his baseline pulse rate was always quite high.[130]

176. Dr Brett's attention was drawn to the records reflecting that at this time, Mr Kell was also observed to be incoherent to a degree and struggling with his speech. Dr Brett opined that the records reflect that the day shift doctor asked questions that may have been directed towards symptoms associated with myocarditis. He noted further that it appears clinicians suspected Mr Kell to have used illicit substances, and these recorded symptoms could have been consistent with that as well (as opposed to physical issues).[131]

177. In connection with the reported incoherence and struggle with speech, Dr Brett opined that it would be relevant for the clinician to know whether this is the normal presentation for Mr Kell when he has used substances in the past, or whether the presentation was different. If it

[126] ts 72.
[127] ts 73.
[128] ts 74; ts 80.
[129] ts 76.
[130] ts 76.
[131] ts 77.

was different it ought to be assertively managed by physical examination and general observations such as pulse rate and blood pressure.[132]

178. Dr Brett pointed out that the physical symptoms need to be assessed first, and further decisions taken from there. On his review, the handover from the day shift doctor to Doctor Krishnan was appropriate, and having regard to the fact that Mr Kell's pulse rate had stabilised to normal levels shortly before handover, there was no clinical need for urgent attendance upon him at that stage.[133]

179. At the inquest Dr Brett was asked to comment on the appropriate clinical response when, at approximately 11.20 pm, Mr Kell was found by the nurses to have vomited and been incontinent of a faeces, confused and incoherent. In Dr Brett's view this should result in the on-call doctor being called to assess Mr Kell.[134]

180. Dr Brett's attention was drawn to the events of that night, where the nurses first endeavoured to assist Mr Kell to shower and clean up, and then assisted him to the toilet, following which he became less responsive, and was then moved to the floor, with a Code Blue being called. The issue was whether a doctor should have been called sooner.[135]

181. Dr Brett agreed that in retrospect it might have been better to call the doctor earlier, though he did not consider that it can be shown it would have changed the outcome. Having reviewed the clinical decision making of the nurses at the time, he did not have any concerns about the way they dealt with it.[136]

182. At the inquest Dr Brett explained that his comments about calling a doctor earlier were made having regard to hindsight. At the material time, there was a suspicion that Mr Kell had used illicit drugs and Dr Brett's evidence was that it was reasonable for the nurses to consider that to be the explanation for his symptoms of vomiting and defecating, in part. It is now clear that illicit drugs were not the cause of Mr Kell's vomiting and defecating.[137]

183. Dr Brett opined that, as Mr Kell was being attended to, he appears to have become a lot worse very quickly. He commented upon the nurses' approach to Mr Kell's clinical care as follows:

> "*I expect their first priority was to clean him up and retain his dignity and then they were trying to get obs[ervations] at the same time so they may not have understood the severity of the situation which is understandable. So, yes, I think it's always easier to be wise in hindsight and I expect at the time there was a lot of things going on.*

[132] ts 78 to 79.
[133] ts 79.
[134] ts 79.
[135] ts 79 to 80.
[136] ts 80.
[137] ts 90 to 91.

He wouldn't have been the only client on the ward. It would have been very difficult to escalate it at that time."[138]

184. Dr Brett added that as at the material time, he was not aware of this risk with clozapine, and that now if there is a patient on clozapine who is vomiting it would ring alarm bells. This is because now there is a lot more understanding of clozapine-induced gastrointestinal hypomotility. Dr Brett's expectation is that under the same scenario now, the nurses would be more likely to call the doctors earlier.[139]

185. At the inquest Dr Samir Heble, consultant psychiatrist and A/Head of Clinical Services at Graylands Hospital, consistent with Dr Brett, also noted that as at 2015, psychiatrists had a very low index of suspicion of hypomotility and the symptoms. The understanding has developed since 2015.[140]

186. Dr Heble's evidence, also consistent with Dr Brett, was that in his experience, the use of illicit drugs can also result in symptoms that include vomiting and defecation. He also noted that incoherent speech was part of Mr Kell's psychiatric illness, and that he was already known to have tachycardia.[141]

187. At the inquest, independent expert and specialist general and colorectal surgeon Dr Levitt had regard to Mr Kell's presentation on the night of 25 April 2015, as reflected in the clinical notes, including his drowsiness and subsequent unrousability. His evidence was that this would not have indicated a gastrointestinal problem. As outlined above, he considered Mr Kell's vomiting and diarrhoea to be agonal events.[142]

Conclusions regarding quality of supervision, treatment and care

188. I have taken account of the evidence of Mr Kell's treating psychiatrist Dr Date, and the evidence of the independent expert reviewing the medical treatment, Dr Brett, in addition to all of the evidence of the circumstances leading to Mr Kell's death. I have had regard to Mr Kell's status as an involuntary patient for a significant period of time, and the final extension of Mr Kell's involuntary patient order for a further three months from 27 March 2015. I have considered the decisions made in respect of grant and subsequent withdrawal of escorted ground access.

189. I am satisfied that Mr Kell's supervision, treatment and care was appropriate to his needs, and that reasonable efforts were made to balance the need for his detention under the Mental Health Act for his safety and the importance of fostering interaction with his family and the community.

[138] ts 89.
[139] ts 91.
[140] ts 98 and 99.
[141] ts 106 to 107.
[142] ts 131 to 132.

190. I have had regard to what was known about the effects of clozapine as at 2015, and in particular the primary focus upon the serious haematological and cardiovascular adverse effects. I have taken account of Mr Kell's long term diagnosis of treatment resistant schizophrenia, and the benefits to be gained from treating this condition with clozapine, in accordance with the prescribing guidelines. I am satisfied that Mr Kell's overall medical treatment was of a proper standard, and directed towards his needs.

191. Mr Kell's deterioration immediately before death was sudden and unexpected. A Code Blue was called within a suitable time frame. Clinical staff responded immediately and appropriately and paramedics were called but unfortunately Mr Kell was unable to be revived.

IMPROVEMENTS

192. At the inquest I was assisted by evidence related to the available guidelines in connection with the prescribing of clozapine, in order for me to consider the improvements in those guidelines that have taken place since Mr Kell's death, and to assess the desirability of making recommendations for further improvements.

Updates to Maudsley Guidelines

193. Dr Date informed the court that in 2015 the Graylands Hospital practices were influenced by the *Maudsley Prescribing Guidelines in Psychiatry* (Maudsley Guidelines). This is a useful evidence based clinical guideline commonly used at mental health services in Western Australia.[143]

194. In 2015 the 11th edition of the Maudsley Guidelines had a brief mention of clozapine-induced constipation and it was listed under common side effects. There was a separate section relating to its serious haematological and cardiovascular adverse effects.[144]

195. At the inquest, attention was drawn to the Maudsley Guidelines, that have now been updated to incorporate a comprehensive section on clozapine-induced gastrointestinal hypomotility. The updated advice in the Maudsley Guidelines includes information on the level of risk and incidence of fatality, including information on prevention and management of the condition, stating: "*There have been case reports of fatalities occurring only hours after first symptoms present, and this emphasises the urgency for prompt assessment and management.*"[145]

[143] Exhibit 3; ts 22 to 23.
[144] Exhibit 3.
[145] ts 53 to 59; ts 61 to 62; Exhibit 3.

Updates to NMHS Clozapine Prescribing Policy

196. Ms Courtney, senior pharmacist with the North Metropolitan Health Service whose evidence is referred to above, reported that at the time of Mr Kell's death in 2015, the *North Metropolitan Health Service Clozapine Prescribing Guidelines* had no mention of constipation. They did include suggested monitoring for other serious adverse effects including myocarditis and mandatory monitoring for agranulocytosis.[146]

197. Ms Courtney confirmed that in 2015 whilst it was known that clozapine could commonly cause constipation and that in very rare circumstances it could be fatal, this was not highlighted in the Clopine Approved Product Information provided by the manufacturer. The prescribing information at that time stated:

> *"Probably on account of its anticholinergic properties, clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus. On rare occasions these cases have been fatal."*[147]

198. Following Mr Kell's tragic death, and having become aware of the circumstances, Ms Courtney conducted an extensive literature search for evidence based recommendations on the monitoring and management of clozapine-induced constipation. Upon her recommendations, the *North Metropolitan Health Service – Mental Health Clozapine Prescribing Policy* (NMHS Clozapine Prescribing Policy) was updated in March 2016, requiring that patients be monitored for clozapine-induced gastrointestinal hypomotility.[148]

199. The NMHS Clozapine Prescribing Policy now cautions that clozapine is a high risk medication, with the significant risks being:

a) agranulocytosis (lowered white blood cell count);

b) myocarditis (inflammation of the heart muscle); and

c) relevantly to this inquest, gastrointestinal hypomotility (which was not referred to in the previous policy).

200. The NMHS Clozapine Prescribing Policy continues to give guidance as to when a patient is to be taken as being non-responsive to or intolerant of other antipsychotics, requiring amongst other things the demonstration of a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic medications prescribed for at least 12 weeks total. This is similar to the previous policy and reinforces the high risk nature of the medication.[149]

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[146] Ibid.
[147] Ibid.
[148] Exhibit 3; ts 50 to 52.
[149] Ibid.

201. Importantly, the NMHS Clozapine Prescribing Policy now makes specific reference to monitoring for clozapine-induced gastrointestinal hypomotility and states as follows:

> "*Weekly stool charts should be used as a minimum for the first 18 weeks, then four weekly thereafter, for the duration of the clozapine treatment. Assertive treatment of any emerging constipation is necessary including a review of other medication that may be contributing. Signs and symptoms that warrant immediate medical attention include moderate to severe abdominal pain, distension, vomiting, overlfow diarrhoea and symptoms of sepsis.*"[150]

202. Following endorsement, this updated NMHS Clozapine Prescribing Policy was made available on the WA Health Policy Hub and on the Statewide Formulary. It is important to bear in mind that practitioners who are prescribing clozapine must be registered with the Clozapine Centre, with the aim of ensuring that they adhere to the prescribing and monitoring requirements.[151]

203. Ms Courtney outlined the increased focus and awareness of clozapine-induced gastrointestinal hypomotility throughout the Department of Health, including the Clozapine Constipation Awareness Campaign presented to all hospital inpatient wards across North Metropolitan Health Service (Mental Health) and Clozapine Nurses in Community Clinics.[152]

204. Steps have also been taken by the Department to educate and involve dieticians, physiotherapists and pharmacists, to assist with establishing baseline bowel habits prior to commencing patients on clozapine, and to recognise the difficulty some patients have in disclosing that they are constipated, or having an awareness that they are constipated. Bowel Elimination Charts are now recommended for all patients prescribed clozapine, and there are minimum requirements for clinicians to ask patients about symptoms of constipation.[153]

205. At the inquest Dr Date confirmed that after Mr Kell's death, he and his colleagues reviewed the way in which patients who took clozapine were monitored. Consistent with the updated NMHS Clozapine Prescribing Policy, on the ward where he works, all patients on clozapine have bowel charts which are ongoing (not just for the earlier stages of the treatment). Ms Courtney explained the process whereby this monitoring system was developed, as it is understood that patients often do not report being constipated, or do not know they are constipated. Similar procedures were also described by Dr Krishnan, and supported by independent expert Dr Brett.[154]

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[150] Ibid.
[151] Ibid.
[152] Ibid.
[153] Ibid.
[154] ts 23 to 24.; ts 40 to 41; ts 56 to 57; ts 81.

206. Most of the patients on the ward where Dr Date works have been on clozapine for longer than 18 months. He is not aware of issues having arisen since with potential hypomotility, and he noted this is said within the context of patients being charted in relation to regular laxatives, ensuring that they are agreeable, and highlighting the importance of good bowel health.[155]

207. I have considered some of the comments made at the inquest about pre-emptively prescribing laxatives to patients on clozapine. There is a difference between constipation (which may be treated with laxatives), and clozapine-induced gastrointestinal hypomotility (which might not always respond to laxatives).

208. This is a matter that has since been considered by the Patient Safety and Clinical Quality Directorate of the Department of Health, within the context of their review of suggested amendments to the psychotropic section of the *Guidelines for Managing Specific High Risk Medications Relevant to the Organization*, and is addressed within the context of *Recommendation 1*, below.[156]

209. By reason of the improvements referred to in this section, namely the updating of the NMHS Clozapine Prescribing Policy to warn of the risk of clozapine-induced gastrointestinal hypomotility, it is unnecessary for me to make a recommendation to address these factors specifically in the context of the North Metropolitan Health Service.

210. However, upon review of the relevant State-wide guidelines and policy, and for the reasons set out in the below section entitled "*Recommendations*" I have determined to make recommendations in pursuance of the objective of notifying of the risk of clozapine-induced gastrointestinal hypomotility and the importance of gastrointestinal monitoring, at the State-wide level.

RECOMMENDATIONS

211. At the inquest Ms Courtney confirmed that through her inquiries regarding clozapine, she ascertained that mortality associated with constipation was greater than that due to agranulocytosis. She opined that this was probably due to the risk of agranulocytosis being mitigated as a result of the existing monitoring system. It was of concern to her that a patient is more likely to die from complications arising from constipation, and yet at the material time there was no monitoring regime in place for constipation, nor any guidance on this risk through policies.[157]

212. The following recommendations are made with the aim of avoiding future deaths in similar circumstances.

[155] ts 23 to 24.
[156] ts 64 to 65; Exhibit 11.2.
[157] ts 52 to 53; ts 60.

Updating WA Guides and Policies

213. At the inquest, the court was informed that in 2017 the Department of Health issued the *WA Health Guidelines for Safe and Quality Use of Clozapine in the WA Health System* (WA Guidelines on Clozapine), and this medication is also subject to the Department of Health's *WA High Risk Medication Policy* (WA High Risk Medication Policy), from the Office of Patient Safety and Clinical Quality.[158]

214. Dr Heble, whose evidence is referred to previously, was supportive of updating of the WA Guidelines on Clozapine, so that attention is drawn to the risk of clozapine-induced gastrointestinal hypomotility. In connection with the WA Guidelines on Clozapine, Dr Heble stated:

> "*Having heard everything [t]hat we have listened to today I think it will be reasonable to expect that there will be a separate section specifically dedicated to clozapine induced gastrointestinal hypomotility with separate specific recommendations because it's more risk than the agranulocytosis so we need to give more attention than the other risk factors.*"[159]

215. Dr Heble was asked about the desirability of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) issuing a position statement in relation to clozapine-induced gastrointestinal hypomotility, given it has not been widely known. He was supportive, though noted the need for consultation.[160]

216. After the inquest through counsel assisting, the RANZCP was consulted, and they suggested the court works with the Chief Psychiatrist for the development of a clinical practice guideline.[161]

217. Counsel assisting the coroner consulted with the A/Chief Psychiatrist who through the manager referred to the WA Guidelines on Clozapine having been developed with input from the Chief Psychiatrist, and expressed the view that, given their comprehensives, there is no further need for input.[162]

218. Ms Courtney, whose evidence is referred to previously, had reported to the coroner that the WA Guidelines on Clozapine and the WA High Risk Medication Policy are to be updated as part of a scheduled review. I am greatly assisted by her evidence in my consideration of factors impacting upon the safe use of clozapine.

219. Counsel for the Department of Health informs the court that the department supports a recommendation concerning the updating of the WA Guidelines on Clozapine, so that they include a reference to

[158] Exhibit 3; ts 50 to 52.
[159] ts 100 to 101.
[160] ts 101 to 102.
[161] Exhibit 9.
[162] Exhibit 8.

clozapine-induced gastrointestinal hypomotility, and a reference to gastrointestinal monitoring.

220. I am assisted by the provision by the Department of Health through its counsel as part of their submissions, of the draft High Risk Medication Policy, and the draft Guidelines for Managing Specific High Risk Medications Relevant to the Organisation.[163]

221. I have noted the following amendments incorporated into the draft Guidelines for Managing Specific High Risk Medications Relevant to the Organisation:

a) "*A serious and under-recognised effect is clozapine induced gastrointestinal hypomotility (CIGH). This can range from mild constipation to fatal bowel obstruction and/or ischemia and fatalities reported are higher than those related to agranulocytosis*;"

b) "*Stool charts and the Rome III criteria for diagnosing functional constipation should be used for monitoring patients when performing routine full blood counts as a minimum. Laxatives should be considered pre-emptively for all patients prescribed clozapine, unless contraindicated, and extra vigilance is required when other medications that cause constipation are prescribed.*"[164]

222. Consideration ought to be given to introducing this guidance into the general WA Health Guidelines for Safe and Quality Use of Clozapine in the WA Health System, and I therefore recommend as follows:

Recommendation 1

I recommend that Department of Health amend its guidelines for the Safe and Quality Use of Clozapine Therapy in the Western Australian Health System to include reference to clozapine-induced gastrointestinal hypomotility as a serious side effect to the use of clozapine and recommend gastrointestinal monitoring in accordance with the draft "Guidelines for Managing Specific High Risk Medications Relevant to the Organisation".

Updating the Prescribing Information

223. At the inquest, Ms Courtney drew attention to the prescribing information for clozapine, that does not refer to the risk of clozapine-induced gastrointestinal hypomotility in its prominent "*boxed warning*" section at the beginning of the document.[165]

224. Clozapine is marketed in Australia under the brand name Clopine (by Pfizer Australia) and Clozaril (by Mylan Australia). Ms Courtney

[163] Exhibits 11.1 and 11.2.
[164] Exhibit 11.2.
[165] Exhibit 3; ts 59.

addressed the importance of a boxed warning on the prescribing information provided by Pfizer Pty Ltd, the manufacturer of clozapine, that is accessed by clinicians through *MIMS Online* (MIMS Full Prescribing Information), updated as at 1 May 2019. Ms Courtney noted that there is a prominent boxed warning that outlines the risks of myocarditis and cardiomyopathy reported in patients on clozapine. However, there is no reference to clozapine-induced gastrointestinal hypomotility in a prominent boxed warning.[166]

225. On the fifth page of the MIMS Full Prescribing Information, under the heading "*Anticholinergic effects*" it is noted that clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, megacolon and intestinal infarction/ischaemia. It is stated that on rare occasions these cases have been fatal, and that patients should be questioned about bowel habits and monitored for constipation.[167]

226. However, Ms Courtney opined that the MIMS Full Prescribing Information should also include a prominent boxed warning for clozapine-induced gastrointestinal hypomotility, to highlight it as a serious warning for prescribers, nurses and pharmacists who refer to the material. At the inquest, Dr Date and Dr Brett also supported this approach.[168]

227. After the inquest through counsel assisting, the manufacturers Pfizer Australia and Myaln Australia were afforded an opportunity to comment upon a potential recommendation to the effect that consideration be given to amending the manufacturer's product information for Clopine and Clozaril, respectively, to include a boxed warning with regard to clozapine-induced gastrointestinal hypomotility.

228. I am assisted by a response from Pfizer Australia to the effect that the Clopine (clozapine) product information was updated in 2018 in consultation with the Therapeutic Goods Administration (TGA), to include the section regarding "*Anticholinergic effects*" referred to above. I am informed that Pfizer Australia considers the Clopine product information, approved by the TGA on 14 March 2019 to contain all relevant information regarding risks and benefits of clozapine, including sufficient information regarding gastrointestinal hypomotility.[169]

229. I have carefully considered the response, however note that there is no highlighted boxed reference to clozapine-induced gastrointestinal hypomotility in the product information of Pfizer Australia or Mylan Australia, and as noted above, the information concerning the anticholinergic effects appears on the fifth page of the MIMS Full Prescribing Information for Clopine. On balance I am persuaded by the

[166] ts 59; Exhibit 3.
[167] Ibid.
[168] ts 24 to 25; ts 84.
[169] Exhibit 10.

evidence in support of the boxed warning, to highlight the risk, and therefore recommend as follows:

Recommendation 2

I recommend that Pfizer Australia and Mylan Australia, in consultation with the Therapeutic Goods Administration, consider highlighting the risk of clozapine-induced gastrointestinal hypomotility in the boxed warning that appears at the beginning of their Product Information, and that if so altered, that it appears in the MIMS Full Prescribing Information and the Consumer Medicine Information.

CONCLUSION

230. Mr Kell had suffered from chronic treatment resistant schizophrenia for many years, and for a significant portion of his adult life, he had been detained as an involuntary patient under the Mental Health Act. This detention was necessary for his safety. It allowed for an environment where he could be treated appropriately for his ongoing psychotic symptoms. The only medication that provided him with some relief from the severity of his symptoms was clozapine.

231. Mr Kell was treated with clozapine in accordance with the prescribing guidelines and policies that applied at the material time, and his medical treatment was appropriate to his needs.

232. Unfortunately at the time Mr Kell was being treated, it was not generally known that one of the significant and potentially fatal side effects of this medication is clozapine-induced gastrointestinal hypomotility. This has been an evolving area of medicine.

233. Mr Kell died from the complications of an acute large intestine obstruction, and the clozapine contributed to his death, by reason of the intestinal hypomotility. His deterioration at Graylands Hospital in the early hours of 26 April 2015 was sudden and unexpected.

234. Mr Kell's father supported him, he stood by his beloved son and that support was undoubtedly a great comfort to him. It is hoped that with the increased awareness of clozapine-induced gastrointestinal hypomotility, gastrointestinal monitoring will be highlighted, to mitigate the risk of this serious side effect.

R V C FOGLIANI
State Coroner

6 August 2020