QUEENSLAND COURTS

CORONERS COURT OF QUEENSLAND

FINDINGS OF INQUEST

CITATION:	**Inquest into the death of Janis Ellen Doherty**
TITLE OF COURT:	Coroners Court
JURISDICTION:	BRISBANE
FILE NO(s):	2020/2039
DELIVERED ON:	8 October 2025
DELIVERED AT:	BRISBANE
HEARING DATE(s):	8 – 11 April 2024, and 15 - 16 April 2024.
FINDINGS OF:	Stephanie Gallagher, Deputy State Coroner
CATCHWORDS:	Coroners: inquest, health care related death, sodium valproate, prescribed, “off label”, drug induced liver injury.
REPRESENTATION:	
Counsel Assisting:	DJ Schneidewin with Ms C McKeon,
Doherty family:	Mr N Turner instructed by Clutch Legal
Dr Walsh:	Mr C Templeton instructed by Moray & Agnew

Metro North Hospital	Ms S Robb KC: instructed by Metro North Hospital and Health Service and Doctors Borthwick, Rafiei, Skoien and Gonsalkolara:

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Introduction

1. Janis Ellen Doherty (**Mrs Doherty**) was born on 29 September 1962.

2. Mrs Doherty died at the Royal Brisbane and Women's Hospital (**RBWH**) on 16 May 2020.

Coronial jurisdiction

3. At the time of her passing, Mrs Doherty was a patient at the RBWH.

4. I consider that Mrs Doherty's death was a health care related death as defined by the *Coroners Act 2003* (**the Act**). Mrs Doherty's death was thereby a reportable death under s.8(3)(d) of the Act.

5. Pursuant to s.28(1) the Act of the, I was satisfied that it was in the public interest to hold and inquest into Mrs Doherty's death.

6. An inquest is intended to provide the public and the family of the deceased, with transparency regarding the circumstances of the death, and to answer any questions which may have been raised following the death.

7. The role of the Coroner is to independently investigate reportable deaths to establish, if possible, the identity of the deceased, the medical cause of death, and the circumstances surrounding the death, i.e. how the person died. Those circumstances are limited to events which are sufficiently connected to the death. The purpose of a coronial investigation is to establish the facts, not to cast blame or determine criminal or civil liability. Those are matters for other courts.

8. The relevant standard of proof is that of the balance of probabilities, with reference to the *Briginshaw*[1] standard. Accordingly, the more significant the issue for determination, the clearer and more persuasive the evidence must be for the Coroner to be sufficiently satisfied on the balance of probabilities that the issue has been proven:

> *But reasonable satisfaction is not a state of mind that is attained or established independently of the nature and consequence of the fact or facts to be proved. The seriousness of an allegation made, the inherent unlikelihood of an occurrence of a given description, or the gravity of the consequences flowing from a particular finding are considerations which must affect the answer…In such matters 'reasonable satisfaction' should not be produced by inexact proofs, indefinite testimony, or indirect inferences.*[2]

[1] *Briginshaw v Briginshaw* (138) 60 CLR 336
[2] *Brigance v Briginshaw* (138) 60 CLR 336, 362 – 363 (Dixon J)

9. In adjudicating the significance of the evidence, the impact of hindsight bias and affected bias must also be considered.[3] As outlined in 'The Australasian Coroners Manual':

> *Hindsight bias is the tendency after the event to assume that events are more predictable or foreseeable than they really were. What is clear in hindsight is rarely as clear before the fact…It is an obvious point, but one that nonetheless bears repeating, particularly when coroners are considering assigning blame or making adverse comments that may damage a person's reputation. … Coroners should attempt first to understand the circumstances as they appeared at the relevant time to the people who were there. … Hindsight, of course, is a very useful tool for learning lessons from an unfortunate event. It is not useful for understanding how the involved people comprehended the situation as it developed. This distinction needs to be understood and rigorously applied.*[4]

Coronial investigation

10. The coronial investigation revealed the following factual circumstances.

11. Mrs Doherty had a past medical history of:

    (a) Smoking 20 cigarettes daily;

    (b) Consuming about 6 standard drinks per week;

    (c) Obesity with a body mass index (**BMI**) of 31.1 kg/m2 (normal range 20 - 25 kg/m2);

    (d) Hashimoto's disease;

    (e) Depression;

    (f) Dyslipidaemia;

    (g) Cholecystectomy;

    (h) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, known as **CADASIL** syndrome; and

    (i) Migraine.

12. In April 2019, Mrs Doherty underwent pathology testing which revealed that her liver function tests (**LFTs**) were normal.

[3] Findings of the inquest into the death of Pasquale Roasario Giorgio, [140] – [142]
[4] Hugh Dillon and Marie Hadley, The Australasian Coroner's Manual (The Federation Press, 2015) 10

13. On 31 July 2019, Mrs Doherty was referred by her general practitioner, Dr Parvin Delshad (**Dr Delshad**), to neurologist, Dr Michael Walsh (**Dr Walsh**), for management of migraine in context of her known CADASIL.

14. Mrs Doherty consulted Dr Walsh on 1 November 2019.

15. Dr Walsh commenced Mrs Doherty on Epilim (sodium valproate) 200mg to treat her migraine and it was planned to increase the daily dose after two weeks to 400 mg daily (at night). The prescription was "off-label". Dr Walsh organised to perform LFTs pathology testing at two and four weeks following Mrs Doherty's commencement of the Epilim.

16. On 19 November 2019 (not at 2 weeks or 4 weeks as planned), Mrs Doherty undertook the pathology tests ordered by Dr Walsh. Her LFTs were normal. Mrs Doherty's full blood count and serum biochemistry were also normal.

17. Subsequently there was an email exchange between Mrs Doherty and Dr Walsh's practice staff which culminated in communication to Mrs Doherty that no further blood tests (LFTs) were required.

18. An MRI scan, which Mrs Doherty underwent on 21 November 2019 was reported as showing diffuse bilateral cerebral and cerebellar and pontine leukoencephalopathy, with small left basal ganglia lacuna infarcts in keeping with the known CADASIL.

19. On 9 December 2019, Mrs Doherty was seen by another neurologist, Dr Peter Patrikios, following referral from another general practitioner, Dr Sai Gayatri. There was some improvement in her headaches and a change in the sodium valproate dose was recommended, from 400 mg at night to 200 mg twice daily.

20. On 7 January 2020, Mrs Doherty was seen by Dr Delshad, who did not order any further LFTs.

21. On 18 February 2020, Mrs Doherty was seen by Dr Walsh. She reported ongoing headaches. Dr Walsh recommended the addition of candesartan to treat the headaches. General management of cardiovascular risk factors including smoking cessation were also discussed. Dr Walsh did not order any further LFTs.

22. The following day, on 19 February 2020, Mrs Doherty saw Dr Delshad but could not recall the name of the new medication to be commenced (candesartan).

23. On 9 April 2020, Mrs Doherty consulted Dr Delshad by telehealth and reported 2 weeks of nausea, abdominal pain, anorexia, dark coloured urine and constipation. Dr Delshad subsequently consulted Mrs Doherty in person and arranged pathology testing.

24. On 10 April 2020, Dr Delshad was notified by Sullivan Nicolaides Pathology that Mrs Doherty's liver enzymes were very high, being well in excess of the reference range on most of the relevant markers.

25. Dr Delshad contacted Mrs Doherty and advised her to attend hospital urgently.

26. Later, on 10 April 2020, Mrs Doherty was admitted to Caboolture Hospital under the general medical team.

27. Mrs Doherty was subsequently transferred and admitted to the RBWH on 20 April 2020.

28. On 15 May 2020, Mrs Doherty was transferred to ICU at RBWH with multi-organ dysfunction.

29. On 16 May 2020, Mrs Doherty was declared deceased. She was aged 57 years.

30. A more detailed summary of the facts will be outlined below where relevant.

Death Certificate

31. At autopsy performed on 1 June 2020, the cause of death found by Forensic Pathologist, Dr Beng Ong (**Dr Ong**), was:[5]

> "1(a) Multi-organ failure due to, or as a consequence of
> 1(b) Drug induced liver injury (sodium valproate)."

Inquest

32. Pre-Inquest Conferences was held on 28 November 2023 and 20 December 2023.

33. The Inquest commenced on 8 April 2024 and continued for a period of 6 hearing days, ending on 16 April 2024. The Brief of Evidence (**BOE**) was formally tendered at the start of the Inquest.

Issues for Inquest

34. On 4 April 2024, the List of Issues for the Inquest was revised as follows:[6]

> "1. The findings required by s45(2) *Coroners Act 2003;* namely the identity of the Mrs Doherty (deceased), when, where and how she died and what caused her death.
>
> 2. Whether the treatment and management of the deceased provided by Dr Michael Walsh, Neurologist, was appropriate, including:

[5] Ex A1 BOE
[6] Previous Issues 2A, 3A and 5(b) were removed from the List of Issues prior to the commencement of the Inquest.

a) Whether it was appropriate to prescribe sodium valproate for the symptomatic management of migraines suffered by the deceased in the context of her known CADASIL; and

b) The appropriateness of his education and monitoring of the deceased for the signs and symptoms of the side effects of sodium valproate, including liver dysfunction;

3. Whether the treatment and management of the deceased provided by Dr Parvin Delshad, General Practitioner, was appropriate;

4. Whether the treatment and management of the deceased provided at the Caboolture Hospital in the period 10 April 2020 to 20 April 2020 was appropriate, including:

a) The appropriateness of the timing of the decision to cease sodium valproate on 14 April 2020;[7]

b) Whether L-carnitine should have been administered to the deceased?

c) Whether a liver biopsy should have been performed and, if so, when?

d) Whether the deceased should have been seen by a Hepatologist at a time earlier than she was?

e) Whether the deceased should have been transferred to the Royal Brisbane and Women's Hospital at a time earlier than she was?

5. Whether the treatment and management of the deceased provided at the Royal Brisbane and Women's Hospital on and after 20 April 2020 was appropriate, including:

a) Whether it was appropriate to recommence the deceased on sodium valproate in the period 27 April 2020 to 3 May 2020?

b) The appropriateness of the timing of the liver biopsy performed on 30 April 2020;

c) Whether L-carnitine should have been administered to the deceased?

6. Whether any aspect of the treatment and management provided to the deceased from 1 November 2019 caused or hastened her death?

[7] This should refer to 17 April 2020

7. Whether any failure to provide treatment and management to the deceased from 1 November 2019 caused or hastened her death?"

35. On Day 5 of the Inquest, I observed that there was no evidence before the Court to suggest Dr Delshad's treatment and management of Mrs Doherty was not appropriate.[8] On that basis, Mrs Doherty's Next of Kin (**NOK**) agreed that Issue 3 from the List of Issues could be deleted.[9] No other party objected to that course and Dr Delshad's legal representatives were excused.

36. On Day 6 of the Inquest, I queried whether it was necessary to proceed with Issue 2(a) in light of the evidence then before the Court.[10] Counsel for the NOK indicated that the NOK might take a similar position in respect of Issue 2(b)[11] and that, in any event, he would be in a position to notify the Court of the NOK's position in respect of each issue shortly following the Inquest.[12]

37. On 22 April 2024, the solicitor for the NOK notified Counsel Assisting as follows:

> "*We note that at the conclusion of the hearing of evidence, the Coroner directed that the family indicate whether they wish for issues 2(a) and 2(b), relating to Dr. Walsh, to remain as issues for the Coroner to consider.*
>
> *We are instructed that the family agree that the issue 2(a) namely the appropriateness of the decision to prescribe Epilim, can be removed as an issue for consideration.*
>
> *However, in respect of issue 2(b) namely the care and management of Ms. Doherty by Dr. Walsh including monitoring, it is the family's wish that the issue remains for consideration by the Coroner."*

38. Consequently, there was no requirement for any party to make any submissions in relation to Issues 2(a) and 3.

39. Counsel Assisting did not make submissions in respect of Issues 4(b) and 4(c).

Witnesses called

40. In addition to the evidence contained in the BOE, the following witnesses provided oral evidence at the Inquest:

    (a) Dr Walsh;[13]

    (b) Dr Iain Borthwick;[14]

[8] T5-46; LL 31-34
[9] T5-46; LL 26-29
[10] T6-29; LL 5 - 10
[11] T6- 29; LL3-4
[12] T6- 29; LL18 - 20
[13] Ex C4.1 BOE; T1-10 – T1-41
[14] Ex C7.1 BOE, T2-5 – T2-19

(c) Dr Nastaran Rafiei;[15]

(d) Dr Enoka Gonsalkorala;[16]

(e) Dr Richard Skoien;[17]

(f) Dr Delshad;[18]

(g) Dr Siddarth Sethi (expert witness);[19]

(h) Associate Professor David Anderson (expert witness);[20]

(i) Associate Professor Avik Majumdar (expert witness);[21]

(j) Dr Daniel McLaughlin (expert witness);[22]

(k) Dr Kee Meng Tan (expert witness).[23]

Submissions

41. In addition to Counsel Assisting's written submissions, written submissions by the following have been received and considered by me in preparing these findings:

    (a) Mr Turner for the Doherty Family;

    (b) Ms Robb KC for Metro North Hospital and Health Service, Dr Borthwick, Dr Rafiei, Dr Gonsalkorala and Dr Skoien; and

    (c) Mr Templeton for Dr Michael Walsh.

Evidence and findings on issues

The aetiology of Mrs Doherty's drug induced liver injury

42. It is convenient to deal with this issue at the outset as the likely cause, mechanism and timing of Mrs Doherty's drug induced liver injury (**DILI**) informs a number of the issues considered at the Inquest.

<u>The likely cause of Mrs Doherty's DILI</u>

43. Mrs Doherty's liver was biopsied at the RBWH on 30 April 2020.

[15] Ex C7.4 BOE; T2-19 – T2-39
[16] Ex C2.7 BOE; T2-41 – T2-66
[17] Ex C2.15 BOE, T3-3 – T3-52
[18] Ex C3.1 BOE; T4-4 – T4-29
[19] Ex D3 BOE; T4-30 – T4-60
[20] Ex D5 BOE; T5-3 – T5-15
[21] Ex D6 BOE; T5-16 – T5-46
[22] Ex D7 BOE; T5-48 – T5-55
[23] Ex D1 BOE; T6-3 – T6-28

44. The initial histopathology report dated 1 May 2020 prepared by Dr Brown found:[24]

> *The major process appears to be a hepatitis as evidenced by the prominent lobular apoptosis. Inflammation is relatively mild and I wonder if this is related to either resolution of the hepatitis or to some treatment that has been applied. The bile ductular proliferation is more than normally seen; however this may be the result of a previously more severe hepatitis.*
> *The possible causes for this appearance included autoimmune hepatitis (plasma cells are absent and the inflammatory infiltrate is not marked as normal), a medication, including over-the-counter medications or herbal remedies and a viral infection.*

45. That is, as at 1 May 2020, the histopathology results, as reported, were not definitive for DILI in Mrs Doherty, incluing DILI caused by sodium valproate.

46. On 6 May 2020, the histopathology was further reviewed by Professor Andrew Clouston (**Prof. Clouston**), an histopathologist with greater expertise in liver biopsies, who provided a supplementary report, by which he found:[25]

> *The pattern fits best with an acute drug-induced liver injury. The absence of plasma cells and relative paucity of inflammatory cells at the interface argue against a diagnosis of autoimmune hepatitis. Discussion of the drug history would favour valproate as the most likely cause – the periportal ductular reaction is consistent with an older injury weeks ago, but the prominent apoptosis seen in the biopsy fits with re-introduction of the drug just before the biopsy was taken. Valproate can cause either a microvesicular steatosis pattern or more conventional hepatitis. The latter is present in this case.*
>
> *Summary*
> *Liver biopsy: Severe acute hepatitis with features favouring drug-induced liver injury (favour valproate as cause).*
>
> (underlining added)

47. Prof. Clouston's findings were also not definitive but by 6 May 2020 it seems that it was considered that Mrs Doherty's liver failure was most likely caused by sodium valproate.

48. At autopsy, Dr Ong concluded:[26]

> *The medical records indicated that she was in liver failure with encephalopathy and kidney failure. Biopsy of the liver tissue showed hepatitis favouring sodium valproate as the agent causing the injury. She developed multi-organ failure and eventually succumbed to the*

[24] Ex B1.3, page 692 BOE
[25] Ex B1.3, page 692 BOE
[26] Ex A1, page 6 BOE

effects of liver failure. ….CADASIL syndrome is considered to be a contributory condition to effect of treatment (sodium valproate) and likely increase vulnerability to hepatic encephalopathy.

49. Dr Kee Meng Tan (**Dr Tan**), a neurologist, opined:[27]

> *I agree that the cause of Mrs Doherty's liver failure was valproate-induced hepatotoxicity, with a delayed onset from commencement of the medication, almost 5 months.*

50. Associate Professor Avik Majumdar (**A/Prof. Majumdar**), a specialist liver transplant physician, opined:[28]

> *The deceased had been appropriately managed at initial presentation to Caboolture hospital on 10th April 2020. The condition of the deceased was undifferentiated and indeed atypical for Valproate (Epilim) induced liver injury, as the high transaminases at presentation (AST and ALT liver enzymes in over 2000) are usually not a feature and similarly the time course is usually within 3 months of commencement of the drug, although can occur up to 6 months. ….The clinical situation on 14 April 2020 was still undifferentiated in terms of the cause of liver injury. As aforementioned, the presentation was not typical for Valproate induced liver injury…*
>
> (underlining added)

51. Dr Daniel McLaughlin (**Dr McLaughlin**), a neurologist, opined:[29]

> *The liver biopsy obtained on the 30th April,2020 was reviewed By Dr Andrew Clouston, an internationally recognised liver pathologist. His report notes the absence of microvesicular steatosis and centrizonal necrosis which are seen with valproate associated hepatotoxicity in about two thirds of patients. The findings were in keeping with a drug induced liver injury, with valproate the favoured cause. I am satisfied this is the diagnosis.*

52. Although Mrs Doherty's condition was considered undifferentiated and atypical for sodium valproate induced liver injury, I find that the likely cause of Mrs Doherty's DILI was sodium valproate-induced hepatotoxicity.

The likely mechanism of Mrs Doherty's DILI

53. As to the likely mechanism of the sodium valproate induced liver injury suffered by Mrs Doherty, the issue was raised by Dr McLaughlin in the context of monitoring a patient for adverse reaction to sodium valproate (discussed further below):[30]

[27] Ex D1, page 6 BOE
[28] Ex D6 BOE
[29] Ex D7, page 4 BOE
[30] Ex D7, page 2 BOE

The product information provided by the Therapeutics Goods Administration (TGA) states "Although published evidence does not establish which, if any investigation could predict this possible adverse effect, liver function tests should be performed (especially in patients at risk) prior to therapy and frequently thereafter until 6 months after the controlling dose is reached."

The recognition of valproate associated hepatotoxicity occurred in 1979. Although this adverse effect is rare, it has been the subject of considerable study and research as sodium valproate is widely used around the world. In Australia, this medicine is the most prescribed antiseizure treatment. As yet, no investigation has been found that will predict this adverse effect of hepatotoxicity.

There are alternate recommendations to those of the TGA for minimising the risk of valproate hepatotoxicity.

> *"No laboratory test, certainly not untargeted routine blood monitoring, identifies individuals specifically at risk for valproate hepatotoxicity,"*

This assessment by Bazel et al. (2006) was published in Merritt's Neurology, a leading textbook. Similarly, the observation of Bourgeois (2002):

> *"Although routine monitoring of liver enzymes during valproate therapy is a common practice, the diagnosis of hepatotoxicity depends mostly on early recognition of the clinical features, which include nausea, vomiting, anorexia, lethargy, and at times loss of seizure control, jaundice, or edema."*

(underlining added)

54. In his evidence at the Inquest, Dr Walsh explained, in the context of the issue of appropriate monitoring, that there are essentially two types of adverse response or liver injury associated with taking sodium valproate. The first relates to the patient's tolerance for taking the drug. As to the second, he went on to state:[31]

> *But the other liver problem with valproate is basically, if I was to explain it, it is not this mechanism [intolerance] but almost like a sudden allergy which just happens. ….. Acute onset, bang. It is not a build up from the taking [of sodium valproate], it is an incredibly rare bomb that goes off.*

55. During the course of his evidence, the following exchange was entered into between A/Prof. Majumdar and Mr Schneidewin, Counsel Assisting:[32]

[31] T1-24; LL 33-38
[32] T5-18; L 46 – T5-19; L 28

Doctor, we have had some evidence from other hepatologists who have been involved in giving evidence at the inquest that there are broadly speaking two mechanisms by which sodium valproate might injure a liver. There is the less harmful mechanism, if I can put it that way, where testing, monitoring of the LFTs might reveal an increase in or a derangement, a mild derangement, of the LFTs to suggest that the patient is not tolerating the medication. That's one broad category of injury, if I could put it that way. And the second one we have heard about is this very sudden and rapid onset of acute and significant derangement of the LFTs and liver injury. Would you agree that broadly speaking they're the two main mechanisms by which sodium valproate might injury a liver?---I would agree with both of those. There's also a third type that is associated with the high ammonia level and so patients often present with coma or encephalopathy first up without the same degree of liver injury as such, but it's purely a drug induced phenomenon from valproate where it might increase your ammonia level and they look like acute liver failure with a degree of neurological obtundation. In terms of, you know, the literature with acute liver failure and valproate, it's about one in 40,000, so again a very rare condition and poorly understood. There's no clear time course, which I've mentioned. The Cash report suggested three months is around the time course but it has been reported up to six months or beyond that. So much like, yes, idiosyncratic drug relations to any other drug, antibiotics, over the counter or herbal medications, often the time course situation and severity of liver injury are very unpredictable.

All right. And I accept what you say in relation to being – it being difficult to predict timing of the onset of the injury but are you able to say which of those broad types of injury it is most likely that Mrs Doherty suffered?---The acute idiosyncratic severe injury rather than the chronic form of – with the biochemical derangement I've already mentioned.

Okay. So she falls into the second category I was describing, setting aside the ammonia based condition and that was for a sudden and rapid onset of acute liver injury as a consequence of the sodium valproate at some point in time?---That's correct.

56. Having regard to the qualified opinion evidence I find that the mechanism of Mrs Doherty's sodium valproate induced liver injury was that of sudden acute onset in the nature of the "bomb" injury described by Dr Walsh.

The likely timing of Mrs Doherty's DILI

57. As to the likely timing of Mrs Doherty's DILI, the evidence can be summarised as follows:

    (a) On 19 November 2019, Mrs Doherty undertook the pathology tests ordered by Dr Walsh. Her LFTs were normal. Mrs Doherty's full blood

count and serum biochemistry were also normal. There was no evidence of intolerance to sodium valproate or acute liver injury at that time.

(b) Dr Walsh reviewed Mrs Doherty on 18 February 2020. He did not request further LFTs. The handwritten note of the consultation is brief.[33] Some greater detail about the consultation can be gleaned from the letter he sent to Dr Delshad.[34] Despite the brevity of the record I infer that Mrs Doherty reported no symptoms, and Dr Walsh observed no clinical signs of intolerance to sodium valproate or acute liver injury at that time, noting the absence of any recording of such symptoms and clinical signs.

(c) Dr Delshad reviewed Mrs Doherty on 19 February 2020, 25 February 2020, 10 March 2020 and 26 March 2020. In respect of each consultation, there is no record of Mrs Doherty reporting symptoms, or Dr Delshad observing clinical signs of intolerance to sodium valproate or acute liver injury. At the consultation of 26 March 2020, Dr Delshad recorded that Mrs Doherty was "*doing fine*."[35] In evidence at the Inquest, Dr Delshad explained:

> *Okay. And you've written, "Doing fine". Can you expand on that a little bit?---Very commonly I use that term when the patients have no general concern for that appointment. So they may just come for the scripts, rather than an actual complaint. So that's why I put "Doing fine".*
>
> *Okay. Did you - - -?---Because I do ask them, "Is there something else or are you concerned about anything?" And if they say, "No", I put, "Doing fine".*
> *Okay. What about on that specific day? Do you - - -?---I don't have any specific recollection, but I can trust my note.*
>
> *Okay. Great. So you don't recall, then, whether or not you formed any impression or asked her if she was feeling well; is that the case?---I - - -*
> *Or - - -?--- - - - commonly ask patients if they're doing okay……- - - I would have definitely asked her - - -*
> *Okay?--- - - - how she's doing.*
>
> *Okay. So she hasn't presented to you unwell. She's told you she feels fine. That's fair to say?---That's fair to say.*[36]

(d) Mrs Doherty next consulted Dr Delshad on 9 April 2020 for abdominal pain. Dr Delshad entered the following note into the record:[37]

> *Atacand ceased dizziness and she stopped 2 weeks ago*

[33] Ex B5.1, page 43 BOE
[34] Ex B5.1, page 46 BOE
[35] Ex B4.1 BOE
[36] T4-11, L44 – T4-12, L19
[37] Ex B4.1, page 7 BOE

has been having nausea every day since stopping
no vomiting
abdominal pain almost every day RUQ pain [Right Upper Quadrant]
pain is constant more at night more like
loss of appetite
Urine looks dark
indigestion/ burping a lot
cholcystitis
no fever
been more constipated
no respiratory symptoms

Subjective
Gastrointestinal:
Abdominal pain. Nausea. No vomiting. No heartburn. No dysphagia. No diarrhoea. Constipation. No PR bleeding. Recent change in bowel habit. Anorexia. No weight loss. No reflux. No haematemesis.

(e) Dr Delshad queried whether Mrs Doherty was presenting with liver pathology and arranged for a face-to-face consultation that day for pathology testing to be undertaken. At the Inquest, Dr Delshad explained:

Doctor, in terms of the symptoms of abdo pain, loss of appetite, dark urine, indigestion, burping a lot, those – what you've described as intraabdominal pathology, did she give you an indication of how long she had suffered with those symptoms?---So she has in – I've put in my note that she told me this has happened since she has stopped Atacand, and then in previous line I've written that she stopped Atacand about two weeks ago. So that [indistinct]
So we can say two weeks?---Two weeks.
Thank you.

Ms McKEON: Okay. So could you just talk the court through what your next actions were? Did you order some tests, perhaps?---I would – wanted, actually, urgent blood test. I – I remember we did have restrictions about seeing patients face to face, but I was concerned about her. So I asked her to come to the practice and do a blood test right away. I actually do recall seeing her in the waiting area, waiting to get the blood test done, and I had a good look at her. She was not unwell to an extent that I was worried about her to send her to hospital right away. I do remember that brief in – interaction with her in – on my lunchtime, and I did – again, I told her, like, "Just do the blood test now. As soon as I get the results, I will let you know", and this was a Friday afternoon.

(f) Although it is not entirely clear, based on the history Mrs Doherty provided to Dr Delshad, the onset of the liver pathology symptoms was probably at or about (or shortly following) the previous consultation Mrs

Doherty had with Dr Delshad on 26 March 2020. This is broadly consistent with Mr Doherty's recollection:[38]

> *By the end of March, Janis had stopped eating full meals, and was drinking a lot of water, more than usual. On the morning of 9 April 2020, she came out on the verandah and told our friend, Julie, that her urine was brown. Julie said to her, "That's blood, you better ring the doctor."*

(g) At the face-to-face consultation on 9 April 2020, Dr Delshad did not record any other clinical signs consistent with liver injury, e.g. that Mrs Doherty was jaundiced. At Inquest, Dr Delshad stated:

> *Okay. So in terms of you seeing her face to face - - -?---Yeah.*
> *- - - on the day, did she present with symptoms of jaundice - - -?---She did not - - - - to you?--- - - - from my recollection. I don't remember her having had jaundice. She – because if I had seen her, I would have sent her to hospital just there and then, but she was – she did – she did not look unwell on that day*

(h) The results of the pathology testing came back on 10 April 2020. At Inquest, Dr Delshad stated:

> *And on the 10th, the test results have come back. Can you recall specifically what concerned you about those results?---I actually recall that very clearly. I was still in bed when SNP – someone from Sullivan Nicholaides (sic) contacted me about her. And they – I think I was fortunate that I had access to – remote access because of Telehealth. I opened her chart, looked at the test results, and tried to contact her, because obviously the liver functions are a lot more than just a small liver injury. They were indicative of some serious liver injury at the time.*

(i) By his report, A/Prof. Majumdar stated:[39]

> *It is unclear from the information provided when the liver dysfunction began as there was no record of blood tests being performed between 19/11/2019 and 09/04/2020. The deceased's liver tests were within normal limits on 19/11/2019 and were significantly deranged on 09/04/2020 and it cannot be determined what took place between these dates. During a telehealth (phone) consultation with the deceased's General Practitioner, Dr Velshad, on 09/04/2020 a history of dark urine was noted which may suggest jaundice, but it is unclear when this began. The deceased was appropriately referred to Caboolture hospital urgently by Dr Velshad in response to the abnormal liver test results from 09/04/2020. The initial consultation by Dr Wheldon on 10/04/2020 in Caboolture Hospital Emergency*

[38] Ex C9, paragraph 54 BOE
[39] Ex D6, page 2 BOE

Department suggested a 2-week history of jaundice. Jaundice was not noted in consultations with Dr Velshad on 10/3/2020 or 26/3/2020.

(j) At the Inquest, A/Prof. Majumdar gave the following evidence:[40]

Okay. Now, these are difficult questions I appreciate because they require you to make some assumptions and to accept some, I guess, version of the evidence. In terms of the timing of the likely – the timing of the onset of the acute liver injury, it seems that the evidence comes down to this. When Mrs Doherty last consulted her general practitioner on the 26th of March 2020, the general practitioner did not make any record, and indeed has given evidence, that there was no indication on a clinician sign of liver injury at that time. When Mrs Doherty presented on 9 April 2020 to the same general practitioner, initially by Telehealth, she provided a history of how she experienced dark urine for a period of approximately of a fortnight – possibly to up a fortnight or so and some abdominal pain and some nausea, which she might have attributed to another medication she was previously taking. Now, I understood from your evidence, your report, the clinical presentation of having dark urine might suggest that the patient was jaundiced at that time?---Potentially, yes. I mean, there's lots of causes of dark urine but it's a common clinical question to ask. Usually dark urine will coincide with some jaundice that's detectable in the eye, so that's the yellowing of the whites of the eyes, and also some alterations of pigmentation, although they can be quite subtle. Usually it's not the patient who notices these features but more a relative or someone the patient may co-habit with, but again dark urine can just be a concentrated urine if she was feeling unwell and not drinking much……

….. The next indicia of having suffered a liver injury were of course the LFT test results that were returned following testing on the 9th of April. I think they were available on the 10th of April. You had an opportunity to review those test results yourself?---Yes, yes.
…..
And what did they indicate from your perspective in terms of Mrs Doherty's injury?---Yes, so she had a severe hepathetic (sic) picture, so inflammation of the liver cells and an elevated delivery consistent with an acute liver impairment. At that stage her INR was normal so we would not necessarily call that acute or severe acute liver injury, it's certainly acute liver injury or hepatitis.

…. But in terms of what you could piece (sic) together based on the information that was available as at 9th of April, that is the history of no clinician (sic) signs on the 23rd – sorry, on the 26th of March, those clinical symptoms that I described previously about dark urine, nausea and abdominal pain and then the LFT results of 10 April 2020, does that assist in identifying or narrowing down the point in time

[40] T5-17, L35 – T5-18, L20

when Mrs Doherty suffered the injury?---Not – not really, no. Acute liver failure or the eventual syndrome that this lady developed can present without any significant symptoms until this very point. So jaundice is usually the first presenting feature. Beyond that it goes – it's a very uncommon life-threatening injury, so less than one in 100,000 is estimated in westernised nations. So that pattern of blood tests and no symptoms prior does not really clarify what the diagnosis might be, merely that she has acute failure – or liver injury or there has been some insult to the liver.

(k) At Inquest, Dr Tan gave the following evidence:[41]

…I take from what you've just said, doing the best that you can, having regard to the history that was provided by Mrs Doherty when she presented to the general practitioner on the 9th of April, it would seem that she exhibited clinical symptoms or signs of acute liver injury about two weeks prior to that consultation. That's what you are saying. Correct?---Yes.

And those symptoms and signs included – I won't go through all of them – for example some abdominal pain, some nausea without vomiting, some loss of appetite and dark urine, which might be, together, indicative of liver injury. Is that correct?---Yes.

And it would seem, again just relying on the history that we have, at a consultation with the general practitioner, the last consultation with the general practitioner prior to the 9th of April, which I can tell you was the 26th of March 2020, at least insofar as the general practitioner's view was concerned, those symptoms that were later described were not reported by the patient on that occasion and nor were there any clinical signs apparent to the general practitioner of liver injury at that time. If we accept [that] to be the case, can I suggest this to you – when the bomb went off, it went off somewhere in that period 26 March 2020 to the time those first symptoms emerged a fortnight prior to the 9th of April? Would you agree with that?---I would agree with that, noting that there is barely two weeks between the 26th of March and the 9th of April and of course the two weeks is just an estimate by the patient. But I agree that that suggests that the onset of clinically apparent disease occurred between the 26th of March and the 9th of April. I just note that that interval is – 14 days, isn't it?

(l) Dr Skoien expressed the following view at the Inquest:[42]

What I want to ask you was, is it the case that it's likely that the injury occurred when the clinical manifestations of the injury were present?---If you – if by that you mean the clinical manifestations being an abnormal blood test, because of the severity of the abnormalities I

[41] T6-9; L 40 – T6-10; L15
[42] T3-5; L28 – T3-6, L13

think it's quite logical to assume that the injury happened sometime before that.

Sure?---I think Dr Majumdar correctly says we don't exactly know how far ago – before that had happened. You can – you could use patient's symptoms as a potential way of – of suggesting that – that when a patient's developing symptoms he or she may have been developing liver injury at that time and then went on to have a blood test. So in my mind, the injury probably occurred in the two weeks or so before – before the blood test was taken.

Yes. And just so you're clear, what I was referring to were the clinical signs of injury, such as jaundice for example, the lethargy, the nausea; those sorts of reported symptoms that Mrs Doherty had. Would that by a good or at least some indicator of when the injury was occurring or had occurred?---Yes, absolutely jaundice would be. Jaundice does occur after initial liver injury though. The first signs of liver injury are often very non-specific and can just be fatigue, anorexia, just not feeling right.
Yes. Okay. But you obviously considered this question for yourself and you think probably two weeks prior to presentation is when the injury occurred?---Something – something like that I think seems reasonable to me. I'm reminded of the fact that she had a similar episode to the one that prompted her to get a blood test in early April a few – about a month beforehand, which I believe she attributed to her CADASIL. Whether she was having some form of symptoms related to the injury at that time, and they were fluctuating and then they progressed to become jaundice. I guess we don't know but – but, yes, on balance I think I'd say probably around two weeks.

Right. We haven't heard from Dr Delshad yet but we can see from – at least from the clinical record that there was no noting of jaundice at the last consultation before – which was – I think was in late March of 2020?---Correct. Yes, that's right.
So the period is relatively narrow. It's somewhere between that date, probably the 26th of March 2020, and the presentation on the 9th of April 2020?---Probably, yes.

58. Having regard to the above evidence, I find that Mrs Doherty probably suffered a sodium valproate induced acute liver injury in the period 26 March 2020 to 9 April 2020, although it cannot be determined precisely when in that period the injury was suffered.

59. Whilst there remains the possibility the injury was suffered prior to 26 March 2020, I find that to be unlikely given the absence of any reporting of symptoms and the manifestation of any clinical signs consistent with liver pathology until shortly after 26 March 2020.

Issue 2(b)

The appropriateness of Dr Walsh's education and monitoring of Mrs Doherty for the signs and symptoms of the side effects of sodium valproate, including liver dysfunction

60. In evidence, Dr Walsh outlined his qualifications and experience as follows:[43]

> *I'm a neurologist. I've been practising neurology for almost 25 years. I've practised both in private practice and public practice, I have worked with the epilepsy service at the Royal Brisbane and PA Hospitals for 15 years or so. I also do clinics at the Prince Alexandra Hospital in new (sic) immunology and at Logan Hospital in vestibular neurology and I have a broad private practise and I visit Bundaberg as well.*

61. Mrs Doherty was referred by Dr Delshad to Dr Walsh for management of migraine in context of her known CADASIL. Dr Delshad's letter of referral to Dr Walsh dated 31 July 2019 stated, *inter alia*:[44]

> Thank you for seeing Mrs Janis Doherty, age 56 yrs, for opinion and management.
> Janis Was diagnosed with CADASIL syndrome end of last year which increase her risk of stroke, dementia depression and migraines. gene testing was done at Sunshine coast hospital. He mum died because of this genetic disease in her 70s and her sister is also having mini strokes and dementia. She has been re fared to Sunshine coast university hospital for ongoing follow up and manage. She is currently suffering fro frequent migraines with aura. She reports temporarily loosing her vision when she has headaches. It might even happen while driving. I have advised her to avoid driving until she gets a neurology assessment done. However, there is a long waiting time in public hospital and she decided to seek your help. At present time her physical examination is normal. I would appreciate a timely appointment.

62. Dr Walsh explained the nature of CADASIL and the available treatment options as follows:[45]

> *CADASIL is a genetic disease that causes slow deterioration of blood vessels in the brain. It's associated with an abnormality in a gene called Notch3. It is also very much associated with migraine. The disease progresses and it can cause quite disabling migraine symptoms. There are many opinions about its treatment. There are not many treatments available, a lot of treatment is both symptomatic for the migraine and prevention of other factors that can worsen the hardening of the arteries. So, if a person has another condition or a family history of hardening of the arteries, you want to modify that to try and provide better care.*

63. Mrs Doherty first consulted Dr Walsh on 1 November 2019.

64. Dr Walsh commenced Mrs Doherty on Epilim (sodium valproate) 200mg to treat her migraine and it was planned to increase the daily dose after two weeks to 400 mg daily (at night). The prescription of sodium valproate for the

[43] T1-10; LL 27-32
[44] Ex B5.1, page 1 BOE
[45] T1-10; LL 44- 50

treatment if migraine was “off-label”, however, there is no issue as regards the appropriateness of Dr Walsh prescribing sodium valproate for that purpose.

Educating Mrs Doherty

65. In prescribing sodium valproate to Mrs Doherty, in respect of potential side effects of the drug, Dr Walsh stated that:[46]

> 47. It is my usual practice to warn people taking Epilim that it can sometimes affect the liver and I usually say that it can even come at you at any time.
>
> 48. I would not mention the rate of 1 in 50,000 for liver dysfunction because it can cause patients to discount symptoms which may be attributable to liver dysfunction.
>
> 49. I do not usually discuss the symptoms of liver dysfunction with patients if they appears to have normal intelligence and understanding. In my experience, patients are aware that an abnormal or poorly functioning liver will result in the patient feeling sick and the skin going yellow (jaundice).
>
> 50. If it becomes clear to me that a patient does not understand these signs, I will explain further that you may feel sick or your skin may go yellow.
>
> 51. I prescribed Epilim 200mg tablets as directed with food with two repeats.

66. In his evidence, Dr Walsh stated that:[47]

> *With reference to my usual practice at the time I saw Mrs Doherty, I gave her distinct warning that valproate might affect her liver and my practice is to tell people that it can affect it at any time. There are two, I think there are two things to understand with respect to valproate. One is a small reduction in liver function and platelet function which is testable and predictable by blood testing. And then there is a serious catastrophic, very rare liver disorder. Which is different. And so, I discussed both. I discussed that valproate can affect people at any time. I always warn people and warned people as per my notes, 48, 49, 50, 51, when I talk to people about valproate, both in epilepsy and migraine, I assess their understanding of liver injury. If I don't believe they understand it appropriately, or meet that understanding, it is my practice for 20 years to give the consumer medicine information to the patient so that they can read further. I ensure that they have blood tests for the monitoring of the minor things and warn them, should they feel sick or unwell, or the other things, they should seek medical advice for a blood test. That's my practice now and my practice then.*

67. As to paragraph 48 of his statement, Dr Walsh explained:[48]

[46] Ex C4.1, page 4 BOE
[47] T1-17; L 43 – T1-18; L10
[48] T1-18; LL15 - 28

> *I don't mention the 1 in 50,000 or potentially for Mrs Doherty, 1 in 100,000 risk. Because she actually was not in a high-risk category for the use of this drug unfortunately, despite the outcome. I think sometimes if you give patients infinitesimal risk numbers, they forget the import of the thing that you're telling them about. And therefore, I tend not to quote infanticidally potentially low, if I could make an analogy. If every patient in Toowoomba took valproate, one of them would get hepatic toxicity. Well, every adult…. the risk is very low. So, therefore I don't say it like that. Otherwise, people can dismiss it …. It actually gives them a false sense of security to not – to not watch…*

68. As to his usual practice in describing the symptoms and signs of liver injury to a patient, Dr Walsh stated "*If I ask them what they understand of liver injury and they say to me, 'I go yellow, I get tummy pain, I get sick, I get jaundice,' then I tend to be less heavy on the detail. If patients appear to not be cognizant of that, I am more heavy on the details*".

69. In terms of describing the symptoms/ signs of liver injury to Mrs Doherty, Dr Walsh could not recall "*exactly what words I used with Mrs Doherty and what form that warning took, I cannot remember*", however "*I could say, there is no question in my mind, I discussed that*."[49]

70. Dr Walsh also stated that it was his usual practice to give the consumer medicine information sheet for Epilim (sodium valproate) to patients, although he did not recall if he specifically did this for Mrs Doherty.[50]

71. At the start of the Inquest, the NOK provided a family statement signed by Mrs Doherty's husband,[51] and a document located in the personal effects of Mrs Doherty, being the MIMS publication for Epilim (sodium valproate) dated October 2011 with various parts of the document having been marked with a yellow highlighter (**MIMS publication**).[52] By the family statement, Mr Doherty states:[53]

> *…Recently, I found an Epilim Information sheet at home in a filing tray in our office. ….The information sheet talks about the signs and symptoms for liver damage. I don't remember having a specific discussion with Janis about it, but I believe that she read the information because she always usually asked for a factsheet for any new medication, and she kept them filed in the office.*

72. The MIMS publication was shown to Dr Walsh in evidence. When asked if that was the document he would normally provide to patients he said "*Look, it is the document I would provide. I note that it's a 2011 document. It may have been on my desktop, so absolutely it is typically a document that I would*

[49] T1-18; LL 43-50
[50] Ex C4.10, paragraph 52 BOE
[51] Ex C9 BOE
[52] Ex C9.1 BOE
[53] Ex C9, paragraphs 39 – 40 BOE

provide to her."[54] As to whether the highlighted markings on the document were made by him, Dr Walsh said "*No. I would give the patient the document and I would advise them to read it, but this is not my marking*."[55]

73. Otherwise, Dr Walsh was taken to page 4 of the MIMS publication, specifically to the central column on that page where a bullet point is highlighted in yellow. Dr Walsh confirmed that the signs listed there were of the kind one would expect a patient to present with if they had a toxic reaction to sodium valproate, and he said "…*these are some of the things that I warn the patient of when I discuss it with them*…".[56]

74. On Day 4 of the Inquest, I entered the following exchange with Counsel for NOK:[57]

> *DEPUTY STATE CORONER: Mr Turner, if I may, the – this document – I don't have the exhibit number on it, I apologise……*
>
> *MR TURNER: I think it's C9.1.*
>
> *DEPUTY STATE CORONER: Thank you. Are you able to say who did the highlighting?*
>
> *MR TURNER: We're not, other than to say we're unaware that anybody else would have done the highlighting, apart from either the person that gave it to Ms Doherty or Ms Doherty itself.*
>
> *DEPUTY STATE CORONER: So we're happy that Mr Doherty did not do it?*
>
> *MR TURNER: We are happy, yes.*
>
> *DEPUTY STATE CORONER: Okay. So it might well be safe then to assume, given the evidence of Mr Walsh – Dr Walsh, rather, that it was, in fact, Mrs Doherty who made this marking on this document.*
>
> *MR TURNER: That's a reasonable inference, your Honour.*
>
> *DEPUTY STATE CORONER: All right. Thank you. That's the basis on which I probably - - -*
>
> *MR TURNER: Thank you.*
>
> *DEPUTY STATE CORONER: - - - would proceed."*

75. Dr Delshad subsequently stated that she had not made the highlighted markings on the MIMS publication.[58]

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[54] T1-19, LL 11-13
[55] T1-19, LL 19-20
[56] T1-19; LL36 - 37
[57] T4-2 to T4-3
[58] Ex C9.1 BOE; T4-17, L 25

76. Counsel for NOK submitted that "*generally, Dr Walsh's education…of Mrs Doherty was appropriate*."[59]

77. Counsel for Dr Walsh submitted that:[60]

> *As to the question of education, Dr Walsh adopts the submissions of counsel assisting from paras 55 – 66, and 68 – 69, and in particular the conclusion that it is open to find that Dr Walsh's education of Mrs Doherty about the clinical signs and symptoms of the side effects of sodium valproate (including liver dysfunction) was adequate and appropriate. Dr Walsh notes the family's submission at para 3 that generally, Dr Walsh's education and monitoring of Mrs Doherty was appropriate. Dr Walsh does not make any further submissions as regards this issue.*

78. Having regard to all of the evidence available, in line with the submissions of Counsel Assisting, I find as follows:

    (a) At the consultation on 1 November 2019, Dr Walsh discussed with Mrs Doherty the side effects associated with the use of sodium valproate, including the risk of liver injury, consistent with his usual practice;

    (b) There is no basis for concluding that Dr Walsh departed from his usual practice on the occasion of his consultation with Mrs Doherty;

    (c) It is likely Dr Walsh discussed with Mrs Doherty at least some of the signs of liver injury as referred to on page 4 of the MIMS publication, consistent with his usual practice;

    (d) Again, there is no basis for concluding Dr Walsh departed from his usual practice in this regard;

    (e) Dr Walsh provided to Mrs Doherty the MIMS publication;

    (f) Mrs Doherty was invested in her health issues and generally wanted to be informed about new medications that were prescribed to her; and

    (g) Mrs Doherty subsequently read the MIMS publication and noted specifically, by yellow highlighter marking, various sections of the document including the section that stated " ***Tell your doctor, or go to the Accident and Emergency at your nearest hospital if you notice any of the following:*** *….. signs of liver problems such as vomiting, loss of appetite, generally feeling unwell, tiredness, yellowing of the skin and/or eyes, dark urine or blood in urines, pain in abdomen*…"

79. However, on the evidence available, I cannot determine:

    (a) Precisely when Mrs Doherty read the MIMS publication and made the yellow highlighter markings; and/or

[59] Paragraph 3(a)(i) Submissions of Doherty Family dated 13 November 2024
[60] Paragraph 4 Submissions of Dr Walsh dated 13 December 2024

(b) When, if at all, Mrs Doherty appreciated the manifestation of any signs of liver pathology prior to when she consulted with Dr Delshad on 9 April 2020 and reported a two-week history of some of the symptoms referred to in the MIMS publication as being "*signs of liver problems*."

80. Having regard to what can be reasonably inferred, I find that Dr Walsh's education of Mrs Doherty about the clinical signs and symptoms of the side effects of sodium valproate (including liver dysfunction) by the provision of advice in consultation and the MIMS publication, was adequate and appropriate.

Monitoring of Mrs Doherty

81. As to monitoring for the side effects of sodium valproate, Dr Walsh organised to perform LFTs pathology testing at two and four weeks following Mrs Doherty commencing the sodium valproate.

82. On 19 November 2019 (not at 2 weeks or 4 weeks as planned), Mrs Doherty undertook the pathology tests ordered by Dr Walsh. Her LFTs were normal. Mrs Doherty's full blood count and serum biochemistry were also normal.

83. Subsequently, there was an email exchange between Mrs Doherty and Dr Walsh's practice staff which culminated in communication to Mrs Doherty that no further blood tests (LFTs) were required.

84. No further LFTs were undertaken prior to 9 April 2020.

85. Dr Sethi, Consultant Gastroenterologist and Hepatologist, opined as follows:[61]

> *Epilim is associated with the following side effects:*
> • *Nausea.*
> • *Abdominal cramps.*
> • *Abnormal liver function.*
> • *Weight gain.*
> • *Diarrhoea.*
> • *Tremor.*
> • *Fatigue.*
> • *Sedation.*
> • *Confusion.*
> • *Dizziness.*
> • *Alopecia.*
> • *Thrombocytopenia.*
> • *Anaemia.*
> • *Leukopaenia.*
> • *Toxic epidermal necrolysis.*

[61] Ex D3, starting on page 16, BOE

It is well described in the medical and scientific literature that Epilim can cause fulminant liver failure leading to death..[62]

…..

There is a place for routine laboratory testing. This should occur once every two months for the first six months. This is well described in the medical and scientific literature and is detailed below.[63]

This did not occur in Ms Doherty's case.

…

There is a clear place for monitoring for clinical signs of liver dysfunction and education of the patient in identifying those signs. This did not occur in Ms Doherty's case.

…

The monitoring that was performed in the case of the deceased was neither appropriate nor reasonable. She was not instructed to undergo follow up testing. Only one test was performed after commencing Epilim.

On 19 November 2019, Ms Doherty exchanged emails with Dr Walsh's practice staff enquiring how often blood tests were to be performed and was advised that no more blood tests were to be performed. Neither Drs Walsh or Parvin organised further LFT testing.

….

Dr Walsh and Dr Parvin were both responsible to ensure appropriate monitoring in the case of the deceased. In my opinion, the greater responsibility lay with Dr Walsh given that he prescribed Epilim.

86. The inference to be drawn from the above opinion is that had Mrs Doherty been monitored by routine laboratory testing at the intervals suggested by Dr Sethi, the DILI might have been avoided (or, at least, detected earlier) and Mrs Doherty might have survived.

87. Dr Skoien maintained a similar view about the role regular monitoring might have played in avoiding Mrs Doherty's demise. He stated:[64]

> *I note the Consumer Medicine Information and Australian Product Information for sodium valproate/Epilim, reproduced as a single attachment* ***(Exhibit D1 .2).*** *These documents provide advice regarding risks of hepatoxicity and death due to liver failure that seems consistent with the information provided in my earlier statement in* ***Exhibit C2.2.*** *On page 7 (page 13 of* ***Exhibit D1 .2),*** *the product insert recommends that "liver function tests should be performed ... prior to therapy and frequently thereafter until 6 months after the controlling*

[62] Citing https://gut.bmj.com/content/gutjnl/25/6/673.full.pdf & https://www.ncbi.nlm.nih.gov/books/NBK548284

[63] Citing *https://www.eclipsesolutions.org/UploadedFiles/656_guidance-for-monitoringdrug-therapy-in-adults-v2-amended-RP.pdf*

[64] Ex C2.14, paragraph 52 BOE; referring also to his earlier statement in Exhibit C2.2

dose is reached". It is entirely possible that the Mrs Doherty's liver function tests were abnormal within 12 weeks of commencing valproate, recognised as the time frame that represents "the period of maximum risk", and would therefore have changed my attitude to valproate as the culprit. If this case were to happen again, I do not suggest that Mrs Doherty's failure to have these tests would necessarily compel me to assess her case in the same way. I do submit however, that this oversight obscured the exact timing of onset of liver injury and, if performed, earlier blood tests may have established valproate toxicity as the correct diagnosis at an earlier time in her illness.

88. At the Inquest, Dr Skoien also provided his views as to the utility of regular laboratory testing as follows:[65]

> *And then there's a type of injury which he described as a bomb, which is an acute and sudden onset of liver failure or liver injury that can occur in an unpredictable way, in the sense that it's not something that can be identified through pathological monitoring. Would you agree with that type of mechanism?---I'd slightly disagree in that, and I think there's expert evidence or guidelines either way, that some doctors don't find that monitoring is useful because it can happen quite quickly and acutely but others, and I'm in that boat, would suggest that if there is a regular test in the – in the at risk period that the patients are prescribed valproate and there is any change in the patient's liver enzymes then that would necessitate further investigation. And if things are escalating quickly you would stop the valproate as a – as a potential cause in that at risk period. I think there is some evidence in the valproate drug insert that – that some monitoring is suggested. I think the neurologists whose statements I've read – statement I've read has said that he doesn't do testing because it can happen unpredictably. My usual practice in starting any medication that could potentially have a – have a toxic effect would be to do regular blood tests. Valproates being – is a commonly-known cause of liver injury.*
>
> *Sure. But in – even in that approach it can be accepted that you might get a normal result but then have a sudden acute onset of injury in a way that might have occurred in this particular case?---Yes. I think that's fair. If you happened to do the test the day before the injury starts and perhaps it's evolved over a number of days you might be weeks down the track before you get the test done. But, <u>on average</u>, you may also be catching it just in its early stages, well before the injury becomes severe.*
>
> (my emphasis)

89. It is not clear what Dr Skoien meant by the reference "on average". It may be that he meant "on the balance of probabilities", but either way there appears

[65] T3-4; L29 – T3-5; L8

to be no support for such a conclusion in the literature referred to by other experts (see below).

90. Dr Tan opined as follows:[66]

> *The Australian product information (PI) for valproate (attached), states (emphasis has been added by me):*
>
> > *Clinical symptoms are usually more helpful than laboratory investigations in the early stages of hepatic failure. Jaundice, serious or fatal hepatotoxicity may be preceded by nonspecific symptoms, usually of sudden onset, such as loss of seizure control, malaise, asthenia, weakness, lethargy, facial oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice. In patients with epilepsy, recurrence of seizures can occur.* ***These are an indication for immediate withdrawal of the medicine.*** *Patients should be monitored closely for the appearance of these symptoms. Patients (and their family and carers) should be instructed to immediately report any such signs to the clinician for investigation should they occur. Investigations including clinical examination and laboratory assessment of liver functions should be undertaken immediately.*
> >
> > *The PI goes on to discuss detection of liver failure as follows:*
> >
> > *Although published evidence does not establish which, if any investigation could predict this possible adverse effect, liver function tests should be performed (especially in patients at risk) prior to therapy and frequently thereafter until 6 months after the controlling dose is reached, when less frequent monitoring may be appropriate. It is also advisable to monitor tests which reflect protein synthesis, e.g. prothrombin time, serum fibrinogen and albumin levels, especially in those who seem most at risk and those with a prior history of hepatic disease.*
>
> *Notably, there is no specific recommendation as to how frequently these tests should be repeated, and other experts do not endorse a role for routine laboratory monitoring.[67] There is a consensus that clinical monitoring (for signs and symptoms of liver disease) is more meaningful than laboratory testing.[68] My impression is that epilepsy specialists in Queensland take very different approaches to testing, including my own rather laissez-faire view that however often the patient's general practitioner requests testing is often enough.*

[66] Ex D1, starting on page 4 BOE
[67] Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults: a national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; 2015
[68] Pellock JM, Willmore LJ. A rational guide to routine blood monitoring in patients receiving antiepileptic drugs. Neurology. 1991 Jul;41(7):961–4.

….
Judging by the nebulous recommendation in the Australian PI, since Mrs Doherty did not have liver enzymes tested prior to commencement of valproate on 1 November 2019, and only had one test performed between then and 9 April 2020, the frequency of testing could not be said to be in accordance with the advice in the PI. However, as I explain in the following section, I consider the failure to perform routine laboratory monitoring to be immaterial to the final clinical outcome.
….
I agree that the cause of Mrs Doherty's liver failure was valproate-induced hepatotoxicity, with a delayed onset from commencement of the medication, almost 5 months. The delays in recognising this diagnosis are not attributable to an absence of routine laboratory testing. There was a delay of approximately 2 weeks from onset of symptoms of liver disease to laboratory testing of liver enzymes and function. There is further delay of approximately 4 days from hospital admission to ceasing valproate. It is very plausible that, had the valproate been ceased earlier, her liver disease may have resolved with supportive treatment.

(my emphasis)

91. At the Inquest, in the context of the nature of the DILI Mrs Doherty likely suffered, Dr Tan gave the following evidence in response to Mr Schneidewin's cross examination about the role and, specifically, the effectiveness of regular monitoring in detecting and avoiding such an injury:[69]

Okay. Before I talk to you about monitoring, I just want to talk to you about the effect that sodium valproate might have on patients from a liver toxicity perspective. And we've heard during the course of the evidence from other experts and also from some of the factual witnesses, including Dr Walsh, that there are a range of potential liver injuries that might arise from the use of sodium valproate, and I'll focus on two of those broad category of injuries. It's been described to us that there is – the first category of injury is the – if I can put it this way – more benign or less serious category of injury where the sodium valproate might cause the patient's liver function test to increase, and is indicative of the patient perhaps not tolerating the medication but without significant injury being suffered to the liver, and that may occur over a period of time and may in fact be chronic if the medication is continued. So that's the first broad category that has been described to us. The second category of injury has been described initially as like a bomb going off. Others have adopted that analogy and that is an injury which occurs by reason of a rapid and sudden, acute and very significant injury to the liver, that could occur at any time when taking sodium valproate. Now, before I descend any further into the questioning, do you agree or disagree with that sort of

[69] T6-8, L43 – T6-11, L45

broad description of the two types of injury that might be suffered?---I agree completely with that premise.

…

Did you have regard to when it was likely that Mrs Doherty suffered her liver injury when you were considering the material, Doctor?---I did my best to pinpoint when the earliest opportunity was to identify that the injury had begun. And so if you'll indulge me, what I cannot say with confidence is how quickly, in that second instance where it's very severe liver injury and it's like a bomb going off. While I agree with that premise, what I cannot say with authority is how quickly that occurs.

Yes?---Because – and the reason I consider that pertinent is because while I have proposed the view of other experts that regular monitoring of liver function tests at frequent intervals, whatever that may be, has no demonstrated value in detecting that severe type of injury at an early stage before clinical symptoms emerge. And I stand by that view. I am aware of a slightly contrary view put forward by the expert liver specialist and the treating hepatologist that had the regular liver function tests been done, that it would have detected the liver injury at an earlier stage and allowed earlier intervention by withdrawing the medication. And so whether or not that contrary view holds up depends upon how quickly the bomb goes off.

Yes?---But in relation to what clinical documentation is available for Mrs Doherty, as best I can tell, the evidence of liver injury is first apparent two weeks before she sees her general practitioner on the 9th of April because that's what she consulted Dr Delshad for was two weeks of symptoms that sound compatible with liver disease.

Yes. You've explored a lot of the issues that I was coming to in your response to that question. Perhaps if I can just narrow the focus slightly and take it a bit more step by step. I take from what you've just said, doing the best that you can, having regard to the history that was provided by Mrs Doherty when she presented to the general practitioner on the 9th of April, it would seem that she exhibited clinical symptoms or signs of acute liver injury about two weeks prior to that consultation. That's what you are saying. Correct?---Yes

And those symptoms and signs included – I won't go through all of them – for example some abdominal pain, some nausea without vomiting, some loss of appetite and dark urine, which might be, together, indicative of liver injury. Is that correct?---Yes

And it would seem, again just relying on the history that we have, at a consultation with the general practitioner, the last consultation with the general practitioner prior to the 9th of April, which I can tell you was the 26th of March 2020, at least insofar as the general practitioner's view was concerned, those symptoms that were later described were not reported by the patient on that occasion and nor were there any clinical signs apparent to the general practitioner of

liver injury at that time. If we accept to be the case, can I suggest this to you – when the bomb went off, it went off somewhere in that period 26 March 2020 to the time those first symptoms emerged a fortnight prior to the 9th of April? Would you agree with that?---I would agree with that, noting that there is barely two weeks between the 26th of March and the 9th of April and of course the two weeks is just an estimate by the patient. But I agree that that suggests that the onset of clinically apparent disease occurred between the 26th of March and the 9th of April. I just note that that interval is – 14 days, isn't it?

…..

Now, it's in that context that I want to then talk about monitoring, if I can. Now as you will appreciate, Dr Walsh's plan was for the patient to have – Mrs Doherty to have – liver function testing and other pathology testing at two weeks following the commencement of sodium valproate, which more or less coincided with the intended increase of the dose to 400 mg and thereafter a further test at four weeks following the commencement of sodium valproate or two weeks following the dose of 400 mg. That was his plan. What in fact happened was Mrs Doherty had the first relevant pathology testing, that is LFT testing some time after that initial two weeks, slightly after two weeks, perhaps closer to three weeks, which were normal results, as you will appreciate from the record. And thereafter it was considered no further testing was required. Now in terms of appropriate monitoring, do you have any comments to make, first of all about Dr Walsh's plan. I will ask you about that first. Do you have any comments about the plan that Dr Walsh had?---The plan for testing at two weeks and then four weeks is reasonable. On the face of it, it seems reasonable. Noting that I continue to support the view that no regular monitoring is necessary as no evidence supports its value, just in terms of the time it seems a bit curious because it only covers those first four weeks. So what I'm saying is on the one hand even though I dispute the value of routine monitoring, if it's going to be done, then merely covering the first four weeks doesn't reflect the period when the patient is at highest risk of developing problems.

All right. Having regard to the normal result that was returned when the test – the one and only test – was done, would you accept or reject the proposition that that normal result was sufficient to satisfy any concern about the patient not tolerating sodium valproate?---My answer is I don't completely agree with that. So I don't agree in the sense that the single test result does not – the single normal test result - does not then predict what's going to happen later. Merely having the first test return normal doesn't indicate that the second test is going to return normal. And then secondly because tolerating the medication is a much broader concept than whether or not blood tests are abnormal. So most patients who are unable to continue taking valproate do that for reasons that have nothing to do with the laboratory tests. They do that because of common adverse effects like weight gain, tremor, hair loss – these factors. But insofar as your question presumably pertains to whether or not their liver tolerates

the medication, then I refer you back to my comment that the blood test being normal at two weeks, or in this case 18 days after she was presumed to start the medication, doesn't predict that further tests done within the next three to six months are going to be normal. And, again, it's reinforced the point that I say this despite not believing that there is a value in doing those regular tests within the first three to six months. It just seems to me that if you are going to do the tests, then in order to [indistinct] some internal logical consistency, that you ought to be looking at doing them over a longer timeframe, if that makes sense.

Yes. I understand. All right. Well, let's then consider the utility – you have repeated your position in relation to the efficacy and the appropriateness of performing testing, regular testing, generally – but in the context of what appears to have occurred here, and that is that Mrs Doherty suffered this bomb-like, acute and sudden onset of injury within that narrow fortnight – relatively narrow fortnight period that we have isolated, I take it that what you're really – what you've said on a number of occasions throughout your evidence is that the regular testing, even if it had been done, and at whatever interval, which is unclear, it would not necessarily predict – or would not predict but would not necessarily reveal the injury that Mrs Doherty had suffered. Is that the point that you are ultimately making?---That's the point that I'm making and try and provide a context of clarification about why I hold that position. Hypothetically, if we knew that Mrs Doherty's symptoms began on the 28th of March, what I can't say is whether doing the blood tests pre-emptively, in a monitoring sense, doing them on the 24th of March or the 14th of March or the 7th of March – because I don't know how quickly that bomb goes off, I wouldn't be able to say how the timing of a hypothetical monitoring test, how that would have lined up with being able to discover that something was amiss before she actually developed symptoms. So had – again hypothetically – had the monitoring been done every month or every two months, which is a frequency that's been proposed in a couple of other reports, it is uncertain whether this would have detected her liver injury before she developed symptoms. And I'm inclined to think it would have been – had the monitoring been done – it would have been no more than a matter of good fortune and coincidental timing that it would have picked up pre-clinical disease.

Yes. More in the nature of almost luck in a sense, is what you would say?---Yes.

And to not be ascertained one way or the other, even on the probabilities, whether regular testing would have revealed this injury at any earlier time than what was in fact the case is your ultimate position, I take it?---Yes, that's my view Yes. More in the nature of almost luck in a sense, is what you would say?---Yes.

And [it could] not be ascertained one way or the other, even on the probabilities, whether regular testing would have revealed this injury at any earlier time than what was in fact the case is your ultimate position, I take it?---Yes, that's my view.

(my emphasis)

92. Overall, the effect of Dr Tan's evidence is as follows:

(a) Notwithstanding the non specific recommendation in the Australian PI, since Mrs Doherty did not have liver enzymes tested prior to commencement of sodium valproate on 1November 2019, and only had one test performed between then and 9 April 2020, the frequency of testing could not be said to be in accordance with the advice in the PI;

(b) However, in his view, no regular pathology testing monitoring is necessary as there is no evidence that supports its value*;*

(c) That said, Dr Walsh's initial plan for testing at two weeks and then four weeks seemed reasonable, although the plan was a "*bit curious*" because it only covered the first four weeks of Mrs Doherty using sodium valproate, which did not reflect the whole of the period when the patient is at high risk of developing problems. That is, if one was to elect to do the testing, the testing should have covered the whole of the period during which the patient was at high risk of developing problems (up to 3 – 6 months);

(d) The single test that was performed was inadequate for predicting that there would be no adverse response to the sodium valproate in the first 3 – 6 month period;

(e) Regardless, any regular testing at the intervals proposed was not likely (i.e. on the balance of probabilities) to have detected Mrs Doherty's sudden and acute onset liver injury (i.e. "the bomb"), other than by happenstance or luck; and

(f) Clinical monitoring looking for signs and symptoms of disease, or being vigilant for signs and symptoms of disease, is more meaningful than the laboratory testing.[70]

93. Dr McLaughlin, a neurologist, opined as follows:[71]

The product information provided by the Therapeutics Goods Administration (TGA) states "Although published evidence does not establish which, if any investigation could predict this possible adverse effect, liver function tests should be performed (especially in

[70] T6-12; LL1-3. This obviously harks back to the need to educate the patient about such symptoms and signs. We reiterate that it is open to Your Honour to find that Dr Walsh's education of Mrs Doherty in this regard was adequate and appropriate.
[71] Ex D7 BOE

patients at risk) prior to therapy and frequently thereafter until 6 months after the controlling dose is reached."
The recognition of valproate associated hepatotoxicity occurred in 1979. Although this adverse effect is rare, it has been the subject of considerable study and research as sodium valproate is widely used around the world. In Australia, this medicine is the most prescribed antiseizure treatment. As yet, no investigation has been found that will predict this adverse effect of hepatotoxicity.

There are alternate recommendations to those of the TGA for minimising the risk of valproate hepatotoxicity. "No laboratory test, certainly not untargeted routine blood monitoring, identifies individuals specifically at risk for valproate hepatotoxicity," This assessment by Bazel et al. (2006) was published in Merritt's Neurology, a leading textbook.[72] *Similarly, the observation of Bourgeois (2002) "Although routine monitoring of liver enzymes during valproate therapy is a common practice, the diagnosis of hepatotoxicity depends mostly on early recognition of the clinical features, which include nausea, vomiting, anorexia, lethargy, and at times loss of seizure control, jaundice, or oedema."*[73]

94. Dr McLaughlin also referred to the recommendations of Gelisse and Genton to minimise the risk of valproate hepatotoxicity, which include the recommendation for blood testing prior to the commencement of treatment and at one month after, with further blood tests undertaken only if significant clinical symptoms arose.[74] He suggested that:

> *Dr Walsh's management was in accordance with the above recommendations. The normal liver function tests in April 2019 were reasonable to reuse as a pretreatment measure. The liver function tests, electrolytes and urea as well as a full blood count were performed 18 days after commencement of intake of sodium valproate rather than 30 days as recommended. Bilirubin is measured as part of the liver function tests and platelets as part of the full blood count. These results were normal, and no further test recommended by Dr Walsh. post treatment. This is slightly different to the advice of Gelisse and Genton (2002) but not to a significant degree. Prothrombin time would be measured if the liver function tests were abnormal as might amylase. Mrs Doherty was seen on a second occasion, 18th February 2020, 3 ½ months after commencing the medicine. Dr Walsh noted migraine aura was less and some headache still occurring. He did not record any tolerability issues following the introduction of sodium valproate.*
>
> (my emphasis)

[72] Bazil CW, Morrell MJ and Pedley TA. "Epilepsy" in Merritt's Neurology (Eleventh Edition) Rowland LP Ed. 2005 Lippincott Williams & Wilkins, Philadelphia pp1002-3
[73] Bourgeois, BFD "Valproic Acid Clinical efficacy and use in epilepsy" in Antiepileptic Drugs (Fifth edition) Levy, RH et al. (Eds) 2002 Lippincott Williams & Wilkins, Philadelphia page 814
[74] Genton P, Gelisse P "Valproic Acid Adverse effects" in Antiepileptic Drugs (Fifth edition) Levy, RH et al. (Eds) 2002 Lippincott Williams & Wilkins, Philadelphia page 843

95. In summary, Dr McLaughlin considered that Dr Walsh's initial plan for laboratory testing was reasonable and mirrored his own practice.[75]

96. Under cross-examination by Counsel for NOK, in respect of his statement that "*the normal liver function tests in April 2019 were reasonable to reuse as a pretreatment measure'* and whether LFTs should have been performed prior to and closer in time to commencing sodium valproate, Dr McLaughlin explained:[76]

> *Was it appropriate or do you think it is or it isn't appropriate to have a liver function test done prior to the commencement of sodium valproate?---It is.*
>
> *And close in time to when the sodium valproate is going to be commenced?---Close in time depending on the person's health. If that level was normal in the previous year, and there's been no suggestion of any other health problems, I can't imagine why I'd want to repeat it again. I would have been satisfied with that result.*
>
> *But if the patient, in this case Ms Doherty, let's be specific, she's been referred to a neurologist by her GP for a specific reason. An increase in migraine?---Yes.*
>
> *So there has been a change in her health?---There has, but it relates to the occurrence of migraine, which isn't going to influence the health of her liver. So that hearing that history isn't one where I'd think we must do tests on liver function and in fact I wouldn't – I can't really think of a scenario where an increase in migraine activity would trigger me to look at that unless there was another episode in the patient's previous health.*

97. Further as to Dr Walsh's compliance with TGA recommendations and the recommendations stated by Gelisse and Genton, Dr McLaughlin's evidence was:[77]

> *Are you also of the opinion that him not following the recommendations in the table you've provided in your statement was also a reasonable course of action for him to take?---The single test that was done was done on day 18 of the commencement of therapy. The recommendation is at one month; we'll call that day 30. I didn't regard that as being a major aberration. And, subsequently, when Dr Walsh was to see this lady again, there's no reports in his notes that she suffered any issues of tolerability with the introduction of sodium valproate. However, just by itself, just the fact that he's done a single blood test I wouldn't regard as being a major problem in the utilisation of sodium valproate at commencement.*

[75] Ex D7, page 4 BOE
[76] T5-52; LL 10 - 26
[77] T5-53; LL 8 - 27

Even though it's not consistent with either the product information or the table you provided?---It's not word perfect, and part of the reason for providing you with what I think is the best statement is that, contrary to what the Therapeutic Goods Administration, which is full of very capable people, have currently supplied, and as a result, the point is no one knows the absolute correct answer. It is not at a stage where you could be laissez-faire about the introduction of the drug or monitoring. The emphasis from the data, where, by the mid-90s, 134 people had died is they need to be informed the drug can cause liver damage because that can be a fatal problem.
How many people have died in that manner since the mid-90s?---From the mid-90s, it's estimated about another 60 cases.

98. Finally, Dr McLaughlin responded to Mr Schneidewin's questioning as follows:[78]

Yes, she complained of dark urine, but certainly it's noted that she had – she appeared jaundiced at the hospital. Do you think any testing regimen contemplated by the materials set out in your report would have, if followed in the strictest sense, would have afforded those treating her an opportunity to get a better outcome than she sadly suffered?---I think not, because the evidence has been that it doesn't work if it goes on further, and it did happen. During the late-80s, in the mid-80s it became apparent that this was rare but devastating, so I agree with your assessment. It's catastrophic. But blood tests were done more frequently. There was recognition of the high-risk groups. They were looked at more closely. And it didn't directly alter the occurrence of the condition. It was when the drug was shifted away from high- risk groups that the mortality rates actually dropped. And so the initial advice of taking lots of liver tests made sense at the time, but by the middle of the 1990s it became apparent that that had made no impact. And further analysis showed that those who had symptoms and were recognised as such, they were the ones who had the best outcome.

The evidence we've heard suggests that this sort of catastrophic injury, iatrogenic catastrophic injury, occurs in the instance of something in the order of one in 40,000?---That's the low estimate rate. And I've been happy to use that in my report. There have been further analysis that were done depending on the time of study. So the large American study by Dreyfus and colleagues was done between '84 and '86 and they identified children under 2 high risk, people taking more than one anti-seizure drug high risk, people taking a single drug, and the effect was around one in 50,000 for that analysis. When they examined the next three-year period, the risk in people over the age of 20 who were on valproate as an only treatment was up over one in 100,000. And because the figures aren't big enough, I'm not going to argue that point strongly.

[78] T5-54; L 26 – T5-55; L20

If you had been prescribing sodium valproate to Mrs Doherty for the reasons that Dr Walsh prescribed it, would you have warned her of the risk of catastrophic, unsurvivable liver injury in the order of one in 40,000?---I wouldn't have used that figure. I would have informed her that – and remember I come from a point of bias. But so there's one warning that I think is very important because the treatment's being started, it has a potentially fatal outcome, I think people ought to know about that before they decide to take it. And the advice is, yes, it is rare. It has its symptoms that lead into it, so if you lose appetite, you become nauseated, or you feel generally unwell, you have to see your GP and have blood tests done or, depending on where they live, they might be better off contacting me. If it is just being started for epilepsy or for migraine, they're discontinued the drug because we can do that safely in the short term while we sort this out.

Do you think that is an approach that the majority of your peers would take in respect of warnings about this drug?---I can't give you an accurate answer. I've not discussed it at length with anyone.

99. Counsel for NOK submitted:

(a) "*Generally, Dr Walsh's … monitoring of Mrs Doherty was appropriate*";[79]

(b) "*It would have been preferable for Liver Function Testing to be ordered in accordance with the MIMS publication (or similar contemporary guidelines). This is particularly so for Mrs Doherty given she had a complex medical presentation, including CADASIL syndrome*";[80]

(c) "*While clinical monitoring of symptoms may be more meaningful than LFTs, a reliance on the identification and reporting of clinical symptoms was less appropriate in Mrs Doherty's case, given her complex medical presentation, that included a condition that commonly causes symptoms of cognitive deterioration and dementia (CADASIL), and Dr Walsh's knowledge of Mrs Doherty's existing cognitive difficulties (by the time of the second consultation on 18 February 2020). A requirement to also be regularly tested may have kept the monitoring of symptoms front of mind for Mrs Doherty, her family and her GP*"[81];

(d) "*The MIMS publication notes that liver injury is common and severe liver injury and/or hepatic failure resulting in fatalities has occurred to those on sodium valproate treatment. While valproate associated hepatoxicity is rare, it has been the subject of considerable study and research as sodium valproate is widely used around the world. LFTs "should be performed (especially in patients at risk) prior to therapy and frequently thereafter until 6 months after the controlling dose is reached, when less frequent monitoring may be appropriate." Those at higher risk of liver*

[79] Paragraph 3(a)(i) Submissions of Doherty Family dated 13 November 2024
[80] Paragraph 3(a)(ii) Submissions of Doherty Family dated 13 November 2024
[81] Paragraph 3(a)(iii) Submissions of Doherty Family dated 13 November 2024

injury include those with a congenital metabolic or degenerative disorder and those with an organic brain disease"[82];

(e) "*Dr Walsh prescribed Epilim to Mrs Doherty on 1 November 2019. On 19 November 2019 she had a LFT that was normal. Dr Walsh next saw Mrs Doherty on 18 February 2019 (3.5 months after commencing Epilim) and did not order any further testing at that time. Despite Dr Tan not supporting regular testing he did note that testing over only the first four weeks was curious given "the first four weeks doesn't reflect the period when the patient is at highest risk of developing problems," and that if testing is going to be undertaken it should occur over a longer timeframe*"[83]; and

(f) "*Counsel Assisting, in their submissions, refer to 'more contemporary Guidelines' (than the Australian PI or information provided by the TGA) and provide an example of Gelisse and Genton (who recommend testing prior to the commencement of treatment and at one month after). It is unknown what Guidelines Counsel Assisting is referring to. Gelisse and Genton was a 2002 publication and no other sources were referred to that post-date the PI (December 2021) or MIMS Publication (June 2016). Gelisse and Genton's recommendations should not be given any more weight because they are the recommendations that most resemble Dr Walsh's initial testing regime*."[84]

100. Counsel for Dr Walsh submitted:[85]

(a) *"The blood test on 19 November 2019 was 18 days after Dr Walsh prescribed sodium valproate, i.e. in reasonably close to the middle of the planned 2 and 4 week blood tests*";

(b) "*The Product Information, which includes the nebulous recommendation for liver function tests 'regularly' until 6 months after the controlling dose is reached expressly notes that published evidence does not establish which, if any, investigation could predict the adverse event. The suggested approach is also inconsistent with the practice of Dr Walsh, Dr McLaughlin (whose practice mirrors Dr Walsh's), Dr Tan (who does no testing), and the Australian Prescriber publication Safe use of sodium valproate (ex. C4.3) (which recommends laboratory studies before commencing, but states that regular monitoring is not required for most patients)*";

(c) "*At paras 74 – 75, counsel assisting refer to Dr Sethi's evidence. However, at the outset of his evidence, Dr Sethi conceded that having reviewed the expert evidence and guidelines, his assertion that regular blood test monitoring was required could not be maintained and*

[82] Footnotes omitted
[83] Footnotes omitted
[84] Footnotes omitted
[85] Paragraph 6 Submissions of Dr Walsh dated 13 December 2024

accepted that there were diverse views regarding the frequency of such blood test monitoring and its efficacy in detecting hepatotoxicity caused by an idiosyncratic reaction to sodium valproate";

(d) "*Dr Tan's opinion was that no regular monitoring was necessary because no evidence supported its value. Dr Tan agreed under cross-examination by counsel for the family that it was reasonable to rely on blood testing with normal parameters performed 6-12 months ago as a baseline. He considered that Dr Walsh's plan for testing at 2 and 4 weeks was reasonable on its face (albeit Dr Tan considered that if it was going to be done, the first four weeks would not represent that period in which the patient was at greatest risk (see p.26 of submissions of counsel assisting)). Dr Tan considered that it was uncertain that any routine testing would have detected Mrs Doherty's liver injury before she developed symptoms, and it would have been coincidental had it done so (see p.27). Dr Tan accepted under cross-examination by counsel for Dr Walsh that Dr Walsh's practice in ordering blood tests was substantially similar to the guidelines by Gelisse and Genton, and exceeded his own practice*"; and

(e) "*Dr McLaughlin's opinion is set out at paras 82 – 87 of the submissions by counsel assisting. In short, he considered that Dr Walsh's reliance on liver function tests taken in April 2019 was reasonable. The testing proposed by Gelisse and Genton (2 and 4 weeks) was Dr Walsh's initial plan, and although the testing which actually occurred (at 18 days) was at some variation to this, it was not to a significant degree. Dr McLaughlin said that Dr Walsh's practice mirrored his own. Dr McLaughlin also expressed the view that the Guidelines proposed by Gelisse and Genton 'are the best to date' (see ex. D.7, p.5). Of those to express an opinion on the issue, Dr McLaughlin has the greatest clinical and academic knowledge of valproate induced hepatoxicity, having been been part of a team of investigators based at the Department of Medicine, University of Queensland who published journal articles of original research on the metabolism of sodium valproate during hepatoxicity and in healthy volunteers from 1990 to 2001. His doctoral thesis focused on a specific route of metabolism of this medicine and its likely role in hepatotoxicity (see ex. D.7, p.1). His opinion on the utility of testing, the appropriate regime, and the adequacy of Dr Walsh's monitoring, should be preferred*".

(f) "*Dr Walsh's regime for monitoring Mrs Doherty mirrored, or exceeded, his peers. The proper conclusion is that his monitoring was appropriate*."

101. I find as follows:

(a) Having regard to the testing recommendation in the Australian PI for sodium valproate, since Mrs Doherty did not have liver enzymes tested immediately prior to commencement of sodium valproate on 1

November 2019, and only had one test performed between then and 9 April 2020, the frequency of testing could not be said to be in accordance with the advice in the PI or the information provided by the TGA;

(b) That said there are other, more contemporary Guidelines which are premised on the recognition that, although routine monitoring of liver enzymes during valproate therapy is a common practice, the diagnosis of hepatotoxicity depends mostly on early recognition of the clinical features, which include nausea, vomiting, anorexia, lethargy, and at times loss of seizure control, jaundice, or oedema. See, for example, the recommendations of Gelisse and Genton, which include the recommendation for blood testing prior to the commencement of treatment and at one month after, with further blood tests undertaken only if significant clinical symptoms arose. In this regard I acknowledge the submission of Counsel for NOK to the effect that regularly testing may have kept the monitoring of symptoms front of mind for Mrs Doherty, her family and her GP, but I do not think it is likely that would have caused Mrs Doherty to report any symptoms earlier than was the case (or that such would have been apparent to her GP) since, for the reasons discussed above, it is unlikely clinical symptoms manifested until the two weeks prior to her returning the deranged LFTs on 9 April 2020;

(c) Strictly speaking, Dr Walsh also did not comply with the Gelisse and Genton recommendation. However:

  (i) In the absence of any change in Mrs Doherty's medical condition/ health that would suggest a change in her liver function, Dr Walsh's reliance of the LFT results of April 2019 was adequate as a pretreatment measure or indication of Mrs Doherty's liver function in November 2019; and

  (ii) Dr Walsh's initial plan was for laboratory testing at 2 and 4 weeks following the start of sodium valproate. Although this plan was not adhered to, with Mrs Doherty undergoing a single test at about 18 days following the start of valproate, this ought not be considered a significant departure from the recommendation for testing at 1 month;

(d) It is not clear whether Dr Walsh had the Gelisse and Genton recommendation in mind when he set the initial plan for laboratory testing, but as it turned out, the laboratory testing/monitoring that Mrs Doherty underwent was more or less in line with that recommendation and, thereby, within the scope of what those authors considered to be adequate and appropriate practice;

(e) Added to this, there is little support (if any) in the literature for the utility of serial laboratory testing at the intervals suggested by the PI/ TGA and Dr Sethi for the detection of valproate hepatotoxicity in a patient;

(f) Further, there seems to be a range of views amongst Neurologists as to what is considered an appropriate level of laboratory testing/monitoring;

(g) Dr Tan describes his own view as a "*rather laissez-faire view that however often the patient's general practitioner requests testing is often enough,"* although he referred to Dr Walsh's initial plan was a "*bit curious*" because it only covered the first four weeks of Mrs Doherty using sodium valproate. His reason for this was that such testing did not reflect the whole of the period when the patient is at high risk of developing problems. The single test that was performed was inadequate for predicting that there would be no adverse response to the sodium valproate in the first 3 – 6 month period. Although his evidence appears somewhat contradictory, I take Dr Tan's opinion to be that laboratory testing is of no utility at all in detecting valproate hepatotoxicity in a patient;

(h) Dr McLaughlin considered that Dr Walsh's initial plan for laboratory testing was reasonable and mirrored his own practice;

(i) Dr Sethi's opinion that there should be regular, two-monthly, laboratory testing in the first 6 months is a representation of the guidelines he cites but overlooks the nuance that serial testing at that interval may not detect sudden and acute onset of valproate hepatotoxicity, as appears to have occurred in the case of Mrs Doherty;

(j) Dr Skoien acknowledges the "hit and miss" nature of serial testing at the intervals proposed for the detection of sudden and acute onset of valproate hepatotoxicity, but his assertion that serial testing should be performed nonetheless because "*on average, you may also be catching it just in its early stages, well before the injury becomes severe"* is not supported by any data and is, with respect, without reason unless the serial testing was very regular (e.g. fortnightly);

(k) The most effective means for the early detection of sudden and acute onset of valproate hepatotoxicity is to watch for clinical signs and symptoms in the patient. As I have already found, having regard to his usual practice, Dr Walsh's education of Mrs Doherty about the clinical signs and symptoms of liver injury was adequate and appropriate;

(l) The sudden and acute onset of valproate hepatotoxicity in a patient is rare;

(m) Although:

(i) Dr Walsh's plan for laboratory testing was not in accordance with the PI and TGA recommendations; and

(ii) the single test that did occur was also not strictly in accordance with guidelines referred to by Dr McLaughlin based on more contemporary data and may have been inadequate on its own for

predicting that there would be no adverse response to the sodium valproate in the first 3 – 6 month period;

where:

(iii) there is little support in the literature for the utility of serial laboratory testing in detecting sudden and acute onset of valproate hepatotoxicity in a patient; and

(iv) the interval period proposed for serial laboratory testing in the first 6 months (e.g. two-monthly) leaves open the prospect that a patient who develops sudden and acute onset of valproate hepatotoxicity might fall through the gap; and

(v) the incidence of sudden and acute onset of valproate hepatotoxicity in a patient is rare;

I find that the serial laboratory testing planned by Dr Walsh, and that which occurred, was adequate and appropriate.

102. Otherwise, even if it were the case that regular serial laboratory testing had been arranged by Dr Walsh and performed in accordance with the PI and TGA recommendations (or otherwise more regularly than occurred), it cannot be concluded, to the requisite standard, that such testing would have detected valproate hepatotoxicity in Mrs Doherty at a time any earlier than was the case.

Conclusion

103. In respect of Issue 2(b) I find that Dr Walsh's education and monitoring of Mrs Doherty for the signs and symptoms of the side effects of sodium valproate, including liver dysfunction, was adequate and appropriate.

The status of Mrs Doherty's DILI as at 10 April 2020

104. Before proceeding to the next issue, it is convenient to have regard to the status of Mrs Doherty's DILI at or about the time she was admitted to the Caboolture Hospital, as that might have had some bearing on her hypothetical prognostic outcome if her treatment and management had been different to what in fact was the case.

105. The issue was most clearly articulated by A/Prof. Majumdar:[86]

> *It is unclear from the information provided when the liver dysfunction began as there was no record of blood tests being performed between 19/11/2019 and 09/04/2020. The deceased's liver tests were within normal limits on 19/11/2019 and were significantly deranged on 09/04/2020 and it cannot be determined what took place*

[86] Ex D6 BOE

*between these dates. During a telehealth (phone) consultation with the deceased's General Practitioner, Dr Velshad, on 09/04/2020 a history of dark urine was noted which may suggest jaundice, but it is unclear when this began. The deceased was appropriately referred to Caboolture hospital urgently by Dr Velshad in response to the abnormal liver test results from 09/04/2020. The initial consultation by Dr Wheldon on 10/04/2020 in Caboolture Hospital Emergency Department suggested a 2-week history of jaundice. Jaundice was not noted in consultations with Dr Velshad on 10/3/2020 or 26/3/2020. The deceased only met the accepted definition of **severe acute liver injury** (jaundice together with INR ³1.5) on **16/04/2020**. This coincided with the development of ascites detected on ultrasound on 16/04/2020, which also indicates significant liver injury. The diagnosis of **acute liver failure** requires the presence of hepatic encephalopathy, which was being actively assessed for and was not present up until the time of transfer to Royal Brisbane and Women's Hospital (RBWH) on **20/04/2020**. The first suggestion of encephalopathy being present (that is, suggesting the diagnosis of **acute liver failure**) was on **01/05/2020** and clinically confirmed on **03/05/2020**. The distinction between the diagnosis of acute liver injury and acute liver failure is important as these are prognostically different, with the former having a better prognosis in terms of spontaneous recovery without liver transplantation.*

(my emphasis with underling and in bold)

106. At the Inquest, A/Prof. Majumdar further explained:[87]

*Now, I'll just take you back to the point that you raised a little while ago in your evidence and that is that at the time of presentation on the 10th of April, Mrs Doherty's INR levels were still within the normal range and you indicated that that meant something about the acute diagnosis at that point. Can you just explain what you were referring to there in some more detail?---Yes, so the INR or international normalised ratio, is essentially a measure of clotting function. The liver produces most of the body's clotting factors and it's a very good marker of the synthetic function where there is multiple functions. The synthetic function to produce proteins is one of them. The INR provides us a very rapid assessment of liver function without many confounders. So each of the tests we use unfortunately are all have confounders or different things that may elevate them and they are not specific. So the international definition that was initially proposed by the Acute Liver Failure Study Group in the US looking for **acute liver failure**, was that you had to have jaundice, you had to have an INR over 1.5, the normal range is 0.9 to 1.3 and then onset of encephalopathy or confusion added to inadequate nitrogenous waste clearance. **Acute liver injuries**, a stage before that, where you don't have the clearance of nitrogenous waste and that is jaundice with an*

[87] T5-19, L30 – T5-10, L 21

*INR over 1.5. Before that, which is the stage where Mrs Doherty presented, is **acute hepatitis, so inflammation of the liver**. And, again, that is because without that synthetic dysfunction the degree of injury is fairly – not minimal but the liver, as you are probably aware, has a remarkable potential to regenerate or recover after acute injury and that is really apparent in people who have **an acute hepatitis without synthetic dysfunction** so they do not meet the criteria for **acute liver injury**. In those people, the chances of treating the cause or withdrawing the causative agent maybe more successful than those who have already developed severe injury synthetic dysfunction.*

*All right. So it really is a – it goes to the question of prognosis, I suppose, in terms of those three stages that you have described. And **acute hepatitis**, as Mrs Doherty strictly presented when she first presented, had a better – she had a better prognosis at that point in time than she did when she formally met the criteria for **acute liver failure**?---Yes*

*And that was when her INR was measured above 1.5 on the **16th of April 2020**, I think you have identified in your report?---That was **acute liver injury** and **acute liver failure** I think was on the 20th when there is first documentation of her having encephalopathy – – –*

*Can I – – –?---I'm sorry, it was on the **1st of May** – the 1st of May she had been actively assessed for encephalopathy on a daily or twice daily basis up until that point..*

(my emphasis with underlining and in bold)

107. I find that at the time of her presentation to Caboolture Hospital, Mrs Doherty met the diagnostic criteria for acute hepatitis without synthetic dysfunction, and subsequently progressed to satisfying the diagnostic criteria for acute liver failure with synthetic dysfunction on or about 16 April 2020, and finally demonstrated the clinical signs (encephalopathy) of acute liver failure on or about 1 May 2020, with that latter diagnosis being clinically confirmed on 3 May 2020.

108. I also find that at presentation at the Caboolture Hospital on 10 April 2020, when Mrs Doherty met the diagnostic criteria for acute hepatitis without synthetic dysfunction, treating the cause or withdrawing the causative agent may have been more successful with a better prognostic outcome compared to after the point in time when she progressed to acute liver failure with synthetic dysfunction on or about 16 April 2020.

Issue 4

Whether the treatment and management of Mrs Doherty provided at the Caboolture Hospital in the period 10 April 2020 to 20 April 2020 was appropriate

Initial presentation, review and management in the period 10 April 2020 to 14 April 2020

109. Dr Sethi opined:[88]

> *When Ms Doherty was found to have abnormal LFTs on 10 April 2020, her treating doctors at Caboolture Hospital should reasonably have considered the diagnosis of drug induced liver injury (DILI) from Epilim on admission itself and accordingly immediately ceased this agent.*

110. Mrs Doherty presented to the Emergency Department (**ED**) of the Caboolture Hospital on 10 April 2020.

111. Dr Catherine Wheldon (**Dr Wheldon**) received handover of Mrs Doherty from fellow emergency department registrar Dr Hildemarie De Bruto (**Dr De Bruto**) between 1700-1730 hours on 10 April 2020.

112. Details of the handover included that Mrs Doherty had increasing jaundice, lethargy, abdominal pain and nausea without confusion or fever. An ultrasound of Mrs Doherty's abdomen showed no obstruction. A CT of Mrs Doherty's abdomen and pelvis was completed but the report was pending at the time of the handover.

113. Dr. De Bruto had referred Mrs Doherty to both the surgical and medical registrars. At the time of the handover to Dr Wheldon, the surgical registrar had reviewed Mrs Doherty and medical review was pending.

114. The medical registrar was Dr Samuel Robins (**Dr Robins**). He reviewed Mrs Doherty at or about 1830 hours on 10 April 2020.

115. As to his review of Mrs Doherty, Dr Robins states, *inter alia*:[89]

> *In some cases, where the diagnosis is unclear or the case complex, and if the patient was acutely/severely unwell, I would discuss them with my senior for further guidance. The senior in these cases would be the medical consultant on call. On this occasion I discussed Mrs Doherty's presentation with Dr Borthwick.*
> *…*
> *My role in admitting her was to make an initial assessment and management plan and decide whether or not she needed admission and then hand her over to the accepting consultant/team….*
>
> *[Mrs Doherty] was referred to me with undifferentiated deranged liver function tests (LFTs). She had a clinical history of Hashimoto's thyroiditis, depression, laparoscopic cholecystectomy and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). She was known to a private neurologist and had*

[88] Ex D3, page 14 BOE
[89] Ex C7.5 BOE

also been seen at Sunshine Coast University Hospital by a public neurologist. She had been prescribed aspirin and sodium valproate for headaches/migraines associated with this condition by her specialist neurologist. This information is detailed in my admission notes.[90]

….

A summary of the history that I gathered from Mrs Doherty was as follows:

- *Referred into hospital by her GP for unexplained derangement in LFTs, no clear cause.*
- *Recent history of toothache treated with amoxicillin which finished 2 weeks prior to presentation (relevant since potential LFT derangement with amoxicillin).*
- *2 weeks of generalised/non-specific abdominal pain.*
- *No bleeding from the rectum but had stools change colour to pale/yellow. Dark urine. Both of these can indicate obstructive liver disease. Note that Mrs Doherty had a prior cholecystectomy.*
- *No lower urinary tract infective symptoms.*
- *Nausea without vomiting.*
- *Mild anorexia, no weight loss.*
- *No fevers, viral symptoms or infective symptoms.*
- *No intravenous drug use, no recent foreign travel, no unusual foods, not sexually active, no foreign tattoos, denied using alternative /herbal therapies, denied overdose, denied use of illicit drugs (above is screening for potential causes of viral hepatitis).*
- *Noted 2 new medications – amoxicillin but ceased 2 weeks prior and candesartan, which had also stopped 2 weeks prior to her presentation due to dizziness. (This was relevant since I was assessing and looking for a drug induced cause of hepatitis).*
- *Medication history as described in notes – CNB complex and coenzyme Q10 highlighted by me as potential causes of hepatitis/unusual medications.*
- *Social history – noted smoker, noted minimal alcohol intake (making alcohol induced hepatitis less likely).*

A summary of the examination and investigation findings that I gathered from Mrs Doherty was as follows:

[90] Ex B1.1, pages 247 – 250 BOE

- *Essentially Mrs Doherty had stable observations. On examination oxygen saturations were 90% (but in the context of a current smoker). Her heart rate was 75bpm, her Blood Pressure was 105/70 – (low side of normal but acceptable in this context). She had no temperature and a normal respiratory rate.*

- *Cardiovascular system – normal heart sounds, no peripheral oedema/swelling, no calve tenderness, normal heart rate.*

- *Mild tenderness was noted in her abdomen but no peritonism and not a surgical abdomen/acute abdomen.*

- *Mild crackles in lung bases, a common finding of varying significance.*

- *Venous blood gas – normal lactate which was reassuring, no acidosis, also reassuring.*

- *Bloods – mildly reduced platelets but not at a transfusion requirement level. However, can be part of liver failure sequalae. Normal haemoglobin, no anaemia, Mrs Doherty had normal white cells which make infection (particularly bacterial) less likely.*

- *Renal function and electrolytes were normal.*

- *Grossly deranged Liver Functioning Tests, identified as increasing since the last known set of results. It was unclear if there was an obstructive cause or not at that point.*

- *CT report of Dr Murray Bartlett dated 10 April 2020,*[91] *of the abdomen and pelvis – showed heterogenous appearance to the liver, which may represent hepatitis. There was no liver mass lesion, no pancreatitis, conclusion on summary was possible hepatitis but could not confirm this.*

A summary of my impression and management plan following my initial review/admission note from seeing Mrs Doherty was as follows:

- *My impression was likely hepatitis (as documented). At this stage (first review by me/the medical team and only a few hours after referral from ED) it was unclear what the cause of the hepatitis was.*

- *In my differential I have highlighted that likely causes of hepatitis in her case could be drug induced hepatitis or autoimmune hepatitis. Other causes of hepatitis including obstructive or viral*

[91] Ex B1.1, pages 144 – 145 BOE

seemed less likely given previous cholecystectomy and imaging did not suggest an obstructive cause as well as no real risk factors for a viral hepatitis and normal White blood cell levels, nor any fever or prodromal viral symptoms.

- *I concluded that most likely Mrs Doherty had a hepatitis caused by either an autoimmune pathology or a medication she was taking. In the context of newly deranged LFTs, if a medication was the cause it is sometimes difficult to ascertain which one. Therefore, usual practice would be to start investigating if there have been any recent new or changed doses of medications. Hence my previous line of questioning. With regards to determining the exact cause, this would be beyond the timeframe/scope of my interaction with the patient during an emergency department admission since all of these things take time to isolate the cause and a number of the tests sent off take many days to yield a result. Therefore, it would not necessarily be expected to gain an exact answer at the time of presentation or at the time that I admitted her.*

My Initial Management Plan for Mrs Doherty was as follows:

- *Admit her to the medical ward since it was unclear what the cause of her deranged LFTs was and this would need close monitoring and further investigation to determine the above.*

- *I ceased candesartan and co enzyme Q10 as potential causative agents of her deranged LFTs (candesartan was a new medication) (coenzyme Q10 is a medication that has multiple interactions and can cause LFT derangement). These medications were both non-essential medications and so I felt safe to cease at the point of admission.*

- *I obtained blood tests and requested a clotting screen for the patient since deranged LFTs can also be associated with deranged clotting factors. Due to this, I also avoided prescribing her blood thinners for VTE prophylaxis until the clotting screen was completed (if clotting factors were deranged it would not be appropriate to administer blood thinners).*

- *I requested daily LFT testing for her to monitor the trend of her LFTs.*

- *I recommended avoiding any hepatotoxic drugs including paracetamol.*

- *requested a viral hepatitis and a liver autoimmune screen on the bloods which would take several days to yield results.*

- *I considered starting prednisolone in case it was an autoimmune cause.*

- *Because of the complexity of the case, I then discussed the case with the consultant on call (Dr Ian Borthwick) at the time of admission to relay the history/exam/findings to my senior and to check that my management plan was appropriate and to ask for any further advice or recommendations from them.*

- *Following this discussion my plan was agreed with Dr Ian Borthwick with the addition of a recommendation to not start steroids at this point, adding on paracetamol levels in case of an undeclared overdose, giving some IV fluids and considering an Magnetic resonance cholangiopancreatography (MRCP), a special kind of MRI test, the following week to obtain further detailed imaging of the biliary and pancreatic system. This includes the pancreas, the pancreatic duct, the bile ducts, gallbladder, and liver.*

116. It appears Dr Robins was aware of the history that Mrs Doherty had been prescribed Epilim 400 mg (sodium valproate) in the context of her CADASIL.[92]

117. It is not clear from his statement whether Dr Robins appreciated, at the time of the initial review, that sodium valproate was a hepatotoxin (in addition to the other drugs and supplements he noted as "*potential causative agents of [Mrs Doherty's] deranged LFTs"*). I observe that Dr Robins did discuss Mrs Doherty's complex case with Dr Borthwick so, for reasons discussed below, it probably does not matter one way or the other whether Dr Robins appreciated, on his own, the potential significance of the sodium valproate being a hepatotoxin.

118. In any case, Dr Robins does not state why the sodium valproate was not ceased following the initial review and at the time of admission. I observe that it was part of Dr Robins' plan to "(*6) Avoid paracetamol/ hepatotoxins*"[93], which would include avoiding sodium valproate. Again, I note that it was documented by Dr Robins that " *D/W Dr Borthwick – agrees [with] above plan*."[94]

119. Despite the plan to avoid hepatotoxins, the clinical record reveals the following:

    (b) On 10 April 2020, Dr Robins ordered sodium valproate 400mg, which was administered at or about 2055 hours (prior to admission to the ward);[95]

[92]Ex B1.1, page 247 BOE
[93] Ex B1.1, page 250 BOE
[94] Ex B1.1, page 250 BOE
[95] Medication Chart, Ex B1.1, page 333 BOE

(c) Dr Robins prescribed, as a regular medication, sodium valproate 200mg EC Tablets, 400mg Oral At Night (2000 hours), commencing from 11 April 2020;[96]

(d) The indication for the said prescribing of sodium valproate was "*for migraines*";[97]

(e) It is recorded that the said prescribing of sodium valproate was part of the doctor's plan on admission;[98]

(f) Sodium valproate was subsequently administered as follows:[99]

(i) 11 April 2020, 400mg at 1936 hours;

(ii) 12 April 2020, 400mg at 1850 hours;[100]

(iii) 13 April 2020, 400mg at 1943 hours;

(iv) 14 April 2020, 400mg at 1920 hours;

(v) 15 April 2020, 400mg at 2042 hours; and

(vi) 16 April 2020, 400mg at 1915 hours.

120. At the Inquest, A/Prof. Majumdar put forward the following hypothesis:[101]

> *It has been suggested by some others who have given evidence, including treating medical practitioners, with the benefit of hindsight that in considering that drug induced liver injury category of potential differentiated causes in those early stages that sodium valproate should have been stopped immediately upon presentation on the 10th of April. I understood from your evidence you were perhaps a little more conservative, if I could use that term, than that. Do you have any comment to make about those that have expressed the view that valproate should also be immediately stopped?---Yes, I think my understanding of what the situation involved, this is a lady who had been on the drug for six months, as mentioned. There is still, you know, a whole host of causes that hadn't been ruled, and again I don't know the turnaround time for results to come back, but there's time – was time to establish a drug time, again it wasn't documented in the medical notes when that was done but in terms of other drug and herbal over the counter medications, they often can cause a similar syndrome or similar presentation. The third thing to say is that it's not unreasonable when people are on a drug for a condition that is complicated to be sure that it can be safely stopped. I think that might have been the – you know, putting myself in the shoes of the*

[96] MedChart printable Medication Chart, Ex B1.1, page 335 BOE
[97] Ex B1.1, page 339 BOE
[98] Ex B1.1, page 339 BOE
[99] CRIS Report, Ex B1.1, page 347 BOE
[100] It is recorded that this dose was "*administered at doctor's request*."
[101] T5-21; l50 – T5-22, L40

treating team, there might have been some reluctance to stop it early given you see the diagnosis of CADASIL and the patient is on valproate, which you assume is for seizure prophylaxis, which actually was not the case for this lady as it turned out. Perhaps that conversation with the neurologist didn't happen until a few days later. So I do understand how it can happen. If someone called me tonight and said, look, we have a patient with acute hepatitis in the Emergency Department, she's on valproate, would I stop it straight away? The answer is most likely not until I had further history and further understanding before I stopped a potential medication that might result in further problems. The association, I guess, for non-neurologists with CADASIL and valproate is the assumption that CADASIL has caused a seizure focus in the brain and this patient is taking valproate to prevent seizures. That would be the general medical assumption, which was not the case in this – in Mrs Doherty's notes from her – or letter from her neurologist. It was due to migraines rather than stroke prevention – sorry, seizure prevention, I should say.

Can I – arising out of that, which is what you have just indicated, can I put this to you? If you were confronted with a patient with one of the differential categories of injury was that of a drug induced liver injury who was on valproate but were not clear why that was the case on the history that was provided or else not clear on whether it was safe to cease the drug, even though it might be the [causal] agent, can I put this to you, it would have been an opportunity at that early stage to consult directly with prescriber of that drug to ascertain its purpose and whether or not it was safe to cease at that time?---<u>Yes, I agree a conversation with the prescribing specialist should have taken place.</u>

(my underlining)

121. There is no record of Dr Walsh having been contacted to ascertain the purpose for which sodium valproate had been prescribed.

122. Dr Walsh states that he "*was not contacted by the Caboolture Hospital at any time*."[102] He says that he "*was only contacted by the [RBWH] on one occasion in May 2020 by which time Mrs Doherty was in extremis*."[103]

123. Had Dr Walsh been contacted, it is likely it would have been confirmed to the practitioners at Caboolture Hospital that the prescribing of sodium valproate was for the purpose of symptomatic treatment of migraine, or as a prophylaxis for migraine (which appears to be the indication for which the drug was prescribed at the hospital in any event), as opposed to it being prescribed, for example, to control seizures.

[102] Ex C4.1, paragraph 146 BOE
[103] Ex C4.1, paragraph 154 BOE

124. Albeit in a slightly different context, I observe that Dr Walsh gave the following evidence at the Inquest:[104]

> *…on 9th of April 2020, Mrs Doherty presented to Dr Delshad with a cluster of clinical signs that were – included those that we've been talking about as indicators for liver injury, for example, the anorexia, the nausea. The dark urine, etcetera. And there's various, I guess, histories provided about duration of those, including up to two weeks duration. I just want you to assume that for the moment, you indicate there that you were not notified about that presentation nor the LFT results that were available the following day on the 10th of April. First thing I want to ask you is, would you expect to be notified by the general practitioner of that presentation and those findings on LFT's?---If a patient was on a medication that can have liver injury that I had given, it would be nice to have known that. Had I had an opportunity to be involved, I may have been more vociferous in the management. But I was not given the opportunity and I'm not blaming anyone particularly.*
>
> *No?---But it it's the case.*
>
> *I guess you've – you've half answered my next question. If you had been informed of the LFT findings on the 10th of April. And I guess in the context of your understanding that valproate might result in liver dysfunctional injury, what do you think you would have done?---<u>I would have called the GP immediately and – or the hospital, wherever the patient was, and made sure that they'd considered valproate as a possibility and seek advice regarding it.</u>*
>
> (my underlining)

125. Later, under cross examination by Counsel for NOK, Dr Walsh responded to questing as follows:[105]

> *The information suggests Mrs Doherty went to Dr Delshad. And said that she had about two weeks of – and I'll go to the date just to be sure. This was on – excuse me a minute, Doctor. This is the 9th of April, 2020, and she told Dr Delshad that she had two weeks of nausea and abdominal pain and anorexia, dark urine, and constipation. You were never informed of that consultation, where (sic) you? If you hadn't been, what – I think you answered this earlier, would you have contacted Dr Delshad directly and – and immediately?---In – given – yes, absolutely. And the patient. Had I known that.*
>
> *…..*
>
> *And that isn't one of the reasons for that perhaps that testing, whilst not everything is used, in addition to someone having clinical symptoms?---In – so, if I can just again go back to the two types of liver*

[104] T1-27; LL 1 -23
[105] T1-37; L 26 – T1-38, L 10

injury. One is the tolerance which the patient had clearly tolerated because they were well and not unwell when they'd seen the general practitioner and the bomb. The presentation, the history, the fact that Mrs Doherty was unwell for a relatively short period of time. Four or five months after starting the valproate, was that this was the bomb. This was not a tolerance issue. This was the sudden bang. Had I, at that point, been informed, there is no question in my mind that I would have added voice to ceasing the valproate, hospitalisation, which I believe Dr Delshad did properly. But I may have been able to expedite in the hospital system. Because normally, and this is an observation of mine, when a general practitioner sends a patient in, the hospital will do the stuff. But when a consultant calls another consultant in a hospital and says, "You really need to look at this, I'm worried that something bad is going on", action happens more quickly. And that's not to denigrate general practitioners. But this is – if I had the opportunity to do so, I would have.

(my underlining)

126. Having regard to this evidence, I find that had Dr Walsh been contacted by the medical practitioners at the Caboolture Hospital it is likely that, in addition to confirming the purpose for which sodium valproate had been prescribed, he would have recommended ceasing the drug.

127. Returning to the evidence of A/Prof. Majumdar at the Inquest:[106]

Okay. If the information had been conveyed that it was being used for the, if I can put it this way, symptomatic management of migraines as opposed to seizure control, would you have a different view about ceasing it earlier than was the case in this case?---Possibly, as long as the more common issues had been ruled out. Again, viral hepatitis serology is something that comes back very quickly. So acute hepatitis B, for example, it does a history of that. But, yes, I would – if there is confidence in the safety of being able to stop the drug without invoking seizure activity then, yes, I perhaps would have considered stopping it earlier.

And would that be the case even if the viral causes still hadn't been ruled out at that stage?---Possibly, yes. Yes.

Yes?---It's hard to say.

Okay.

DEPUTY STATE CORONER: Before you move on, Mr Schneidewin, I think in this instance the drug was actually not just prescribed for symptomatic treatment, it was prophylactically prescribed. Does that make a difference to the Doctor's answer?

[106] T5-22; L 43 – T5-24; L4

MR SCHNEIDEWIN: Doctor, did you hear her Honour?---Yes. If it was prophylactically prescribed, yes, that's another reason to be more confident in ceasing the drug.

DEPUTY STATE CORONER: Thank you.

MR SCHNEIDEWIN: …... I think in your report you say, if I can just take you to it, on the third page in response to question 3, you indicate there that by the time the INR level had increased further on the 16th of April 2020, that is when it reached a level above 1.5, and at which point acute liver injury was strictly diagnosable, you indicate there that it may have been reasonable at that time to cease the valproate. Is that the latest that you think the valproate should have been ceased?---Well, I guess that – to me that felt like the earliest situation where, from like gathering the notes, the cause was still undifferentiated. There was a suspicion potentially of CMV, again which is a very uncommon cause of acute liver injury, very common cause of acute hepatitis, but once you start to get the synthetic dysfunction, you know, I guess CMV becomes less of a – still a relevant differential – but less of a causative agent that can cause such severe liver injury. Again we have transplanted in Australia CMV hepatitis, but not in mass patients, so it does happen, but again it's not the – it wouldn't be the primary diagnosis that I would be chasing. Certainly as the INR had gone up, I would be stopping all potential causes by that stage and that risk-benefit of ceasing a chronic or a long-term medication that may have benefit versus, again, if you're in the situation and you go through all the list of medications that could potentially be causing liver injury, you would often take patients off everything that they're on long-term. And so it does require a bit of clinical judgement of when to cease something based on the risk-benefit profile. Certainly by the time the INR is going off then you should try and stop any potential of hepatotoxin. And so that's why I made that distinction for the 16th. Again, if the reason was prophylaxis and that was clear from the very beginning then that would be a reason to stop earlier. And also when a cohesive drug timeline had been taken, one of the more common emerging causes for this kind of presentation is actually over-the-counter herbal supplements, which then often is not apparent to most people when they get asked what their medications are, what their herbal or natural remedies may cause this situation. So I can understand there being a little bit of reticence in the early period from, again, this is all reading between the lines of what was presented. But, you know, as you know, medical records can be quite scant from the emergency department about these things. I'm sure someone would have taken a drug timeline; it just wasn't formally written down in the evidence that I got.

(my underlining)

128. Later in his evidence, A/Prof. Majumdar stated:[107]

> *DEPUTY STATE CORONER: ….. I note that the medical records show that the sodium valproate was actually prescribed for migraine at Caboolture hospital as early as the 11th of April 2020. Does that change anything that you've obtained from this doctor?*
>
> *….*
>
> *DEPUTY STATE CORONER: There was some discussion about whether or not Dr Walsh or the prescribing -- the prescriber of the valproate ought be contacted to see what it was prescribed for and those sorts of things, but it seems to me that the – at the very first ward round undertaken there was the consultant, I would have thought, was alive to the fact that it had only been prescribed for migraine and not for seizure.*
>
> *MR SCHNEIDEWIN: Yes. Doctor, I think the question that her Honour has raised is, if we accept that from early after admission to the Caboolture Hospital, the prescribing of, or the ongoing prescribing of sodium valproate was for the purpose of the migraine, so the symptomatic treatment of migraine, as opposed to it being for, you know, seizure Control or any of – or any other reason. Would that have – does that change your view in any way as to the question – the weighing up of the risks associated with ceasing that drug earlier on compared to the benefit that the patient might be receiving? So, if it's for that purpose and it's understood to be being given for that purpose, does that change your view in terms of whether it should have been ceased at that earlier time from the 10th of April?---<u>I think, if the reasons were established from the outset, then, you know, you would entertain the – that risk-benefit profile, stopping the drug, you know, would favour potentially stopping it earlier, yes</u>*
>
> (my underlining)

129. Mrs Doherty was admitted to the Medical Ward under Dr Borthwick, Consultant Physician, at or about 2235 hours on 10 April 2020.

130. Dr Borthwick and his team took up daily review of Mrs Doherty from on or about 11 April 2020.

131. On the issue of the then possibility that Mrs Doherty's hepatitis was drug induced and the decisions made around ceasing certain medications (but not sodium valproate initially), Dr Borthwick provided the following evidence at the Inquest:[108]

> *All right. And in terms of the drug induced causes, what could they possibly include, having regard to what you understood about Mrs*

[107] T5-34; LL 5 - 31
[108] T2-9; L 45

Doherty's history at that time?---Well, antibiotics are often found to be causing liver damage but usually that resolves with cessation. There's a few other drugs like statins which are very widely prescribed these days and a tiny, but not insignificant, number of people get affected by that and usually go off it with the muscle aches and pains that are associated with that and they usually recover with cessation as well. So they are kind of examples of drugs we think about that ordinarily a vast majority of the population tolerate quite well. But there always seems to be someone who doesn't so you can never be quite 100 per cent sure that something is clear. We all know Panadol, which is a very safe drug, if you take a big overdose of it, it will destroy your liver and you don't survive. So it's the context we think about these things.

Well, just focusing on the antibiotics for a start?---Yes.

The history indicated that Mrs Doherty had undertaken a recent course of Amoxicillin, I believe?---That's correct.

And you understood that to be the case?---Yes.

And that it had been ceased prior to the presentation, some weeks prior, I think, is the – – –?---Within two weeks I think is what's written, yes.

Within two weeks of the presentation. Would that exclude – the fact that it had been ceased two weeks prior to the presentation, would that exclude Amoxicillin as a likely agent causing drug induced liver injury?---Not necessarily, but you would certainly have it lower down on the list of risks. I've had patients with Amoxicillin toxicity before and it can persist for a little while.

What about the statin Mrs Doherty was taking, was it a possible agent to cause the injury?---Well, again, it's rare but statins can cause liver damage and muscle damage.

I think there was a decision to withhold the statin – – –?---Yes, there probably was. Yes.
– – – given Mrs Doherty's presentation I think by the 11th of April, if I am correct. Is that what you understood the history to be?---That's correct, yes.

Yes. And also you would have been aware that Mrs Doherty was taking sodium valproate at the time of presentation?---That's correct.

Now, before I ask you any more question about sodium valproate, can you just provide a summary of your experience of patients that you have managed who might taking sodium valproate and the side effects that you are aware of that can be caused?---Okay. Well, I haven't seen a case before this one or since of valproate toxicity. I do

prescribe it quite a lot in a different group of patients who have behavioural disorders or complaints, in the older population with more moderate to advanced dementia and I often will prescribe that over the course of days up to a final dose of 1,000 mg a day. I will just do that on a stepwise process, under supervision. These people are in hospital for that time. Obviously there's not many of them but it's well known as a mood stabiliser and has a very high success rate in settling people down.

…..

You would have understood, though, at this time, although you had not seen it yourself, that sodium valproate was an agent that could cause liver injury?---Yes, it could. I guess my feeling about most medications is you're looking for high doses to be administered that might be more likely to cause problems but, as we know, sometimes even much smaller doses of medications can still cause harm.

If I could put this to you. Were you aware at the time that the kind of liver injury that might be suffered from a patient taking sodium valproate is not related to dosage levels?---Well, it often doesn't have to be but typically the higher the dose the more likely the side effects and that's the way most medicines are labelled.

Yes. And you were aware what dose Mrs Doherty was taking of the sodium valproate?---I think it was 2 x 200 mg so a modest to small type size of dose, at least compared to what I'm used to.

Yes. You made a decision, or the team made a decision, in those first few days, I think on about the 11th, I have already mentioned this, to take Mrs Doherty off the statin, what is called the statin, and also another drug, I believe. What – why was there a consideration to leave her on the sodium valproate at that stage?---Probably because at that point we thought any benefit accrued from it was outweighing what was going on. It was a small dose and at that point it didn't really look like the likely culprit, which wasn't revealed until much later, as you know.

In terms of the benefit that you understood that Mrs Doherty was receiving from the sodium valproate, what was that so far as you were aware?---Well, I gather she'd been started on the valproate <u>for migraine prophylaxis</u> and, as you know, they may have decided that with her other condition of the CADASIL that may have been an appropriate medication for her at that time.

All right. <u>So is it the case that you were – or the team considered that the benefit she was receiving from the sodium valproate was the symptomatic relief of her migraine headaches at that stage?---Mmm</u>.

(my underlining)

132. Under cross examination by Counsel for NOK, Dr Borthwick responded:[109]

> *And you were aware, weren't you, that she had had a couple of consultations in the months leading up to being admitted to Caboolture Hospital with a neurologist, a Dr Walsh?---I saw that via the registrar's note that she'd seen somebody back in November 2019, and it was written there in the notes that she'd been started on valproate – – –*
>
> *And you – – –?--- – – as a migraine prophylaxis.*
>
> *Yes. Was that your understanding of why she was on sodium valproate?---That's right, yes.*
>
> *Did you see any need yourself to contact Dr Walsh to obtain the history about Ms Doherty or her treatment?---Not particularly. We quite commonly see po – see people on migraine prophylaxis so the – there's – a couple of other anti-seizure medications are also used and – and they come through the system and it's an incidental thing while they're there. So the focus was not so much on the drug. We could see the drug was there. I think we'd see the – in the past there'd been normal liver function. I think – also, I hadn't seen Ms Doherty before. She'd been in for a cholecystectomy I think in 2017.*

133. In respect of Dr Borthwick's and/or his team's management of Mr Doherty's case, I find that:

    (a) Dr Borthwick aware Mrs Doherty was taking sodium valproate;

    (b) Dr Borthwick was aware that sodium valproate could cause liver injury i.e. that sodium valproate was a hepatotoxin;

    (c) Dr Borthwick considered Mrs Doherty to be on a moderate to small dose of sodium valproate, at least in comparison to what he had been used to prescribing;

    (d) Dr Borthwick understood that sodium valproate hepatotoxicity "*often doesn't have to be*" related to dosage levels, but also considered the higher the dose the more likely there would be side effects;

    (e) Dr Borthwick was aware that the purpose for which Mrs Doherty had been prescribed sodium valproate was for "*migraine prophylaxis.*" Being so aware, he did not consider there was any particular need to contact Dr Walsh to obtain a history;

    (f) In the early period following Mrs Doherty's admission to Caboolture Hospital, the medical team did not consider sodium valproate a likely cause of Mrs Doherty's hepatitis, seemingly because of the relatively low dose she was taking, and "*probably because at that point we thought any benefit accrued from it [prophylaxis against migraine] was*

[109] T2-19; LL 11 - 29

outweighing what was going on [a serious liver injury potentially caused by a hepatotoxic drug]."

134. At the close of evidence at the Inquest, I entered the following exchange with Counsel for the Caboolture Hospital, Ms Robb KC:[110]

> *DEPUTY STATE CORONER: Thank you very much. Our condolences of course to the family, and thanks for the kind words. Just one last thing before I rise, Ms Robb, for your client there's one issue that continues to trouble me particularly and I'll just draw it to your attention so it can be dealt with in submissions. I am still struggling with the cessation of the two, the statin and the CQ10 on presentation by the PHO in conjunction with the consultant physician, but given particularly the evidence of this expert we've just heard from, why all of the drugs weren't ceased on the 10th, and I accept there is a lot of evidence about what the sequalae may well have been had all drugs been ceased on the 10th, but it's an issue for me that I'd like dealt with clearly in subs.*
>
> *MS ROBB: Your Honour, I can only deal with it clearly to the extent the evidence allows me to. And I suspect that that will involve a degree of making submissions about context and circumstances that include the weight of the expert evidence has been that the approach of the general physician on and over that weekend was reasonable and that the decision to cease sodium valproate was made reasonably. Was it desirable it was ceased earlier? That is unequivocally the case. But the expert evidence, I would say, assists my client in that regard, your Honour. Again, it would have been – I don't think your Honour would consider making a recommendation that all medication is ceased on presentation to a hospital where a drug-induced liver injury may be one of the differential diagnoses.*
>
> *DEPUTY STATE CORONER: One might, Ms Robb, when the drugs in question aren't drugs that are – can't otherwise be – the conditions with which one suffers can't otherwise be managed as an inpatient.*
>
> *MS ROBB: I think, and this is also out of submissions, the evidence will – a search of a calendar in the piece unfortunately demonstrates the day she presented was also Good Friday, which may – and so which means it was also Easter Monday, so further informs – so it may be – I mean we don't – loathe to suggest recalling Dr Borthwick, but he may have a particular experience with statins that he doesn't have with valproate. And although we know, based on the document that I'm grateful to your Honour for taking me to, that Mrs Doherty had clearly given a history, there was a question I have for that history, which doesn't mean that it wasn't accepted or that it was being*

[110] T6-31. L12 to T6-32, L8

seriously queried, but this is the patient's history on intake the day before seen by the physician on Easter Friday. So, as to why exactly it was not stopped, I'm not sure I'll be able to tell your Honour that.

DEPUTY STATE CORONER: I don't think the evidence is that clear, Ms Robb.

MS ROBB: No, but as to whether or not it was reasonable not to, I will be making a submission that, again, whilst unfortunate, that it was.

135. By her written submissions of 14 February 2025, Ms Robb KC did not advance this issue further other than to state that "*counsel assisting addresses this matter and sets out the relevant evidence at pages 35 to 49 and [219], [220], [223] and [227](e)(iii) of the closing submissions. In addition to the oral submissions made in the relevant exchange with her Honour on 16 April 2024, the submissions of counsel assisting are adopted*."

136. Counsel for NOK submitted:[111]

    (a) "*Generally, the treatment and management of Mrs Doherty while at the Caboolture Hospital was appropriate*";

    (b) "*Hospital staff noted on admission that the sodium valproate was prescribed for migraines, kept an open mind about possible diagnoses, conducted a variety of tests, consulted broadly, ceased sodium valproate (eventually), and made arrangements for Mrs Doherty to be transferred to a tertiary hospital that had more experienced specialists and the capacity to perform liver biopsies*";

    (c) "*Sodium valproate should have been withheld when or shortly after it became known that it had been prescribed to Mrs Doherty for migraine relief*"; and

    (d) "*Efforts should have been made to consult with Dr Walsh*."

137. Having regard to the evidence available, I make the following findings:

    (a) Dr Robins' review, assessment and plan for Mrs Doherty's treatment and management at the initial consultation was adequate and appropriate;

    (b) More particularly, Dr Robins' consideration of the likely causes of Mrs Doherty's hepatitis was appropriate. In that regard Dr Robins considered that her hepatitis could have been drug induced hepatitis or autoimmune hepatitis. He thought that other causes of hepatitis, including obstructive or viral causes, seemed less likely given previous cholecystectomy and imaging did not suggest an obstructive cause, as well as there being no real risk factors for a viral hepatitis, with normal WCC levels, no fever, and no prodromal viral symptoms. I find that Dr Robins was "*on the right track*" from the outset;

[111] Paragraph 3(b)(i) – (iv), written submissions of the Doherty Family dated 13 November 2024

(c) Where sodium valproate had been prescribed for prophylaxis against migraine, it could have been safely ceased and without material harm to Mrs Doherty, except for potential recurrence of migraine;

(d) There is no evidence the medical team gave any detailed consideration to the risks/ benefits of keeping Mrs Doherty on sodium valproate other than, it seems, a consideration that she was on a small dose and at that point *"it didn't really look like the likely culprit";*

(e) With the knowledge from the outset that the purpose for the sodium valproate was for migraine prophylaxis (as opposed to, for example, seizure control), and with the knowledge that sodium valproate hepatotoxicity "*often doesn't have to be*" related to dosage levels, in giving consideration to the risks/ benefits of continuing sodium valproate, it would have been appropriate to cease the drug at admission (or soon thereafter) along with the other potentially hepatotoxic drugs and agents that were ceased (which, according to Dr Borthwick, were not particularly likely to be causative agents in any event);

(f) In giving appropriate consideration to the risks/ benefits of continuing sodium valproate, it would have been appropriate to contact Dr Walsh[112] at the time of admission (or shortly thereafter) to seek his input, particularly if there was any concern that ceasing sodium valproate might have been unbeneficial to Mrs Doherty but, in any case, to confirm the purpose for which the drug had been prescribed;

(g) If Dr Walsh had been contacted, it is likely that he would have:

    (i) confirmed to the medical team at Caboolture Hospital that the prescribing of sodium valproate was for the purpose of providing a prophylaxis for migraine; and/or

    (ii) recommended the cessation of sodium valproate;

(h) In not ceasing sodium valproate at admission (or shortly thereafter) Mrs Doherty received up to seven doses at 400mg daily[113] before her condition was noted to have progressed from acute hepatitis to synthetic liver dysfunction (acute liver injury) with the return of the INR test results of 16 April 2020. It may be that Mrs Doherty might have progressed to synthetic liver function at an earlier time but that is unknown because INR testing was not performed in the period 10 April 2020 to 16 April 2020; and

(i) The failure to cease sodium valproate at the time of Mrs Doherty's admission to the Caboolture Hospital (or shortly thereafter) was inadequate and inappropriate treatment and management of her condition.

[112] As well as other prescribers of other drugs being taken by Mrs Doherty as may have been considered necessary
[113] Starting on 10 April 2020 and ending on 16 April 2020

Infectious diseases involvement

138. At Inquest, Dr Borthwick stated:[114]

> *I mean, when we hadn't seen much change by after the weekend, two or three days, then my thoughts were I should ask for other expert help, which is what we did over the next few days. So we had an infectious diseases consultant available, we had a hepatologist available I think from the Wednesday, so they were invited to come and give us some advice about where to next, because it is obvious we weren't pinning down the cause in those early days.*

139. Dr Nastaran Rafiei (Dr Rafiei), Infectious Disease Specialist, became involved in Mrs Doherty's care on 14 April 2020, approximately 4 days after her admission. Dr Rafiei states:[115]

> *On 14 April 2020, I was requested by the medical team to review Mrs Doherty regarding a possible infective cause for her hepatitis. Before I undertook that review of Mrs Doherty, I discussed the review which had previously been undertaken by my registrar, Dr Chap.*
>
> *In taking the history of Mrs Doherty, I found that Mrs Doherty had had a toothache 5 weeks prior to presentation to hospital and had been prescribed a course of amoxicillin, an antibiotic, for 10 days. She described becoming unwell after this with nausea, shakes and jaundice. It was unclear whether the shakes she was describing were in fact rigors associated with fevers. She had no change in her usual cough. She denied any alcohol intake, however her partner told me that she drank 6 – 8 beers per day.[116] She denied any recreational drug use. I found that she had travelled to Millmerran at the end of February, she lived in Woodford, and had had tattooing in December 2019.*
>
> *On my examination of Mrs Doherty, I found she was afebrile, had scleral icterus (yellow eyes) and palmar erythema (red palms). I could not detect any enlarged lymph nodes nor a rash. Her abdomen was soft, with tenderness over the liver edge. She had a few crepitations (crackles) over the left base of her lung.*
>
> *On my review of the results of Mrs Doherty's investigations, I noted that she had a bilirubin of 244 umol/L, conjugated bilirubin of 146 umol/L, AST 2100 U/L and ALT 1470 U/L. She had negative results to Hepatitis A IgM, Hepatitis B surface antigen and Hepatitis C IgG. She had positive CMV IgM and IgG.*

[114] T2-12, LL 26 -31
[115] Ex C7.4 , starting at paragraph 9 BOE
[116] Mr Doherty disputes this history, but ultimately nothing turns on the issue

Mrs Doherty had had abdominal imaging which showed a normal sized spleen and liver with heterogenous appearance but I could not ascertain the liver size.

My impression was that although an infection was a possible cause for Mrs Doherty's acute hepatitis, that the differential list remained broad at that point in time. It was possible but not certain she was describing an infective syndrome prior to hospitalisation. In light of the information provided by her partner about Mrs Doherty's alcohol intake, I felt the differential diagnosis also included alcoholic hepatitis and drug induced liver injury due to amoxicillin due to the timing and the history provided.

Furthermore, I felt that the Cytomegalovirus Immunoglobin G (CMV IgG) could be a false positive due to cross- reactivity of Immunoglobin M (IgM). I suggested further infective testing including CMV avidity, leptospirosis, Q fever and hepatitis E serology, Hepatitis B core antigen and surface antibody testing. I also recommended a gastroenterology review and adding thiamine to her medications.

140. At the Inquest, in relation to the positive CMV IgM and IgG result, Dr Rafiei explained:[117]

It may be significant or it [may] be completely non-significant. So, I think it would be helpful if I maybe explain a little bit about CMV, because it's kind of a complicated topic. So, CMV is a virus that is actually really common and it's one of the herpes viruses, or a virus from the herpes family, which is important because it means that, once you have it, you have it for life. So, you know, like cold sores, all right, like once you have it, you have it with you for life and it can wake up at different periods of time. CMV can cause a variety of different infective syndromes and by far the most – and it really depends on the patient and what their immune status is. So in an immune-competent patient like Mrs Doherty, the clinical syndrome you would see would be with primary CMV, so that's when you see CMV for the first time. And actually primary CMV is commonly asymptomatic. People won't have any symptoms at all. If you do have symptoms, generally it's fevers, feeling a bit unwell, but generally fevers would be the common thing. It's kind of like glandular fever in fact, a little bit different, but similar to glandular fever. And in fact it's a self-limited, benign, you don't really need to treat them type of disease. Now, if you do a blood test on those patients, you can see subclinical hepatitis. So their liver enzymes are up a bit, a few times the upper limit of normal, but they have no symptoms of liver disease. That is quite common that they don't have that. And there are other blood markers which you can have, like atypical lymphocytes in her blood. So that's, I guess, primary CMV. Non- primary CMV, or what we commonly think of as reactivation CMVs, and really seen in those

[117] T2-30; LL 1 - 50

patients whose immune system is very poor, so patients, for example, who've had a bone marrow transplant and we've given them very strong immune suppression. And in those patients they can reactivate CMV in particular. And there they can get, you know, again, febrile illnesses, but they are more likely to get sort of organ-specific complications of CMV, for example CMV colitis, which is affecting your bowel, or pneumonitis, or even hepatitis, particularly in liver transplant patients. So, in my – you know, what I would think is that Mrs Doherty's not going to have reactivation CMV disease, she is not in the right population cohort. Could she have primary CMV? Now, at this point, which is why I'm interested in fever history, because that's kind of pretty important to have, and I would have looked through her fever chart, because I always do, and I haven't made a note, but she hadn't had any fevers. Now, when you're in hospital, you don't have the nurse with you all the time, it's possible that you have fevers at home and we just haven't captured them. So, having said that, it really wasn't a – it wasn't really the crux of her presentation. It's really jaundice and these liver enzymes are really very high. Now, so it's certainly not classical for CMV, not common even for CMV, this would be a very, very, you know, uncommon finding for CMV. Now, the thing is that, if you look in the literature, you will always find case reports of people having very unusual presentations of things. So, is it possible? Yes. But it would be exceedingly, I think, uncommon, which is why when I write that we can do this testing, but I would keep a broad differential, I'm trying to stop people from putting their focus and their attention in this thing, yes, we can look for it because it's important, because this is an important presentation, but we need to keep an open mind and not just go down this one rabbit hole I guess.

So, can I put it to you this way, at the 14th of April, when that CMV markup was available to you, really from your perspective, all that did was raise CMV as a possible causative factor in the liver injury?---Yes.

Not that it was necessarily the more likely causative factor?---I did not think it was likely.

Yes. Compared to other potential causes, which included, at that time, drug-induced liver injury as well as the possibility of an autoimmune injury?---Yes. And I guess, for me, I'm not a hepatologist. I mean, obviously in my basic training I've gone – you know, I've read about liver diseases and I have some understanding of them, but I'm aware of my limitations in that. So, again, because I'm an infectious disease doctor, I ask people about antibiotics, so I've stuck in my mind that she'd been on amoxicillin and I know that that can cause liver injury. But really I think I'm at that limit where I'm like, I think she really needs somebody who's got more expertise in liver disease in particular.

….

So, just to cover off on the CMV possibility, you thought, as I understand your evidence or your statement, that it ought be investigated further, potentially to exclude it, or mostly to exclude it, is that right?---Yes, to sort of – to put it at rest to be honest, to – you know.

And because you're concerned that in fact what was available to you, the markers that were available to you, were a false positive?---Yes, which is common with IgMs, they're sort of notoriously cross-reactive.

(my underlining)

141. In order to exclude CMV as a possible cause of Mrs Doherty's hepatitis, Dr Rafiei arranged avidity testing. At Inquest, she went onto explain:[118]

And can you explain to me just what that involves and the purpose of doing that testing?---Yes, sure. So, when we – when our body first sees an infectious agent for the first time, we, you know, we've got an immune system which has many arms to it, one of which is producing antibodies. Our body actually produces a number of different antibody types, the two most common we test for in medicine, in clinical medicine, are IgM and IgG. IgM is the first antibody your body produces in relation to an infection. It's sort of clunky antibody. It's got lots of arms, but it's not particularly specific. So what you really want when you're fighting an infection is something which recognises that infective particle and nothing else, and binds it really well and alerts the immune system that this is what we've got try to destroy. IgM is not perfect at that, but it's fast, which is why it's useful. And then what your body does through your immune system, your lymph nodes and various other things, is it produces better and better antibodies. And then you develop IgG antibodies, which take some time to come out, and they are more specific for binding something. So – and again with different infections the timing of those for the IgM and the IgG can be different. With CMV in primary infection, it's got a relatively long incubation period, so you can actually, in primary infection, have IgM and IgG at the same time. Now, if you've got a young person who's come to you, you know, with fevers and they've got a child in daycare and they've got atypical lymphocyte, that's classical IgG – CMV and you find that, that's fine. You don't really need to do anything else for it. But in certain situations it's really important to try to figure out if this is primary infection or not. You know, for example, in pregnant women, where it's really important to find that out, because it's dangerous to the baby. So what you do is avidity testing, which is actually with – to figure out how well that IgG is binding. And the idea is that, with time, your avidity is high, meaning that you've been exposed to this for a long period of time. So high avidity means that it's not early infection, low is early infection.

[118] T2-31; LL 30 – 50 – T2-32; LL 1 - 13

And what you're looking for in terms of this liver injury, is this acute CMV, primary CMV, so that if the avidity comes back high that excludes the possibility of it being a primary CMV?---Yes, exactly. And we know that, you know, a lot of us will have had seen CMV at some point in our lives, not known about it, and we'll just have IgG floating around, yes

142. The avidity testing result was returned on or about 16 April 2020. At the Inquest, Dr Rafiei provided the following evidence about the result:[119]

Now, the CMV avidity testing result, I'm going to paragraph 16 of your statement, doctor, came back on the 16th of April 2020, so about two days after you ordered the tests. And the result, if I can put this to you, confirmed your view that CMV was not a likely cause of the liver injury. Is that correct?---Yes.

Because the avidity result was high?---Yes.

Which did not suggest – which was against the theory that this was a primary CMV infection causing the liver injury?---Yes.

143. Whilst CMV was, at that point, excluded as a cause of Mrs Doherty's hepatitis, other infectious causes were not. At the Inquest, Dr Rafiei explained:[120]

So, in my initial investigation, in my initial note, I do suggest testing for other infective causes. I have to say I didn't think any of them were particularly likely because, you know, she wasn't really having fevers. And, like I said, it wasn't really suggestive of this, but because of the, you know, I think every time you do testing for something, you've got to think of the likelihood and the severity of something. So, you know, I think in this case I was thinking, look, I think these are unlikely, but this is a really important thing that we look for. So therefore we will do that testing. It's not to say that, if they come back positive, we go, well, right, that's it. You must still interpret the result in the context in which you see the patient. So, you know, by the time it comes back and you're like now it's really been five, six days with no fevers at all. Then you're like, it makes it far, far less likely. So you can have false positives with any of these results to be honest.

Okay. Now, included in that list of other potential infective processes that might be causing the injury, and ones which you thought were not very likely, was Q fever?---Yes.

Is that correct?---Yes.

And, can I put this to you, notwithstanding your view as to the likelihood, the history that you had taken from Mrs Doherty in terms of where she resided and where she had travelled to, etcetera,

[119] T2-33; LL 28 - 37
[120] T2-33; L40 – T2-34; L 21

caused you to, notwithstanding, arrange that testing as a mechanism for excluding it as a cause, is that a fair way of putting it?---I think a negative test would have been very useful because you would have said, yes, this is – we're very happy with this. A positive test still needs to be interpreted because I think the pretest probability is low.

So, as it happened, there was an initial positive result for the Q fever; is that correct?---Yes.

And that was available on the morning of the 20th of April 2020?---Yes

(my underlining)

144. On 20 April 2020:

(a) The Q Fever testing that had come back returned a phase 2 IgM positive result with a negative phase 2 IgG result;

(b) Mrs Doherty was not seen by Dr Rafiei and instead was seen by Dr Sonet Chap (**Dr Chap**), an Infectious Diseases Basic Physician Trainee at the relevant time;

(c) A further history was taken by Dr Chap in terms of potential exposure for Q Fever. According to Dr Chap's statement, the impression was, at that time, that acute Q Fever was a possible cause of the hepatitis,[121] although there was no identifiable source from the history that was taken by Dr Chap[122];

(d) According to the record, Dr Chap's impression was "*Acute Q fever likely cause of acute hepatitis but no identifiable exposure*"[123]; (my underlining), and

(e) Further investigations were recommended to rule in or rule out Q Fever as a cause for the hepatitis, including a further antibiotic (doxycycline) to manage the Q Fever.

145. In respect of Q Fever being a "possible" or "likely" cause of Mrs Doherty's hepatitis and the plan that was entered, Dr Rafiei responded as follows in her statement and at the Inquest:

(a) It is not documented anywhere that the Q Fever serology result and the decision to commence Mrs Doherty on doxycycline was discussed with her[124];

(b) As to whether Q Fever was a likely cause of Mrs Doherty's hepatitis: "*I think that would have been very unlikely, the Q fever, because at this*

[121] Ex C7.2, paragraph 15 BOE
[122] Ex B1.1, pages 288 -290 BOE
[123] Ex B1.1, page 290 BOE
[124] Ex C.4, paragraph 18 BOE

point she would have been in hospital for 10 days, I believe, without any fevers. And that result, in fact it says it at the bottom of our pathology system, it could be early infection or this could be a false positive. And I think that it was unlikely to be, yes"[125]; and

(c) The absence of fever in Mrs Doherty rendered acute Q Fever as a very unlikely cause of her hepatitis.[126]

146. Otherwise, Dr Rafiei agreed that by the time Mrs Doherty was transferred to the RBWH on 20 April 2020, it was very unlikely that her hepatitis had been caused by an infection.[127]

147. I observe that Dr Rafiei's view as to Q Fever being a very unlikely cause of her hepatitis is not documented in the records of the Caboolture Hospital.

148. I also observe that at the ward round at 0910 hours on 20 April 2020, Mrs Doherty's presentation was documented as "*Acute liver failure ? [secondary] to Q fever/ CMV known to ID + Gastro….commenced on Doxy as per ID.*"[128]

149. I further observe that shortly prior to Mrs Doherty being transferred to the RBWH on 20 April 2020, Dr Peerbaccus and team documented the following discussion at the medical ward review of 1430 hours:[129]

> *Discussion with husband + pt regarding current findings of cause of acute liver failure. Possibility of Q-fever + CMV causing liver failure., on Doxy for that…*[130]

150. There is no documented mention that a possible drug induced cause or auto-immune cause for the hepatitis was being entertained at the ward rounds/ reviews prior to her transfer on 20 April 2020.

151. Dr Sethi opines that:[131]

> *Given that she was positive for IgG and IgM antibodies, the diagnosis of CMV hepatitis was neither reasonable nor likely. Q fever was also a very unlikely and improbable cause.*
> *…*
> *Apart from Epilim, there were no other potential causes of the deceased's severe liver dysfunction in April 2019. She did not have CMV hepatitis and/or Q-fever.*
> *…*
> *Considered prospectively, none of these other potential causes were more likely than Epilim. They did not play any causative role whatsoever.*
> *…*

[125] T2-34; LL43 - 46
[126] T2-35; L 2
[127] T2-36; LL 1-3
[128] Ex B1.1, page 290 BOE
[129] ExB1.1, page 295 BOE
[130] We note that by ExC7.3, Dr Peerbaccus otherwise appears to acknowledge that by 20 April 2020 the CMV testing which was undertaken to "*confirm the presence of the virus*" was negative.
[131] Ex D3 BOE

The timing for the exclusion of the other potential causes was not appropriate. That is to say, that they could reasonably have been excluded earlier. I shall outline my reasoning below.

On 14 April 2020, CMV serology was positive for IgM and IgG antibodies. This conclusively excluded CMV infection given that positive IgG antibodies indicated chronic rather than acute infection.

There was no evidence to suggest acute Q fever infection in this case. It was far more likely and probable, on the balance of probabilities, that she had liver toxicity from Epilim.

152. I make the observation that the avidity testing result confirming chronic, as opposed acute CMV infection, was not available until 16 April 2020. It seems this was not appreciated by Dr Sethi. Nevertheless, when this was pointed out to him at the Inquest, he remained unmoved from his assertion that CMV ought to have been excluded earlier than it was, citing Mrs Doherty's age (it was necessary to correct his understanding of her age) and the fact that she was not immune depressed as factors which made CMV "*a most unlikely cause*" for her hepatitis.[132]

153. Otherwise, Dr Sethi agreed under cross examination that, notwithstanding his view that Q Fever was an improbable cause of Mrs Doherty's hepatitis, it was reasonable to commence Mrs Doherty on an antibiotic in the circumstances where Q Fever could not be positively excluded for some time, given the testing process.[133]

154. A/Prof. Andresen opined:[134]

In the first few days of management of a hospitalised patient with acute hepatitis, results of the diagnostic tests (for infectious and other pathologies) take a variable length of time to become available. As a result, where there is not a clear favoured diagnosis, the relative likelihood of the main diagnostic possibilities does fluctuate over time as more results come to hand. On 15 April 2020, Ms Doherty's available CMV tests were a positive IgM and IgG serology result, which would have been consistent with (but not diagnostic of) acute CMV infection. At this stage neither the avidity studies nor the blood DNA PCR results were known. It was reasonable, therefore, to consider CMV as an important diagnostic possibility at that stage. …..
…
The referral for CMV nucleic acid amplification was completely appropriate. The testing for Q-fever was presumably based on Ms Doherty's semi-rural residence (Woodford) and was reasonable once more common infectious causes were excluded. Having said that, the hepatitis of acute Q-fever infection is rarely of the severity experienced by Ms Doherty…

[132] T4-52; LL 15 - 39
[133] T4-53; LL9 - 11
[134] Ex D5 BOE

….
As noted above, acute Q-fever is well known to cause hepatitis, though rarely of the severity experienced by Ms Doherty. Consideration of this possibility once CMV had been plausibly excluded was quite reasonable, as this infection is treatable with antibiotics. Although this bacterial infection is a zoonosis, direct animal contact is not necessary to acquire infection. Cases of Q-fever are seen in rural and semi-rural areas, and are presumed to be due to inhalation of the infectious bacteria from animal products in the environment …. Ms Doherty's subsequently unfavourable clinical course also makes Q-fever less likely, since there are very few reports of Q fever hepatitis being sufficiently severe to require liver transplantation or to lead to death….
…
At the time of her transfer to RBWH, CMV infection had been adequately excluded as the cause of Ms Doherty's hepatitis, as had the usual hepatotrophic viruses. Her positive Q-fever IgM result had been noted and antibiotics started accordingly.

In this context it is worth noting that IgM testing can be technically problematic, prone to cross reactivity, and otherwise unreliable. Definitive diagnosis of an acute infection by serology therefore requires IgG seroconversion or a significant rise (or fall, in late infection) in the strength of IgG or total antibody reactivity on paired (acute and convalescent) sera. Reliable diagnosis cannot be made on an IgM result alone, as demonstrated for both CMV and Q-fever in Ms Doherty's case.

Given the untrustworthiness of positive IgM results in isolation, an appropriate level of scepticism about Ms Doherty's isolated Q-fever Phase 2 IgM result was appropriate. The decision to perform convalescent testing, treat with doxycycline pending these results, and continue to pursue other diagnostic possibilities was also quite reasonable.
….
As noted above, it was reasonable to regard Q fever as a possible diagnosis, continue doxycycline, and perform convalescent serology to confirm or refute the Q fever Phase 2 IgM result. Ultimately, the IgM result appears to have been a false positive, but that was not known until the convalescent serology results became available around 25 April.

155. At the Inquest, as to eliminating CMV as a possible cause of Mrs Doherty's hepatitis, Dr Andresen gave the following evidence:[135]

So at that point in time on the 14th of April with the serology results that were available to the infectious diseases specialist, a CMV infection was a possible cause of the liver injury. You agree with that?---Yes.

[135] T5-6; LL 15 – T5-6; L 25

And until – – –?---Yes, although – although the severity of the hepatitis was a little bit disproportionate but it was certainly a possible – a diagnostic possibility.

Yes, I was going to ask you about that disproportionality separately but since you've raised it we'll deal with it now. It's the case, as I understand it from the literature that you've referred to or you've attached to your report, that it would be quite unusual or quite rare for somebody to present with this degree of seriousness of injury if it's a CMV infection. Would you agree that that's the case?---Very uncommon, yeah. But not impossible.

Not impossible. Very uncommon but not impossible. So appropriate therefore to do – to take steps to either confirm the IgM is a false positive or otherwise eliminate CMV as a possible, albeit not very likely, cause of the hepatitis as at 14 April 2020, correct?---Yes, absolutely.

And the first step towards that is to arrange for avidity testing and you've explained the mechanism by which the avidity testing will reveal whether this is an acute infection or not. And it is the fact of it being an acute infection which would make it a potential candidate for the cause of the liver injury, is that correct?---Exactly. We don't really see CMV reactivation causing a nasty hepatitis, except perhaps in a very immunocompromised host, which Mrs Doherty wasn't.

And when you talk about CMV reactivation in a patient, you mean a patient who has had the CMV infection a long time ago and it may be laying dormant in their system, and – – –?---Exactly. CMV has the – sorry.

You go on, sorry?---CMV has the biological property of latency, which means it can lie dormant and then reactivate at times of physiological stress or at times of immune compromised.

And patients where it does reactivate, very unlikely that it would cause a hepatitis condition in a patient, so what we're really looking for – what we're really looking for is an acute infection or I think it's been described by others as a primary CMV infection. Is that consistent with your view?---Yeah, exactly.

Okay. And by that avidity testing where the result is high avidity, that essentially eliminates this CMV infection or this CMV result being one which is acute or primary?---Exactly.

Okay?---That's right.

Now, the avidity results were available on the 7th – sorry on the 16th of April 2017, and you mentioned that further testing might also be

prudent. I think you referred to it as a PCR test, is that right?---Yeah, so that's a test for the DNA of the virus itself. Serology is fundamentally indirect testing whereas looking for the DNA of the virus is a direct test. It's like is there a virus in this patient at this moment?

Okay. So PCR testing might reveal the absence of the virus at all, is that what you're saying, in the patient?---That's right.

And what I wanted to explore with you is in terms of what was known by the 16th of April, that is that there was a high avidity test returned, how – to what extent did it remain possible that this might have been a CMV-induced hepatitis once you knew that there was a high avidity, regardless of whether or not a PCR test was performed?---<u>It might be that possibility would be very remote</u>.

(my underlining)

156. In examination, Dr Andresen also agreed that until the initial positive result for Q Fever became available on 20 April 2020, it was looking very unlikely that there was an infective cause for Mrs Doherty's hepatitis.[136]

157. As to the positive result for Q Fever that became available on 20 April 2020, Dr Andresen stated:[137]

---Yeah, so this would be the – a phase two IgM would be the earliest serologic marker of a Q fever infection. So this was consistent with Q fever but certainly not diagnostic of that, particularly in someone who had already been noted to have false positive IgM reactivity to other agents. So, I – in my mind this raised that as a diagnostic possibility but not up to the level of saying this is the most likely diagnosis. And I guess what you saw was a somewhat nuanced – appropriately nuanced response to this in that Q fever actually does have – is probably one of the few infectious agents of acute hepatitis for which there is actually a specific therapy, and they commenced that therapy while initiating additional diagnostic studies to confirm or refute the possibility that this was Q fever. So I'd like to think that I would have done exactly the same thing. That was – that was a nice nuanced response to a – to an equivocal but sort of interesting result.

All right, so the therapy that you're referring to is the commencement of the antibiotics, doxycycline in particular, is that correct?---Yes, that's right.

All right. And in terms of the result itself, just to be clear, what it really meant at that point in time in a patient such as Mrs Doherty who had already revealed herself to be throwing up false positive results, is that the <u>Q fever was perhaps a possible cause but not a very likely cause. If I put that proposition to you would you agree with that?---Yeah, that's</u>

[136] T5-7; LL 42 - 50
[137] T5-8; L28 – T5-10; L 9

exactly how I would put it. So the other thing, as we said for CMV, is that it's quite unusual for Q fever hepatitis to be this severe. So again another thing that I guess, sort of, weighs down your assessment of the likelihood that this is the primary problem.

…

Can you explain what would be required to either establish it as a false positive or exclude Q fever as a causative agent or factor?---So again we implement direct testing for the organism which is – which is the polymerase chain reaction, or PCR, test and – what's different with the – this Q fever result is she didn't have IgG, as in contrast to CMV where we had both IgG and IgM. So that leads us down a slightly different pathway. So instead of using avidity testing we use a convalescent serum and what we're –what we're hoping to or looking to see is what's called IgG serum conversions so if she's gone over a period of one to two weeks from IgG negative to IgG positive, that's strong support that this is early Q fever infection. If she doesn't that's actually very strong evidence against this being a Q fever infection because you really should be making IgG by two weeks.

….

And so to eliminate Q fever completely as a potential cause for the liver injury you require that, if I can put it this way, incubation period of about a fortnight in order to see whether the patient produces the IgG?---That's right. So you – you would do a second serum at ideally 10 to 14 days. If there was huge clinical urgency you might run one off at seven days after the first serum for an early indication, but you really wouldn't put your hand on your heart and say we've fully ruled out Q fever until you had a second serum at 10 to 14 days after the first one.

All right. Now, that Q fever – the convalescent Q fever serology result, that was implemented for that purpose, was returned on the 25th of April 2020. And I think you say in your report that that result, presumably because there was no IgG, adequately excluded it as being a reasonable cause for the severe liver injury at that stage, do you agree with that?---Yes. Absolutely.

……

….is it the case that all of those infectious causes that were being considered or that were reasonably likely or potential for the injury, had they all been excluded by the 25th of April?---Exactly. That's not inconceivable that the liver biopsy might have eventually – the pathologist may have raised the possibility of, "Oh, this looks like a really rare infection" and that would have triggered another cycle of confirmatory testing. But in the absence of that finding, yes, for practical purposes, infection had been excluded as the cause here.

(my underlining)

158. At the Inquest, A/Prof. Majumdar gave the following evidence about CMV being a possible cause for Mrs Doherty's hepatitis:[138]

[138] T5-24; L19 – T5-25; L 18

The CMV – the possibility that the CMV was the – a cause of the liver presentation arose out of what, on your reading of the record?---There was a positive CMV IgM antibody level and that was – that's when the suspicion had come about. However, there was also a positive CMV IgG and I couldn't really understand from the record in which order the results became available or if both were available at the same time. Usually, when – so the relevance of that is that – and I'm sure you've heard this from other specialists – that IgM is the first antibody to be made against an infection and so that would include, or it would be suggestive of acute infection. However, the presence of IgG antibodies, which is a second phase immune response, suggests that either the infection might have been resolving or it was prior exposure and it was a false positive IgM. So my reading of the notes suggests that the treating team was waiting for ASEM, the viral load, which again is appropriate and those tests aren't run every day in non-tertiary or non-transplant centres, but that was considered, you know, the main basis for entertaining the diagnosis of potential CMV hepatitis.

Sure. So perhaps we can just cut through this quickly, the initial serology that was available that suggested the possibility of CMV as being a cause of the liver injury, that was on the 14th of April. The main consideration there was the IMG result. Is that correct, or the IgM result?---Yes, IgM, yes, Immunoglobulin M.

And what, in the absence of that, it would not have necessarily been – it would not have been considered a potential cause at that point in time?---That's correct.

And what was required was further testing and what you've described we come to understand is an avidity test to ascertain whether or not the IgM was either a false positive or something other than an acute injury. And that came back indicating a high avidity. That's your understanding of the record?---That's correct.

And that reduced the likelihood of the liver injury having been caused by CMV at that point in time?---Yes.

Did it eliminate the likelihood altogether from your perspective?---It would make it less likely. Again, it's odd for CMV to present with a significant liver injury, but it does happen in certain situations. But again, without the associated viral prodrome, it's hard to definitively use it as a leading diagnosis, in my opinion, reading the notes.

Okay. And we've heard some evidence that further testing, PCR testing, am I describing it correctly?---That's correct. Your Honours, yes, that's right.

It would be required to completely eliminate the role of CMV as a cause of the hepatitis. Is that your understanding?---That's correct. So,

although the viral load doesn't correlate necessarily directly with – so PCR is a way of measuring how much virus particles are in the blood, or active the virus is, and essentially you can have quite severe hepatitis with a low load, but you cannot have it with a negative viral load. So, in that case, a liver biopsy is helpful when the viral load is low and the liver injury is severe

159. As to Q Fever being a possible cause for Mrs Doherty's hepatitis, A/Prof. Majumdar gave the following evidence:[139]

> *Yes. I think Q fever is an extremely uncommon cause of acute liver failure. With acute hepatitis, yes, it can cause acute hepatitis. Again, there was some positive serology noted, which again I think it was quite – my reading of the notes was that it was, you know, that it was there in the list of differentials, but fairly low down. I'll have to go back through the original documents, but I think it was fairly quickly excluded based on the lack of risk factors for developing Q fever. And again the thought would have been this is a false-positive test. But I'm unclear how long the diagnosis was actually entertained for.*
>
> *All right. Can I put this to you: from your perspective, it was a possible causative illness or infection, but from your perspective you would consider it not a very likely cause given the seriousness of the injury; is that right, that was present at that stage?---Yes. That's correct. The progressive nature, yes.*
>
> *Yes. And, although you would not exclude it entirely until more conclusive testing was undertaken, it was well down the list of differential causes from your perspective, all right. There was further testing undertaken, convalescent Q fever serology was performed and the results became available on the 25th of April, which, it has been suggested by others, adequately excluded Q fever as a cause. Would you agree with that proposition?---Yes. Yes, I do.*
>
> *And having regard to the information that you reviewed, or the evidence that you reviewed, was that the last of the potential infective causes that were being considered to be excluded in the management?---That full list, yes, in the list of infective causes, the CMV and the Q fever were the two that were maintained in the notes up until transfer. The only other thing that – the only other infectious agent that I did not see the serology of was hepatitis E – that's E for egg – which again could cause a similar severe acute hepatitis.*
>
> *But, are you satisfied now that that wasn't the cause in this particular case?---I am. I am, having reviewed the entire case.*
>
> *All right, now, so if I can proceed then on the basis that, having regard to those infectious causes that were being considered, it appears that*

[139] T5-25; L25 – T5-26; L11

they were excluded by no later than the 25th of April 2020. Would you agree with that proposition?---That's correct.

160. Having regard to the above evidence, I make the following findings:

(a) Given the lack of progress over the weekend, or during the first two to three days following admission to Caboolture Hospital, it was appropriate for the Medical Team to involve Infectious Diseases in the treatment and management of Mrs Doherty;

(b) The Infectious Diseases Consultant, Dr Rafiei, first consulted Mrs Doherty on Tuesday, 14 April 2020. There was, perhaps, some delay in arranging consultant review because of Dr Rafiei's work schedule at Caboolture Hospital, but any such delay was of no consequence to the outcome;

(c) It was appropriate for Dr Rafiei to consider the possibility of an infectious cause for Mrs Doherty's hepatitis;

(d) Nevertheless, in the absence of fever, it was unlikely that there was an infectious cause for Mrs Doherty's hepatitis. This is consistent with Dr Rafiei's own view prior to testing;

(e) Following the positive CMV result of 14 April 2020, it was appropriate for avidity testing to be undertaken to exclude a false positive result and/or to otherwise exclude CMV as a cause for Mrs Doherty's hepatitis;

(f) The avidity test result of 16 April 2020 effectively excluded CMV as a cause for Mrs Doherty's hepatitis on the basis of it then being a very remote possibility;

(g) By 20 April 2020, all other potential infectious causes (except for the very unlikely possibility of Hepatitis E, which Mrs Doherty did not have) had been excluded;

(h) However, the Q Fever results returned on 20 April 2020 indicating a phase 2 IgM positive result with a negative phase 2 IgG result raised the possibility that Q Fever might be the cause of Mrs Doherty's liver injury. Despite this result:

    (i) Q Fever was not then the likely cause of Mrs Doherty's liver injury, as had been recorded by Dr Chap in the clinical notes; [140]

    (ii) Rather, Q Fever was a very unlikely cause of Mrs Doherty's liver injury (consistent with Dr Rafiei's own view, although she says her views were not canvassed at the time); and

    (iii) The latter was particularly so given that by the time the Q Fever result was returned, Mrs Doherty's condition had progressed from acute hepatitis (which can be seen with Q Fever) to an acute liver

[140] Ex B1.1, page 290 BOE

injury with an increase in her INR reported on 16 April 2020, it then being very unlikely that such a serious liver injury had been caused by Q Fever;

(i) Nevertheless, it was appropriate to arrange a polymerase chain reaction (**PCR**) test to exclude Q Fever and to commence Mrs Doherty on doxycycline pending the result of the PCR test;

(j) The PCR test results of 25 April 2020 excluded Q Fever as a cause of Mrs Doherty's (by then) acute liver injury;

(k) As a whole, the entries in the Caboolture Hospital record of 20 April 2020 (the day Mrs Doherty was transferred to RBWH):[141]

(i) Do not reflect that, by then, CMV had been effectively excluded as a cause for Mrs Doherty's acute liver injury;

(ii) Do not reflect that, although Q Fever was a possible cause for Mrs Doherty's acute liver injury, it was a very unlikely cause; and

(iii) Do not indicate that it was more likely Mrs Doherty's acute liver injury was a DILI, or that there was possibly an autoimmune cause, and

(l) The fact that the entries in the Caboolture Hospital record of 20 April 2020 did not reflect or indicate the above evidences, in my view, that the test results that had been undertaken by then had not been adequately and appropriately understood, which led to the an erroneous attribution of the likely/possible cause of Mrs Doherty's acute liver failure as documented in the entries referred to at paragraphs [148] and [149] above.

Hepatology involvement

161. Dr Enoka Gonsalkorala (**Dr Gonsalkorala**), Gastroenterologist and Hepatologist, became involved in Mrs Doherty's care on 15 April 2020, approximately 5 days after her admission. Dr Gonsalkorala states:[142]

I initially saw Mrs Doherty on 15 April 23 (sic) at 1210 hours…[143]

…When I reviewed Mrs Doherty's medication history during the consultation on 15 April 2020, I had noted the following of relevance: Epilim (sodium valproate) was commenced in November 2019, Lipitor (atorvastatin) had been increased from 20mg to 40 mg in February 2020 and she was on two supplements – vitamin B complex and Q10. The hospital medication chart showed that atorvastatin had been withheld from 12 April 2020. (At that time she was also taking levothyroxine, aspirin, sertraline, thiamine, lactulose, targin). I would

[141] Ex B1.1, pages 288 – 295 BOE
[142] Ex C2.7, starting at paragraph 14 BOE
[143] Ex B1.1, pages 270 – 272 BOE

have noted this from the Emergency Department admission records and her inpatient chart (as this was my standard practice when reviewing patients), but for the purpose of this review, it was necessary for me to relist all of her medications at that in her progress notes.

….

On examination she had stigmata of chronic liver disease consistent with palmer erythema. There was no confusion nor any hepatic asterixis to suggest that she had hepatic encephalopathy (HE).[144]*Abdominal examination was normal (no masses or ascites) ad there was no peripheral oedema (swelling in her lower limbs)*

162. At the review of 15 April 2020, Dr Gonsalkorala noted, *inter alia*, the following investigation results:[145]

    (a) Bilirubin on admission was 200 umol/L and had peaked the day prior to review at 244 umol/L;

    (b) Bilirubin on the day of review (15 April 2020) was 236 umol/L;

    (c) ALT on the day of review was improving from a peak of 2410 U/L to 1230 U/L; and

    (d) INR performed on 10 April 2020 was mildly elevated at 1.3 (normal less than 1.2).[146]

163. A liver disease screen had been performed and at the time of Dr Gonsalkorala's review on 15 April 2020, the following results were available:

    (a) Hepatitis A, B and C antibodies were all negative; and

    (b) CMV IgG and IgM was positive.[147]

164. Dr Gonsalkorala noted the abdominal ultrasound performed on 10 April 2020, with the pertinent findings being focal fatty changes, a common bile duct diameter of 8 mm (which was moderately dilated), no biliary obstruction and the spleen size was normal. She also noted the CT abdomen and pelvis of 10 April 2020 where the only notable finding was that of a "*heterogenous appearance to the liver. This may represent hepatitis*."[148]

165. Dr Gonsalkorala's impression was that Mrs Doherty's abnormal LFTs were likely due to CMV hepatitis.[149]

166. Dr Gonsalkorala did consider other causes, including DILI due to atorvastatin (in light of a recent increase in dose) and sodium valproate. However, she

[144] Ex B1.1, page 271 BOE
[145] Ex C2.7, paragraphs 19.1-19.3 BOE
[146] As per the evidence of A/Prof. Majumdar, the INR was not then (10 April 2020) at a level that met the diagnostic criteria for acute liver injury
[147] Ex C2.7, paragraph 19.4 BOE
[148] Ex C2.7, paragraph 19.5 BOE
[149] Ex C2.7, paragraph 20 BOE

observed that it was uncommon for DILI to cause a drop in platelets.[150] [151] She explained that since November 2019 Mrs Doherty's platelet count had dropped significantly, which can be seen in patients with a viral infection such as CMV. She documented' "*However these agents [the drugs referred to above, including sodium valproate] will not cause decrease plt – more likely related to CMV infection.*"[152]

167. At the review on 15 April 2020, Dr Gonsalkorala did not consider that Mrs Doherty then met the diagnostic criteria for acute liver failure. She documented" "*unlikely to have significant liver disease as LFTs and FBC normal Nov 2019 and no signs of portal HTN on imaging*."[153]

168. Dr Gonsalkorala recommended several further tests be performed to complete liver disease screening and daily INR testing (as at 15 April 2020, the last INR test that had been performed was on 10 April 2020, 5 days prior).

169. Dr Gonsalkorala also discussed Mrs Doherty's case with Dr Skoien. She believes this occurred on Wednesday 15 April 2020 (not Monday 13 April 2020 as recorded by Dr Skoien) because she did not work at the Caboolture Hospital on Mondays. There is otherwise no record of her being involved in, or her having a discussion about Mrs Doherty's care prior to 15 April 2020.[154]

170. In any case, Dr Gonsalkorala explains that it was the usual practice to discuss patients with jaundice where the diagnosis was unclear (and who fitted the criteria for acute liver failure or required liver biopsy) with the Hepatologist on ward service at RBWH to determine suitability for transfer of the patient to a tertiary service. She explains that patients with these criteria do not undergo biopsy at Caboolture Hospital.[155]

171. Dr Gonsalkorala stated that after having the discussion with Dr Skoien it was agreed that for the time being Mrs Doherty should remain at the Caboolture because her bilirubin was stable. She also states that Mrs Doherty's INR had not increased significantly (although I observe there is no record that an INR had been performed since admission on 10 April 2020) and her ALT was improving.[156]

172. At the Inquest, Dr Gonsalkorala gave the following evidence as to the nature of Mrs Doherty's liver injury at the time of her review on 15 April 2020:[157]

> *So if we have a look at those blood results from 9 April, 10 April, and 13 April, accepting that you saw the patient two days after the 13th of*

[150] Ex C2.7, paragraph 21 BOE
[151] There was an issue raised by Dr Tan (Ex D2) about the whether it was appropriate to consider the reduction in platelet levels as a basis for excluding the possibility of a DILI at that point in time. There are some factual anomalies in the assumptions Dr Tan made to premise his opinion in that regard. The issue was discussed with Dr Gonsalkorala at T2-50; LL 5- 45. We do not intend discussing this issue further, nor do we intend to make any submission in respect of this issue.
[152] Ex C2.7, paragraph 22 BOE
[153] Ex C2.7, paragraphs 24 - 25 BOE
[154] Ex C2.7, paragraph 29 BOE
[155] Ex C2.7, paragraph 27 BOE
[156] Ex C2.7, paragraph 28 BOE
[157] T2-43; LL4- 19

April, what would you –how would you regard those pathology results in terms of the extent of the liver injury at that time?---So it is a severe liver injury because the patient is jaundiced because their bilirubin is over 50, that's when you start to see the yellowness in the whites of the eyes. The ALT and the AST, those are very liver-related enzymes that go up with an increase with the liver injury. But those tests can go up, and actually the patients can get better very quickly. For example, in an ischemic liver injury, you can get those numbers up to 10,000 and it gets better very quickly as the blood supply is restored. So those numbers per se aren't very useful to say how severe the liver injury is, but the bilirubin and certainly the INR, and then importantly how the patient's presenting, so you would use all those aspects to determine how severe the liver injury is.

Okay. But certainly by the time you saw her, you were satisfied that this was a severe liver injury?---Liver injury, correct

…

And the other thing that I wanted to ask you about is, Dr Majumdar indicates that strictly speaking Mrs Doherty didn't meet the criteria for acute liver injury until her INR level was greater than or equal to 1.5, which was taken on the 16th of April 2020. Do you have any comment about that, whether you agree or disagree with that?---That's an abnormal INR. So whether you say an INR of 1.3 is stating an acute liver injury. Certainly, once it becomes abnormal with somebody who has a high bilirubin, really you're worried that this is a severe liver injury and that's why we would check it more routinely when we're worried because that INR is really important. So whether it's 1.3, 1.4, 1.5, clinically I wouldn't change how I looked after somebody, whether it was 1.3 or 1.5.

173. Consequently, to the extent there might be some concern about the absence of INR testing in the period 10 April 2020 to 16 April 2020, in the sense that Mrs Doherty might have progressed to acute liver injury at a time prior to 16 April 2020, it seems that Dr Gonsalkorala's management would have been no different regardless of whether her INR was 1.3 (as it was on 10 April 2020) or higher. Either way, she regarded Mrs Doherty as having a severe acute liver injury at the time of her initial review.

174. As to whether there was an indication to transfer Mrs Doherty to RBWH on 15 April 2020, Dr Gonsalkorala explained:[158]

So, in trying to form that opinion, so I spoke to Mrs Doherty, examined her and looked at her investigations. So, at that point, she didn't meet the acute liver failure criteria and also there were still a few investigations outstanding. And, at that point, so I had consulted Royal Brisbane Hospital and talked to them about my plan. And so there wasn't anything at that point that would have necessitated an urgent transfer because it was still really in the phases of trying to

[158] T2-44, LL 18 - 25

understand what her liver injury was due to and she wasn't in acute liver failure.

175. As to the potential causes of Mrs Doherty's acute liver injury at review on 15 April 2020, Dr Gonsalkorala's evidence was:[159]

> *---At that point, it was a little bit undifferentiated and when we try and make an impression, we look at patient's history, patient's past medical history, their investigation results and their medications, to see whether there is one outlier or one condition that could cause the liver injury. So, putting the information together that I had at that stage, the differential was quite broad. She'd had what sounded like a febrile illness and she had a CMV positive IgG and IgM. At that point we did not have the avidity results, so it could have been a CMV hepatitis. And then I've noted that she could have a drug-induced liver injury and I'd mentioned atorvastatin, especially because the dose had been recently increased, but that was already ceased by the time I saw her. And then sodium valproate. But the interesting thing in her case is, despite continuing the sodium valproate, some of her liver enzymes had actually improved and her bilirubin had stayed stable for two days, so I used all of that information to come up with some differential diagnoses.*

176. As to her assessment of the likelihood that sodium valproate was the cause of the acute liver injury as at 15 April 2020, compared to the other potential causes mentioned, Dr Gonsalkorala explained:[160]

> *And how do you reconcile the apparent improvement in some of the markers and not significant deterioration in other markers in that period between 10 April and when you saw her on the 15th of April, while continuing on sodium valproate? That does seem a bit inconsistent, doesn't it?---Yes. It does. And so if this was an acute CMV infection, you would expect, as time goes on, the liver tests will improve and she won't become encephalopathic. And, furthermore, the statin therapy had been ceased. So there were two other agents or two other causes that were potentially managed, which could have led to the improvement in her ALT and the stability of her bilirubin. So that's why those two are a little bit more likely at that point when I met her for the first day then.*
>
> *Because the statin had been ceased?---It was ceased I believe on – –*
>
> *And improvement is consistent with CMV infection, is that right?--- Improved, correct, as time goes on.*
>
> *So they were potentially more likely causes at that time because of those markers that you had the opportunity to review?---Yes*

[159] T2-45; LL 9 - 23
[160] T2-45; LL28 – 46; T2-46; LL24 – 45; T2-47; LL1 -15

….
Okay. Now, just returning then to sodium valproate, you will no doubt be aware that it is an agent that can cause liver injury. In terms of that potentiality, was it any less likely to have caused – be the cause of the liver injury compared to the statin, for example, that had been ceased?---At that point, I thought it was less likely. In hindsight, we know that that wasn't the case. So when we're putting together a differential diagnosis, we look at the history, the examination, previous blood test results, and the results available. The results available, I thought at that point, that sodium valproate was not as likely as the other two.

Given the possibility of a DILI and not knowing one way or the other, really, whether that were the case, and that, including the statin, there were other drugs that might have caused that, including the sodium valproate, was there any reason why she could not have been ceased at that time on sodium valproate?---So my understanding was that it was prescribed for CADASIL, so it wasn't for a seizure disorder where you would be worried that they could get a seizure following cessation. So, no, there wasn't a reason that she couldn't stop it at that stage.

Some of the expert opinion in this matter that you might have had an opportunity to read suggests or has indicated that, given the potentiality that sodium valproate might have been a cause of the liver injury, it would have been prudent to cease it from the very beginning?---Yes.
….
… some of the expert opinion that's before the court suggests that, given the potential for sodium valproate being a possible agent for the cause of the injury, that it should have been ceased along with all other possible agents right from the beginning. Would you agree or disagree with that proposition?---So I agree, but one of the other things I would say in addition to that statement is often we see patients, especially in an acute setting, where they have multiple medications that could cause a drug-induced liver injury. And then you've got to make a decision as to which one you stop, depending on all of the other available information. Sometimes there isn't anything else – there isn't enough information to suggest one agent over another, so then we've got to stop all three. Stopping the medication, you've just got to think about the consequences of that. So that was the principle that I was applying at that point because I thought it was less likely. But I agree now, in hindsight, given how she has progressed, had I stopped it at that stage, I'm not sure whether it would have made a difference, but she would have had to two doses – two less doses.

177. Dr Gonsalkorala next reviewed Mrs Doherty at or about 1315 hours on Friday, 17 April 2020. In respect of that review, Dr Gonsalkorala states:[161]

[161] Ex C2.7, starting at paragraph 31 BOE

Mrs Doherty's INR had risen over the previous two days (1.6 on 16 April 2020 and 1.7 on 17 April 2020) and her bilirubin had started to increase and was 310 umol/L and 17 April 2020.

Mrs Doherty's autoimmune liver disease screen was negative and there were outstanding liver disease screen results at that time.

I have documented that at that time she was undergoing a 24 hour urine collection to assess for copper excretion to exclude acute Wilson's disease (another differential cause for jaundice and abnormal liver function tests). At this stage there were multiple possible aetiologies for the liver injury – DILI vs seronegative autoimmune hepatitis. At the time of my 17 April 2020 review, all potential drugs that could cause a liver injury had been ceased: Supplements (B12, Q10)(ceased at admission), atorvastatin (ceased 12 April 2020), and sodium valproate[162] (had been ceased with the last dose given on the evening of 16 April 2020). The initial management of a suspected DILI is to stop the suspected agent/ agents and to assess response (liver function tests) as most cases of DILI improve and resolve upon cessation of the culprit agent. The other possible aetiology that I had considered was seronegative immune hepatitis. Most cases of autoimmune hepatitis will present with abnormal autoimmune antibodies, the most specific of which is smooth muscle antibody. In a small number of cases patients will have autoimmune hepatitis without these antibodies and require a liver biopsy for diagnosis. This disease entity [is] termed "seronegative autoimmune hepatitis".

My Impression and plan at that time was: for daily bloods including INR, and that if there was an ongoing rise in bilirubin and INR over the weekend she would need to be transferred to the RBWH for consideration of liver biopsy. I was not on call for gastroenterology (the service provided by the RBWH) that weekend but I informed the treating physician, Dr Borthwick that I was happy to be contacted by the medical team at Caboolture hospital, via switch. (I was not contacted).

My instructions were, if at any time Mrs Doherty developed hepatic encephalopathy, to contact the gastroenterology registrar at the RBWH as she would need immediate transfer.

This plan was discussed with the treating physician Dr Borthwick and Mrs Doherty.

Following my 17 April 2020 review I also discussed her case with Dr Skoien on 17 April 2020 regarding transfer to RBWH for liver biopsy

[162] The progress notes suggest that it was part of Dr Gonsalkorala's plan to cease sodium valproate that day (Ex B1.1, page 270) and that it was withheld by Dr Borthwick at or about the time of Dr Gonsalkorala's review (1315 hours), with the note "liver failure" Ex B1.1, page 347)

as the aetiology of her liver injury was unclear.[163] *During that discussion with Dr Skoien we agreed that Mrs Doherty may have features of covert or grade 1 HE, and as her bilirubin and INR had been increasing over the preceding days. It was then agreed that she required transfer to a tertiary service, ideally not over the weekend unless there was significant deterioration. Her bilirubin continued to rise over the weekend without significant change in INR (1.6 o 20 April 2020) or overt HE.*

The reason we would not ordinarily transfer a patient over the weekend, (unless they become unstable or deteriorate) is that there would be no change to management or alternative management compared to what she was receiving at Caboolture Hospital. Mrs Doherty required a liver biopsy which would not be performed on the weekend. Urgent liver biopsy during a weekend is mainly considered in cases of rapidly progressive liver failure of unknown cause. It was safer for Mrs Doherty to remain at Caboolture Hospital with a team who were well aware of her presentation thus far. Had she been transferred to RBWH she would be looked after by a new team of doctors (on call registrar and on call consultant) who may not be familiar with the finer details of her case.

178. At the Inquest, Dr Gonsalkorala gave the following evidence:[164]

I saw her on the 17th, so the Friday.

Okay. And what did that result indicate to you in terms of the CMV issue, if I can call it that?---Yes. So I noted in my – in the hospital notes that I did not think then that CMV was the cause of her hepatitis and then we were then moving down to the other possibilities, the drug-induced liver injury, so most of her – the agents had been stopped and I think that day around lunch time there was a stop placed on sodium valproate. The last dose was the day prior. It's such an acute liver injury, though, I just wasn't confident that the sodium valproate alone could explain this and then we talked about a zero negative autoimmune hepatitis, Most commonly patients with autoimmune hepatitis presented with positive antibodies. There's a small fraction who don't. But autoimmune hepatitis can present with high bilirubin, high ALT, and if the liver is unwell enough then the INR starts to become abnormal. So there were still other differentials, given how high her liver tests were, that we couldn't just exclude based on a negative CMV that everything could be delayed because the management would be different if it was autoimmune hepatitis.

All right, okay. Were we, by then on the 17th when you reviewed the avidity results of the 16th, were we in a position to proceed on the basis that it was not CMV at that stage?---Yes.

[163] Documented at Ex C2.7.1, Att ESG2 BOE
[164] T2-50, L50 – T2-52, L2; T2-52, LL23- 44

Were we moving away from the possibility of other infectious causes at that stage, or did that remain as a potential explanation?---No. So, at that point, infections were – I don't think the hepatitis B PCR had come back at that stage, but really this – infections were now less likely from my perspective because CMV was the one that I was worried about and it wasn't so – – –

From your perspective. Yes, okay. So, from your perspective, infections are less likely. The focus then for you was on the drug-induced liver injury or the autoimmune injury – disorder injury?---Hepatitis, correct.

Hepatitis injury. And insofar as the drugs were concerned, is it not possible to differentiate between the drugs at that stage, which might be the causative agent if it was at all; is that right?---That's right. Correct.

So the decision was made by you to cease all potential hepatic drugs that could be causing injury at that stage?---Toxins, yes.

Which included the sodium valproate, okay. And indeed the – I think you gave evidence about this already. The sodium valproate was last given the day – the evening prior on the 16th?---Prior, on the 16th.

Okay. Just bear with me one second. Yes, just in terms of timing, can I take you to paragraph 27 of your statement?---Yes.

And you say that you had a discussion with Dr Skoien about the findings. Is that discussion after the CMV had been eliminated as a potential cause?---So I spoke to Dr Skoien on two occasions. So first on the Wednesday after I saw Mrs Doherty. And at that point, no, it hadn't been excluded because the avidity result hadn't come back at that stage. And then I had a second conversation with Dr Skoien on Friday the 17th of April.

….

Yes, so by that time on the 17th the pathology results or the liver test results were again on the decline, is that right?---Correct. The bilirubin had started to rise and the INR, which when I saw her on Wednesday I only had one INR result, which was from her admission, and per my request the team had then the following day done the INR test. And by Friday two INR tests had been increasing. So her liver injury was worsening by those two parameters.

And, can I put this to you, it seems from your evidence, and also from the record, that it was your view, at least, that Mrs Doherty would require transfer at that point and that she would require biopsy at that point, is that the case?---Yes.

And was that part of the reason for your contacting Dr Skoien on the 17th to discuss the need for transfer and the need for biopsy on the 17th?---Correct, because at that stage we really were still unaware as to what was causing her liver injury. She was in a hospital where gastroenterologists did not admit patients. We did not have a full hepatology service. So when liver tests start to increase, especially INR, really that's the point in time when they need to go to a tertiary centre. And one of the reasons is for more hepatology care, but also for consideration of a liver biopsy. So those are the two main reasons.

And was there any indication – was there anything in your understanding of Mrs Doherty's situation at that time which was against doing a biopsy at that stage?---No, there wasn't

179. As to the decision to leave Mrs Doherty at Caboolture Hospital over the weekend prior to transfer to RBWH on 20 April 2020, Dr Gonsalkorala gave the following evidence:[165]

–?---No, I think we both agreed that it was safer for her to be at Caboolture over the weekend. At that point again, she didn't have hepatic encephalopathy, so she wasn't confused. Now, had she had hepatic encephalopathy, she would have needed to leave that hospital and go to Royal Brisbane. So, on the weekend, what happens at Royal Brisbane Hospital is there's an on-call team, which is a registrar trained in gastroenterology, and there will be a consultant who will be on call. Now, that consultant could be a VMO, could be somebody who works within the department at Royal Brisbane Hospital, but that it's such a busy on-call that really their job over the weekend is to look after very acute illnesses and that mainly being patients who present with either, you know, food bolus in the oesophagus or upper gastrointestinal bleeding, so to move a patient who didn't have encephalopathy to a service where none of the team really knew her we thought would be detrimental, whereas keeping her at Caboolture where all of her notes and all of the medical information was present and easily accessible would have been safer. But I had made the caveat, should she become encephalopathic, she would come across. And each time we bring a patient over from another hospital to Royal Brisbane Hospital, so we need to think about safety and who's around to look after them, but also when will it change management. Bringing a patient over, we wouldn't do a liver biopsy in her case over the weekend because doing a liver biopsy on a weekend requires multiple teams and you're in competition with lots of other acute emergencies. And not only that, you then need to have – to fix the biopsy and get someone who has an expertise to read the liver biopsy. So she wouldn't have had the liver biopsy that weekend, and she would have then sat in a bed without the patient – people who really knew her, and that was Caboolture hospital. So, now that I'm on the other side, so I work as

[165] T2-52; L48 – T2-53, L29

a hepatologist at Royal Brisbane Hospital looking after inpatients. Back then I wasn't; I was just doing outpatient practice. So I can see the bed pressures that we face, you know, we consult all the way up to Mackay and sometimes even Mackay patients, if Townsville don't accept them. So we've constantly got a cohort of patients who we're managing with phone advice, looking at blood tests peripherally, and trying and timing the transfer to Royal Brisbane when we know that the disease or the management would change.

180. As to the timing of the cessation of sodium valproate, I refer back to the evidence of Dr Sethi and A/Prof. Majumdar summarised above.

181. Having regard to the evidence, I make the following findings:

    (a) The 5-day delay in undertaking hepatology review of Mrs Doherty at Caboolture Hospital was caused by the limitations on resources in the public hospital system. Ideally, this should not arise, but it is a feature of the public hospital system that is not readily ameliorated;

    (b) That said, hypothetically, earlier hepatology review of Mrs Doherty at Caboolture Hospital may have afforded her an opportunity to undergo earlier daily INR testing, with the possibility that INR testing may have returned levels warranting an earlier transfer to RBWH;

    (c) Where sodium valproate had been prescribed for prophylaxis against migraine, it could have been safely ceased and without material harm to Mrs Doherty. In those circumstances, it would have been appropriate for Dr Gonsalkorala to cease the sodium valproate at the review on 15 April 2020 given it had not been ceased at admission or at any other earlier time;

    (d) Dr Gonsalkorala's management of Mrs Doherty at the reviews on 15 April 2020 and 17 April 2020 was otherwise appropriate; and

    (e) Once the decision was made on 17 April 2020 to transfer Mrs Doherty to RBWH, it was appropriate that she remain in the care of the medical team at the Caboolture Hospital over the weekend for the reasons explained by Dr Gonsalkorala.

Issue 5

Whether the treatment and management of the deceased provided at the Royal Brisbane and Women's Hospital on and after 20 April 2020 was appropriate

182. Mrs Doherty was transferred to the RBWH on Monday, 20 April 2020.

183. The initial admission note[166] of 1949 hours on 20 April 2020 records, *inter alia*:[167]

[166] Which indicates that Mrs Doherty was admitted to RBWH under Dr Skoien
[167] Ex B1.2, pages 67 and 68 BOE

<u>Impression</u>: *Symptomatic hypotension ? [secondary] to hypoalbuminemia with appropriate end-organ perfusion in the setting of acute liver failure presumed to due to Q-Fever + CMV infection, awaiting further evaluation under the liver team @ RBWH."*

184. There is no record that Mrs Doherty's liver injury was potentially a DILI. The above note likely reflects what was recorded in the Caboolture Hospital progress notes of 20 April 2020 (see above). I reiterate that the entries in the Caboolture Hospital records for 20 April 2020:[168]

    (a) Do not reflect that, by then, CMV had been effectively excluded as a cause for Mrs Doherty's acute liver injury;

    (b) Do not reflect that, although Q Fever was a possible cause for Mrs Doherty's acute liver injury, it was a very unlikely cause; and

    (c) Do not indicate that it was more likely Mrs Doherty's acute liver injury was a DILI, or that there was possibly an autoimmune cause.

185. There is no record of Mrs Doherty being administered sodium valproate on 20 April 2020.

186. The initial hepatology review at the RBWH was undertaken by Dr Skoien and team at or about 0845 hours on Tuesday, 21 April 2020. The progress notes relevantly record the following:

    (a) INR 1.6 "*not ideal for liver biopsy but may need one regardless*";

    (b) Impression: " *? AIH [autoimmune hepatitis] v infection – will require biopsy*." There is no record that DILI was being considered a potential cause of Mrs Doherty's liver failure at that time; and

    (c) A percutaneous liver biopsy was booked for Thursday at 0900 hours – " *need to correct INR to [less than] 1.4.*"[169]

187. Dr Rowe prescribed sodium valproate 400mg (2 x 200mg) nocte on 21 April 2020.[170]

188. At 2000 hours on 21 April 2020, Mrs Doherty was administered one dose of sodium valproate 400mg (2 x 200mg).[171]

189. Sodium valproate was subsequently withheld until 29 April 2020, when it was recommenced at or about 2000 hours. Thereafter doses as prescribed by Dr Rowe [400mg (2 x 200mg) nocte] were given at or about 2000 hours on 30

[168] Ex B1.1, pages 288 – 295 BOE
[169] Ex B1.2, pages 70-73 BOE
[170] Ex B1.2, page 194 BOE
[171] Ex B1.2, page 194 BOE

April 2020, and 1, 2 and 3 May 2020.[172] In this regard I note that a new prescription for sodium valproate (along with Mrs Doherty's other drugs) was written up by Dr Rowe on 29 April 2020.

190. The progress notes do not record the fact of the decision to recommence sodium valproate, or why the decision was taken.

191. Mrs Doherty underwent the liver biopsy on 30 May 2020.

192. The biopsy was initially reported as extracted in paragraph [44] above, then subsequently reported as extracted in paragraph [46] above.

Decision to recommence sodium valproate on 29 April 2020

193. Various explanations for why sodium valproate was recommenced on 29 April 20202 have been put forward, starting with the one provided by Dr Mark Mattiussi, Director of Medical Service RBWH, by his letter dated 5 November 2020 to Acting Coroner Kirkegaard (as Her Honour then was):[173]

> *Sodium valproate that she had been taking for five months was recommenced on day 18 as five months was considered too remote for this pattern of liver injury and there was concern that this was an important treatment for her CADASIL.*

194. Dr Tan opined:[174]

> *Further, after approximately 13 days' hiatus from valproate, the medication was recommenced (27 [sic] April 2020). The reasons for doing so are not documented clearly. A subsequent note of 7 May 2020 documents that her husband expressed concern about stopping valproate a second time, so it may be that there was pressure from the family to recommence the valproate on 27 April 2020. Dr Mattiussi's letter offers two possible reasons for recommencing valproate, however, with the benefit of hindsight, neither is clinically valid. The first, that the commencement of valproate was too remote from the onset of liver disease, fails to recognise that valproate is a notable exception to the rule that drug-induced liver injury occurs soon after commencement of the culprit drug. The second, that it was an important treatment for CADASIL, fails to appreciate that this was a symptomatic treatment for migraine and not a disease-modifying therapy for CADASIL. In other patients taking valproate for epilepsy or mania, abrupt cessation of valproate, especially at high doses, is associated with risk of rebound seizures or rebound mania, and in some cases this may be dangerous. Cessation of valproate in migraine may carry some risk of rebound migraines, however this is not dangerous and is readily managed with other agents. In this case, the benefit-risk balance is clearly in favour of ceasing the valproate and*

[172] Ex B1.2, page 196 BOE
[173] Ex C2.2 BOE
[174] Ex D1, starting on page 6 BOE

not recommencing it until valproate-induced hepatotoxicity has been excluded.

195. The source of the explanation that there was "*concern that [sodium valproate was an important treatment for her CADASIL"* is not revealed by Dr Mattiussi and, in any event, appears to be inconsistent with the decision that was made to cease sodium valproate at Caboolture Hospital. In that regard I note that Dr Gonsalkorala agreed with Dr Tan's opinion that the "*benefit-risk balance*" was in favour of not recommencing sodium valproate until valproate-induced hepatotoxicity has been excluded:[175]

> *Okay. Now, just in terms of your decision to withhold the sodium valproate, was it ever within your contemplation that that might change; that it would be reintroduced?---<u>It wasn't</u>. So really it's kind of my role at that stage was to treat anything reversible and then stop any potential drug injuries, liver injury agents, and then making sure that they got to Royal Brisbane Hospital. And so there were two hepatologists at Royal Brisbane Hospital who have, you know, many years ahead of me in terms of experience and seeing really unwell patients. And then it's really their assessment and results of investigations that would drive whether a drug got restarted or not. And then similarly, now that I'm on the other side, so we would all assess patients as they come through and determine how to progress their management. Certainly things that I've done in retrospect are useful, but you really need to have a look at things from a fresh perspective, have a fresh set of eyes, look through everything from beginning to end, and then that's what we all do. <u>But when I – when she left Caboolture, I wasn't looking after her, but there was no plans in my thinking that she would restart.</u>*
>
> *And can I suggest to you that you were concerned enough for sodium valproate to be a potential cause to cease it. <u>Would you have expected it to be excluded as a cause before it was reintroduced if that was to be the case?---Yes, I would have</u>*
>
> (my underlining)

196. Dr Sethi opined:[176]

> *The decision to recommence Epilim on 27 April 2020 (sic) was highly unreasonable and directly contributed to a poor outcome for Ms Doherty. This was not in keeping with accepted standards of care in Australia at the time the care was administered…..*
>
> *It was entirely inappropriate and highly unreasonable to recommence the deceased on sodium valproate on 27/28 April 2020 (sic) in general terms in the context of severe liver dysfunction. Epilim should have*

[175] T2-52; LL 25 - 43
[176] Ex D3 BOE

been reasonably considered to be responsible for her severe liver dysfunction hence it should not have been restarted….

It was entirely inappropriate and highly unreasonable to recommence the deceased on sodium valproate on 27/28 April 2020 (sic) in the context that Q-fever appears to have been excluded as a cause of the severe liver dysfunction on or about 25 April 2020. Given that Q fever had been excluded as a cause, this logically meant that Epilim may have been responsible hence this should not have been recommenced.

197. A/Prof. Majumdar observed:[177]

> *A single dose of Valproate was adminstered on 21/04/2020 at RBWH and then the drug was withheld until it was recommenced on 29/04/2020 and continued until 03/05/2020. It is not clear why Valproate was re-started on 29/04/2020 in the inpatient progress notes provided.*

198. At the Inquest, A/Prof. Majumdar's evidence was:[178]

> *All right. Can I then take you way back, prior to when the patient arrived at Royal Brisbane and Women's Hospital. As we established, the decision to take the patient off valproate was made on the 17th of April 2020 and there was a subsequent decision to recommence the valproate on or about the 27th of April 2020 (sic). And I just want you to consider this question in the context that it seems that, by no later than the 25th of April 2020, infective causes that were being considered had been eliminated by that time. Do you have any comments about the appropriateness of recommencing the valproate in the context where there had not yet been a liver biopsy, infective causes had seemingly been all but eliminated, and the autoimmune cause, you can indicate to me whether that was still in the frame at that stage or not?---Thanks for that question. I was quite puzzled to see valproate back on the drug chart and as the decision at Caboolture was quite apparent and it was actively recorded as a potential hepatotoxin, I think it was on the 17th of April, and so it is surprising that that was recommenced without any major justification that I could find in the notes. I was able to see that it was recommenced on the administration record, but no clear of justification in terms of, again, if it was for seizure prophylaxis, perhaps a week off the medication might have been a reason to recommence, but by that stage I'm certain that the reasons for being on it would have been known by the treating team. So I was really unclear of why it was started again. And I'd be more of the opinion that it should not have been restarted and continued to be withheld while the situation was undifferentiated.*

[177] Ex D6 BOE
[178] T5-28, L 46 – T5-29, L-21

Okay, so, whilst – at least whilst the situation remained undifferentiated as at that date, your view would be that it ought not have been recommenced at that time?---<u>That's correct. Sorry, and in the context of a patient who is getting worse</u>.

(My underlining)

199. By Exhibit C2.2, Dr Skoien explained his understanding of valproate-related DILI as follows:[179]

> *…While a well-recognised cause of DILI, fatal cases are actually very rare. Approved for use in epilepsy almost 50 years ago, there were fewer than 200 fatal cases reported in the literature worldwide despite regularly appearing in the "Top 200" prescribed drugs.*
>
> *The majority of valproate DILI occurs in children. A 2013 review of cases from a WHO database found that two-thirds of cases occurred in patients under the age of 6.*
>
> *Risk factors for valproate DILI include young age, polytherapy with antiepileptic agents, and congenital metabolic and neurologic conditions – none of which were present in Mrs Doherty's case (as acknowledged by Dr Tan).*
> *This absence of risk factors and the overall rarity of valproate-related DILI as a cause of severe liver injury (and subsequent liver failure) may explain why other causes were considered above valproate. Furthermore, the incubation period from first presentation to onset of hepatotoxicity is usually 1 to 3 months whereas Mrs Doherty presented after more than 5 months of therapy. I believe that all these factors, taken together, explain why valproate-related DILI was not the most obvious diagnosis initially…*

200. Also, by Exhibit C2.2, Dr Skoien provided the following response to the issue of recommencing sodium valproate on 29 April 2020:[180]

> *Regarding re-exposure to valproate on 28th April 2020, it is clear that…I did not consider valproate to be the most likely cause of her liver failure at that time. Furthermore, I was concerned that this medication was important to the management of her underlying CADASIL. As is suspected by Dr Tan, there was some consternation from Mrs Doherty's husband that she had been off her "CADASIL medications" and I felt that this could be contributing to her deteriorating mental state. I now accept Dr Tan's expert opinion that valproate is <u>not</u> a disease-modifying drug in the management of CADASIL and that it could have been safely withheld for the duration of her admission. With hindsight, I also acknowledge that cases can appear in the first 6 months of therapy and valproate- associated liver failure should have remained actively considered as the potential*

[179] Starting at page 6; references removed
[180] Starting at page 7

cause of DILI. Although it is difficult to quantify how the 6 doses contributed to her ultimate outcome in the setting of such advanced liver injury, with the benefit of hindsight, re-exposure was not clinically indicated.

201. By Exhibit C2.15, Dr Skoien said that he had nothing further to add about the decision to recommence sodium valproate on 29 April 2020 beyond the explanation provided in Exhibit C2.2.[181]

202. I pause to make the following observations:

(a) It appears to have been understood from early in Mrs Doherty's admission to Caboolture Hospital that sodium valproate had been prescribed as a prophylaxis for migraine;

(b) The Medication Action Plan (**MAP**) completed after admission to RBWH on 21 April 2020 records that the indication for sodium valproate was to "*prevent migraines*;"[182] and

(c) If there was any doubt about the purpose of the sodium valproate in the management of Mrs Doherty's CADASIL, enquiries could have been made with Dr Walsh but he says that he "*was only contacted by the [RBWH] on one occasion in May 2020 by which time Mrs Doherty was in extremis*."[183] This was after the decision to recommence sodium valproate had already been made.

203. At the Inquest, Dr Skoien gave the following evidence:[184]

> *Can you explain to the court what you were thinking at the time the decision was made to put Mrs Doherty back on to sodium valproate?---When she first was transferred and I was looking at all the potential causes, if we just confine ourselves to the medications, I then looked at all the evidence where we would normally look for causes of liver toxicity and there are a number of different candidates there and also acknowledge there are cases as well that – that help us to – to work out whether – whether a particular drug is the likely culprit or not. My recollection at the time that I decided to start – restart the valproate was that the period of toxicity, the latency period as it's called, is – is up to 12 weeks and I acknowledge that that's not correct and – and that's an error of judgement that I made. It's up to usually six months and in some very, very rare cases could be a bit longer but in my mind I had that it was the first three months that was the risk period and – – –*
>
> *Can I stop you there – – –?---Yes.*
> *– – – and just ask you a question. Did that – because of that, that latency period as you understood it at that time, that not only informed*

[181] Ex C2.15, paragraph 43 BOE
[182] Ex B1.2, page 220BOE
[183] Ext C4.1, paragraph 154 BOE
[184] T3-17; L34 – T3-18, L43

your decision about putting her back on but it also informed your decision about its likely – it being a likely causative factor; is that correct?---It's absolutely true that if I considered that valproate could have caused this she would never have gone back on valproate. So in – in – in making that dec – in making that incorrect recollection of the latency period it meant that she restarted the valproate and I stopped considering that as a cause.

Okay. So that was part of the reasoning. Can I prompt you by indicating this to you, in your statement you suggest that there was also some thinking around the benefit the sodium valproate might have had for Mrs Doherty's CADASIL syndrome?---Yes, that's true.

Can you explain what your thinking was in relation to that?---The medication had been started by her neurologist for complications of her CADASIL. She'd been off the medication for a period of time. If we take the causality out of the equation, it became obvious to me that it may be a useful medication for her to stay on, to allow us to optimally manage her CADASIL so that there wouldn't be any symptoms that could be attributed to CADASIL that we're attributing to liver failure. I know that the patient and her family were concerned about her being off her CADASIL medications, may been influenced by that but – so the decision was made to restart it again as I – as I thought it would be helpful in her case and not – not the – not the culprit.

And it's the case, isn't it, that you subsequently understood that the purpose of the sodium valproate in connection with the CADASIL syndrome was to treat symptoms of migraine as opposed to modifying the disease. If you understood that at the time would that have changed your thinking as to, you know, that consideration for putting her back on?---It's – it's difficult to put myself back in that situation again. I think the question is if this is purely just to manage symptoms and we have alternative treatments to use if those symptoms arise then – then, yes, I think that the cad – valproate – there would be no necessity to restart valproate again.

Okay. With the benefit of hindsight, do you think the decision to put Mrs Doherty back on the sodium valproate because of your then understanding that it might be helpful for the CADASIL syndrome, in managing the CADASIL syndrome, do you think that that was an opportunity for you to contact Dr Walsh and speak to him about the purpose for the valproate and the need for the valproate?---Yeah. My recollection is that – is that I had instructed my team to speak to Dr Walsh. I didn't do that personally and that probably would have been a much more effective way of communicating directly with him to ask that specific question but the team were – were getting letters and other things that – that would give me some advice as to the need for valproate.

(My underlining)

204. In respect of recommencing sodium valproate, Counsel for NOK submits:

(a) Sodium valproate should never have been administered;[185] and

(b) Efforts should have been made to consult with Dr Walsh at an early stage.[186]

205. Counsel for the RBWH did not make any specific submission on the issue of recommencing sodium valproate.

206. Having regard to the above evidence, I make the following findings:

(a) Dr Skoien knew that sodium valproate was "*a well-recognised cause of DILI"* albeit that fatal outcomes were rare;

(b) Regardless of the rarity of fatal outcomes, Dr Skoien should have considered sodium valproate as a potential cause of Mrs Doherty's liver injury until such time as it had been excluded on biopsy, even if he considered it to be unlikely or down the list compared to other differential causes;

(c) To the extent the timing of Mrs Doherty's liver injury influenced Dr Skoien in his discounting sodium valproate as a potential cause (i.e. where the symptom onset for liver injury was more than 12 weeks after Mrs Doherty commenced the drug), Dr Skoien was in error, as he appropriately acknowledged under cross-examination;

(d) It is clear from the records of both the Caboolture Hospital and the RBWH that the indication for sodium valproate was for the prophylaxis of migraine and its symptoms. On review of the record, this should have been apparent to Dr Skoien. That is, it should have been apparent to Dr Skoien that sodium valproate had been safely ceased at Caboolture Hospital;

(e) To the extent there was any doubt about the safety of ceasing sodium valproate in the context of Mrs Doherty's CADASIL, there was an opportunity for Dr Skoien to contact Dr Walsh for a consultant-to-consultant discussion about the indication for which sodium valproate had been prescribed before deciding to recommence the drug, but that did not occur;

(f) To the extent Dr Skoien's decision to recommence sodium valproate was influenced by the concerns of Mrs Doherty and her family about her being off "*her CADASIL medications*", that should not have over-ridden the potential for sodium valproate being the cause of Mrs Doherty's liver injury (even if considered unlikely) until it had been excluded on biopsy;

[185] Paragraph 3(c)(iv) Written Submissions of Doherty Family
[186] Paragraph 3(c)(v) Written Submissions of Doherty Family

(g) Given the indication for which it had been prescribed, there was no reason to recommence sodium valproate on 29 April 2020; and

(h) Considered prospectively (i.e. without the benefit of hindsight), Dr Skoien's decision to recommence sodium valproate on 29 April 2020 was not appropriate.

The timing of the biopsy on 30 April 2020

207. I reiterate that, at the Inquest, Dr Gonsalkorala's evidence was as follows:

> *And was that part of the reason for your contacting Dr Skoien on the 17th to discuss the need for transfer and the need for biopsy on the 17th?---Correct, because at that stage we really were still unaware as to what was causing her liver injury. She was in a hospital where gastroenterologists did not admit patients. We did not have a full hepatology service. So when liver tests start to increase, especially INR, really that's the point in time when they need to go to a tertiary centre. And one of the reasons is for more hepatology care, but also for consideration of a liver biopsy. So those are the two main reasons.*
>
> *And was there any indication – was there anything in your understanding of Mrs Doherty's situation at that time which was against doing a biopsy at that stage?---No, there wasn't.*

208. Mrs Doherty was transferred to RBWH on 20 April 2020. A liver biopsy was not performed until 30 April 2020.

209. Dr Sethi opined that, in his view, liver biopsy should have proceeded very soon after arrival at the Caboolture Hospital (the inference being, that if that were not the case, it should have proceeded shortly after transfer to RBWH).[187]

210. Dr Skoien explained:[188]

> *Liver biopsy is an investigation that carries a rare risk of severe internal bleeding. The official Queensland Health Consent Form for Liver Biopsy quantifies this risk in the vicinity of 1 in 500 patients, though the risk of significant bleeding is higher in patients with liver failure and/or receiving anticoagulant therapy. Death due to severe internal bleeding is a rare complication (1 in 1000 patients is commonly quoted as the risk) but I would suggest that all hepatologists would have had personal experience with this adverse outcome. (It is much more common, for example, than death due to valproate-induced liver failure, which is estimated to affect approximately 1 in 40,000 patients using valproate).*

[187] Ex D3 BOE
[188] Ex C2.15, paragraphs 55(c) and 55(e) BOE

Treating clinicians therefore do not request a liver biopsy for every patient who presents with jaundice and acutely deranged LFTs.

Where the cause for liver injury is not clear and/or there is no improvement after usual management, the potential diagnostic benefits of liver biopsy are considered to outweigh its risks.

Medical practitioners are required to weigh the risks and benefits of all investigations. When a biopsy is ordered, it is because the diagnostic benefit (and possible access to specific treatment) outweighs the rare but severe risks that are associated with this invasive test.

The timing of biopsy, however, depends on other results (i.e. whether the likelihood of a diagnosis is established removing the need for biopsy) and the state of the patient (i.e. impending liver failure). In Mrs Doherty's case, one of the reasons for transfer to the RBWH was for consideration of liver biopsy, but this was only after she had been appropriately assessed at Caboolture Hospital. For this reason, I disagree with the statement that a liver biopsy should have been performed very soon after arrival at Caboolture. It is my opinion that, if applied to every case of unexplained jaundice, the harms associated with this approach would almost certainly outweigh any benefits as the diagnosis can usually be established with less invasive and lower risk investigations and clinical work-up.
….
As discussed earlier, liver biopsy is not undertaken lightly but I agree that it became a necessary investigation in Mrs Doherty's case. At the RBWH, liver biopsy is performed by an interventional radiologist under ultrasound guidance. (Some clinicians still perform bedside liver biopsy but, due to an increased risk of adverse events, most professional guidelines now recommend ultrasound-guided liver biopsy and this has been the standard of care at RBWH since 2007). To minimise the risk of bleeding, it is common for interventional radiologists to ask for a patient's coagulopathy to be corrected (International Normalised Ratio, ***(INR),*** *< 1.5) with clotting factor support (given intravenously) prior to the procedure. Although the medical notes on 21 April 2020 state "need to correct INR to < 1.4", the plan was for Mrs Doherty's INR to be corrected to< 1.5 (i.e. 1.4 or lower), in line with usual practice at RBWH. This required some peri-procedural interventions but did not significantly delay the procedure.*

As outlined in Dr Sethi's report, the biopsy was initially planned for Wednesday 23 April 2020 but this was subsequently deferred on clinical grounds, as explained below:

> *Upon review on 22 April 2020, I assessed Mrs Doherty as clinically stable and possibly reaching the "peak" of her illness. At this time, I discovered that the patient had been given her usual aspirin (200mg mane and 100mg nocte) since*

admission to RBWH (on 20-April-2020). This was immediately ceased as it can contribute to serious bleeding. Whether these two days of aspirin were all that she had received since admission to Caboolture Hospital on 10 April 2020 was unknown.

On further investigation, it became clear that her aspirin had been continued throughout the patient's admission at Caboolture Hospital. This was despite the fact that the need for a liver biopsy was the primary reason for considering transfer to RBWH. Continuous aspirin use prior to liver biopsy increases the risk of severe bleeding and standard practice is for aspirin to be withheld for 1 week prior to liver biopsy.

To assess how this altered Mrs Doherty's management plan, I urgently discussed how any significant increase in bleeding risk affected Mrs Doherty's risk benefit ratio with the interventional radiologist scheduled to perform the procedure.

The advice that I received was that aspirin can be continued where it is critical to the patient's well-being but would definitely increase the risk of bleeding.

*Whether to proceed would depend on whether the benefit of biopsy outweighed the increased risks associated with doing the biopsy on aspirin. In Mrs Doherty's case, on the day of planned biopsy, there was a small but potentially significant improvement in her bilirubin (fell to 390 µmol/L from 450 µmol/L) on the back of a steady and continuous improvement in her transaminases …... Given these results and the increased risk of bleeding associated with her aspirin treatment, I felt that the benefits of proceeding with liver biopsy on 23 April 2020 did **not** outweigh its risks and the procedure was deferred.*

Over the course of the next week, as the effect of aspirin washed out, Mrs Doherty's condition did not improve as expected. The biopsy was then performed as soon as possible.

This was to be undertaken on 29 April 2020 but urgent neurological/stroke cases saw her procedure delayed until 30 April 2020. ("Bumping" of planned procedures due to other urgent, immediately life-threatening cases is an unfortunate fact in the public hospital system where capacity is limited). Although her condition did not improve significantly up until the date of the biopsy, it is worth noting that her LFTs did not get precipitously worse over this time frame.

….

Once the decision is made to perform liver biopsy, it is true that the sooner the result is known the better. It must be pointed out, however,

that liver biopsy does not always provide a clear-cut diagnosis. In Mrs Doherty's case, the biopsy was initially reported as showing a hepatitis pattern with "relatively mild" inflammation and "prominent lobular apoptosis". This did not narrow the list of differentials significantly with possible causes for these appearances reported to include "autoimmune hepatitis ... , a medication .... , and a viral infection". As the changes were not classically diagnostic of one aetiology, and all these possibilities were being actively considered prior to the biopsy, the initial report did not actually provide much additional guidance.

After the initial report, I arranged for Mrs Doherty's slides to be reviewed by a specialist liver histopathologist. This histopathologist (Professor Andrew Clouston) is available on a weekly basis (Wednesdays) to provide an expert opinion on recent liver biopsies. It was after this review on 6-May-2020, that valproate-associated liver injury was favoured as the most likely cause. It is worth noting that, even then, the changes were not typical of those reportedly seen in valproate toxicity and Professor Clouston was only able to conclude that the biopsy showed a severe acute hepatitis with "features favouring DILI". Nevertheless, although this illustrates the limitations of liver biopsy interpretation even for an expert, I agree that this was without doubt the correct diagnosis.

(Dr Skoien's emphasis)

211. At the Inquest, Dr Skoien provided the following evidence:[189]

Now, while we're talking the biopsy, and I won't take you directly to your evidence about this because you outlined in detail in the statement, but one of the considerations in performing the biopsy in a patient such as Mrs Doherty is the risk of bleeding; is that correct?---Yes.

And it's a balancing exercise of whether or not the biopsy is required for diagnostic purposes, as transpired in this case, and balancing that risk of bleeding or making a risk assessment essentially; is that right?---Yes, that's right.

In the case of Mrs Doherty, by the time the decision was made to transfer her on the 17th of April, her INR level had increased to the level that formally resulted in a diagnosis of liver – acute liver injury?---That's correct. And – and – and also had pushed her into a category of patient for whom there was, on balance, a probability, a chance, that she would continue to get worse and so therefore transferring to facilitate a biopsy during the next week made sense.

[189] T3-11, L32 – T3-12, L46

But having an INR level of 1.5 for example, which it was on the 16th of April, isn't a contraindication for liver biopsy, I take it?---Most interventional – all our biopsies at the Royal Brisbane Hospital are done by interventional radiology. We no longer do bed – bedside ones of – of our own because of the risk of bleeding. So the ultrasound guided and the radiologists are generally comfortable with an INR of 1.4, 1.5, usually less than 1.5 is what they ask us to achieve and then they do some techniques that plug the – the – the hole in the liver essentially just to stop any bleeding as well. But less than 1.5 is usually the – – –
Their preference?---Their preference.

All right. Now, just again on the issue of the biopsy, I think there was an initial plan to do a biopsy on the 23rd of April; am I correct?---That's right.

And it became clear to you at your assessment, your initial assessment of Mrs Doherty on the 21st of April, that she was on aspirin?---Yeah. When she had been admitted, because by the evening staff she'd been commenced on medication including her aspirin. Now, obviously for – for a biopsy we want people to be off anticoagulants and so not stopping the aspirin is – was what was advised. But – and then it later became obvious that she hadn't had her aspirin ceased at Caboolture at all and she was still on the aspirin which meant that she essentially had platelets that wouldn't have worked properly. Now, we can do therapeutic procedures on aspirin with minimal bleeding risk but liver biopsy, because any serious outcomes are directly related to bleeding and death is a consequence of bleeding in rare circumstances, the – the ongoing use of aspirin heightened the risk to her of liver biopsy and so that had to adjust the risk assessment, as you say, in terms of whether we go ahead with the biopsy on the 23rd or defer it.

I understand from your statement you consulted the neuroradiologist in relation to that?---That – yeah, that's right, spoke directly to him.

Yes. Or the interventionist radiologist, I should say. And there was – is it the case there was some agreement between the two of you as to what that risk would look like for Mrs Doherty and the decision was made not to proceed at that time?---My conversation with Dr Ngai was along the lines of, "She's had aspirin on board all this time. It raises the risk. How comfortable are you biopsying her on aspirin?"

With an INR of 1.5?---With an INR of – yeah, one – the INR is something we can generally correct periprocedurally and do it for long enough that minimises any ooze that can – can occur. We can't really fix aspirin except to let it wash out and have new platelets time to recover. Even giving patients platelets doesn't particularly reverse the effects of aspirin. And his words to me was, "Well, there's not no risk if you go ahead with this biopsy – no additional risk if you go ahead with this biopsy. There's always some risk. It's really a case of whether you

think she desperately needs it tomorrow or whether she can – or whether she can wait."

Yes?---And I agreed that I would wait for her morning blood test to come back to see whether there had been any significant improvement. If there wasn't, we would have to go ahead. If there was, we could sit tight.

212. Dr Skoien was then taken to some of the blood results from and following 23 April 2020:[190]

---Yeah, you can see her – her bilirubin was 410, 420 then 450 and then the following day when I was having the conversation with the inter-radiologist it had dropped to 390 and her transaminases were 900.

Is the drop to 390 on the 23rd from a level of 450 on the 22, that rather suggest that were an improvement at that stage?---Yes.

Is that for biopsy then or against biopsy?---It – it's usually against biopsy because in many cases of acute liver injury the biopsy may not give you the information you need or will not change your management and so the – the patient recovers and so if you've put someone at risk of an investigation that carries some high risks then you've essentially exposed the patient to risk that he or she didn't need to undergo.

Okay. Now – – –?---And that – that is sort of why racing into a biopsy early in patients with acute liver injury is not something we normally do because most of those patients will recover and if you biopsy a thousand patients you'll – one patient will die.
….
If we go back and look at the bilirubin for the days that follow – – –?---Yeah.
– – – the 23rd, in the period when the sodium valproate had been ceased there is quite a significant increase in the bilirubin?---Yes, that's right.

And how that might be accounted for, even with the benefit of hindsight?---No. What it means is that the improvement in her bilirubin on the 23rd was a false storm that her liver disease was progressing and – and so it tipped the balance back in favour of having a biopsy when it was safe to do so.
…..
When – you indicated just before that when the bilirubin started to rise again from the 24th of April and then quite significantly on the 25th and 26th of April, you indicated that that was – there was a need for a biopsy at that point in time when safe. She'd been off – sorry, Mrs

[190] T3-14, LL1 – 45; T3-15, L 15 – T3-16, L22

Doherty had been taken off the aspirin I think around the 21st of April; is that right?---That's right.

Would it – was it possible that notwithstanding it takes some time for the aspirin to wash out that the biopsy could have taken place on either of those days, that is the 25th or the 26th of April?---My recollection is we didn't have an option to do a biopsy on – on those days, and in fact even when she was scheduled to have a liver biopsy her case, albeit she was very sick, was bumped by another more urgent case which is one of the things at the Royal Brisbane Hospital is – we take everybody from around the state.

Yes. I think it's important that we understand what a biopsy looks like. It's not a simple procedure, is it? Do you want – can you explain to us what a biopsy involves?---So, you're putting a very fine, hollow needle into the organ and the liver, to do its job, is a network of blood vessels and in taking a sample with a – with a needle and it's – it's hollow to take a core, a bit like if you take a core out of an apple. It's obviously much finer than that but you're literally taking a core of tissue out of the – of the patient's liver. You're going to cause some bleeding. It's done under sterile conditions. It's done using ultrasound guidance to make sure that the operator's missing major vessels. The patient may often need some sedation to keep the patient from moving or breathing erratically. The liver moves with respiration so it's a moving target to some extent. So it's – it's not an easy thing to do and it's something that gastroenterologists and hepatologists have stopped doing because it's a risky procedure. So it's – and it's not – it take – it doesn't take – the actual taking of the biops – biopsy itself may take a few minutes to do but actually the preparation in, the booking in, any sedation, the recovery, that – that all takes half an hour, an hour.

And those who are doing the liver biopsies at the Royal Brisbane Hospital I take it are not just doing liver biopsies, they're doing a lot of other things as well; is that right?---They're doing stroke retrieval, treating cancers, stopping bleeding, all sorts of other things that happen in – in a major hospital.

Yes. And so more urgent cases might in fact involve, you know, the need to retrieve a clot from a stroke victim or something like that?---Unfortunately that's the case, yes.

Yes. So those sorts of emergencies trump, you know, the need for a diagnostic procedure which is essentially what the purpose of the biopsy was in this case?---That's true. We – every team who looks after patients is congregating at the point of the operator who can do procedures that day and everyone's pushing for their case to be done and we just sometimes have to triage those according to who needs to be done urgently and who can wait a day or two.

All right. So if I could put it to you this way, after the initial balancing exercise as to – you know, the risk balance exercise in relation to whether the biopsy could have been performed on the 23rd of April, the decision was made to book her in – Mrs Doherty in for the 29th of April, that was the plan?---The plan, yes.

And that would have allowed sufficient time for the aspirin to be washed out of her system so that that additional risk was eliminated and her – Mrs Doherty's INR could be effectively managed leading up to that biopsy. And unfortunately that biopsy didn't go ahead that day because there was an emergency, need for another treatment on that day or another investigation that day?---That's correct.

213. As to whether an earlier biopsy might have altered the outcome for Mrs Doherty, Dr Skoien's evidence was:

> *If a liver biopsy had of been performed at an earlier stage than what it was in Ms Doherty's case, the results from that biopsy would have greatly assisted you in determining how then to conduct the care of her, is that correct?---I think – I think that's fair in that on expert review of the biopsy it became clear, as I said to Mr Schneidewin, that valproate was the culprit. So – yes. Theoretically, if she had had a biopsy much earlier in her care, we may have reached that diagnosis with more certainty sooner. It may not have changed what happened to her. I do acknowledge that L-carnitine wasn't offered in her case.*[191]

214. As to the need to defer the biopsy because Mrs Doherty had been maintained on aspirin, A/Prof. Majumdar gave the following evidence:[192]

> *I think the biopsy had been planned initially for the 23rd of April, shortly after being transferred to the Royal Brisbane and Women's Hospital. And it didn't go ahead. And it didn't go ahead, one of the reasons it did not go ahead is because it was revealed to the treaters at the Royal Brisbane and Women's Hospital that Mrs Doherty had been maintained on aspirin for the period of time that she had been at Caboolture and for the first couple of days at Royal Brisbane. Do you have any – and also her INR level was relatively high by that time. Do you have any comments to make about the appropriateness or not of deferring the performance of the biopsy at that particular time for those reasons?---<u>You know, I guess it depends on local centre expertise. There is a number of ways to perform a liver biopsy, the most standard way is percutaneous or through the skin directly into the liver under ultrasound guidance. The other more – most – sorry, not most common, but the other common way to do this is via a trans-jugular route, so access through the large vein in the neck and that carries a lower risk of bleeding in terms of bleeding from the liver into the peritoneal or into the abdomen peritoneal space. So, usually in these situations where there's a concern about coagulation, a trans-</u>*

[191] T3-27, L 45 – T3 -28, L3
[192] T5-27, L1 – T5-28, L 24

jugular approach is used. Aspirin is really operator-dependent. The decision to stop aspirin, if you take a survey of individual radiologists who do biopsies, you'll find that some will be very adamant in terms of seven days of cessation. Others won't. And, you know, in terms of our local centre practice here, we don't regard aspirin as a problem for liver biopsies, even percutaneous liver biopsies. However, if someone is advancing along the acute cardio spectrum, the relevance of a biopsy, if they are potentially being considered for transplant, it has to be decided, because there is risks associated with biopsy, bleeding, but also if you are using the trans-jugular route, it can cause things like arrhythmia or other – compromise the structures around the liver as well during access. So there's a few – it's not a completely benign procedure, is what I'm trying to convey.

Sure. And can I say to you that, at the Royal Brisbane – the evidence is that, at the Royal Brisbane Hospital, Women's – Royal Brisbane and Women's Hospital rather, the approach to undertaking liver biopsies is for the interventional radiology team to do so under ultrasound guidance. So the percutaneous biopsy that you're describing, just to be clear on your evidence, that does create a higher risk of bleeding than the alternative method that you described through the vein?---Yes.

But, as I understand your evidence, the decision to proceed or not for a patient who is being maintained on aspirin is really the operator's decision; is that right?---That's correct.

Whereas, in your centre, that would not be a significant – the maintenance of the patient on aspirin would not be a significant consideration in circumstances where there was an indication for biopsy?---No, the – sorry, that is correct. There's no standardised guideline that I'm aware of from the international radiology societies that give a consensus recommendation to biopsy on aspirin. It's more a reflection of liver transplant centres who do more biopsies, do more frequent biopsies, and in sicker patients, where the confidence and the centre experience is there. Also, the technical ability, having – doing a larger volume of these biopsies is there amongst the interventional radiology staff. So, it is something that is, not, you know, perhaps universal amongst higher volume centres in terms of liver disease that aspirin wouldn't be a consideration, but there are plenty of places in Melbourne, in Victoria, in Australia, clearly in Queensland, where aspirin would be regarded as a contraindication.

Sure. And we're not really comparing apples and oranges when we're comparing your facility, which is a liver transplant facility, where you've indicated a high level of expertise dealing with very sick patients, compared to a hospital like the Royal Brisbane and Women's Hospital, who are treating and managing and attempting to diagnose the cause of the condition. You would agree that that's not really – the comparison between the facilities is not really a

reasonable – well, not an equivalent comparison, I take it?---No, in terms of interventional radiology expertise for liver biopsy there may be a difference, a difference in practice.

Okay, so you're not critical of the decision then to defer the biopsy because the patient had been maintained on aspirin on this occasion?---I mean, in my own practice in our own centre, we would, as I said, it would not be a barrier to proceeding with the biopsy. But, you know, it's one of these things that the person who's on the end of the needle and doing the procedure really has the ultimate say whether they will go ahead and they feel the risk is appropriate or not. So, you know, if the radiologist who was asked to perform the procedure refused to do it unless the aspirin was out of the picture, then it is very hard to be critical of that without a consensus recommendation from the interventional radiology societies on what to do about aspirin.

(My underlining)

215. Later, under cross-examination by Ms Robb KC for the RBWH, A/Prof. Majumdar stated:[193]

Yes, I would agree that the pressures certainly do result in delays. As you will note it, in the medical record, Mrs Doherty had given a lot of blood products prior to the biopsy, she was initially given blood products on arrival. So cryo precipitate FFP, which had an influence on her INR at that stage. And again she received a similar amount of blood products prior to the scheduled biopsy when it was done on the 30th. And so those logistical issues, you know, do cause a lot of issues in tertiary hospitals that are pressured and we have the same problems here when we do have to administer blood products before the radiologist will do a procedure. The justification from aspirin, I think that probably needs a concerted review in terms of whether aspirin should be a contraindication to percutaneous biopsy. But certainly it isn't generally an issue with trans-jugular liver biopsy. However, there are issues with trans-jugular liver biopsy in that first you need the radiologist who is experienced in trans-jugular liver biopsy and, secondly, you need a pathologist who's happy to report on a trans-jugular biopsy, because the sample is not as – the morphology of the sample is different because of the type of needle used. So pathologists are often less likely to make such detailed assessments as Professor Clouston on a trans-jugular biopsy alone. But I think the aspirin issue is a contentious one in current practice. And it is something that, unfortunately, there is no consensus among radiologists, and perhaps that should be a recommendation from this, whether, you know, there should be a bit more of a firm position one way or the other.

[193] T5-45; LL 3- 46

….. Some evidence was given by Dr Skoien, who was the hepatologist at the Royal Brisbane, to the effect that it wasn't just the case that the radiologist said, "No, I won't do it if aspirin's on board", but that it was a fairly negotiated or nuanced process and he said that he spoke with the interventionist radiologist, they talked about aspirin and the pros and cons, they talked about the INR and the ability to correct that with platelets, but that they couldn't – they didn't have a same way to remedy the aspirin they were aware of and that what they resolved to do was to recheck her results the next morning and make a judgment call based on that. So does something about that degree of interdisciplinary cooperation and concern for the specific variables and the specific patient they're looking at give you some comfort that the clinical judgement made was likely to be sound?---Yes, I think so. And in these situations where there is no formal guidance on what to do and aspiring being a controversy, it is really individual case discussion at a multidisciplinary level, which has seemed to have occurred here. Unfortunately, you know, that's not captured in the evidence that I was given. So it's really hard and, although I was trying to be as circumspect as possible, working in these environments, it's very difficult to know about these conversations if they're not documented. But it does, if it was a concerted discussion and that was the outcome, I think that's reasonable because again there's no guidance on saying, you know, you should or you shouldn't do liver biopsy on aspirin. And this is a rapidly-evolving field in terms of, you know, what we do in terms of procedures to patients with acute and chronic liver failure.

(My underlining)

216. Counsel for NOK submitted that:

(a) "*It is clear from the initial hepatology review at the RBWH on the morning of 21 April 2020 that a biopsy was required. A biopsy was booked for 23 April 2020.35 That same biopsy booking was still being contemplated on the mornings of 22 and 23 April 2020. At 8:30 on 22 April 2020 Dr Rowe made an entry to cease aspirin and notes that Mrs Doherty has had two doses of aspirin as (an) impatient (at RBWH). At 07:45 on 23 April 2020 there is an entry in the Progress Notes by Dr Skoien suggesting the biopsy may not go ahead if there is significant improvement in the LFT. The entry also refers to Mrs Doherty being on aspirin for CADASIL; notes that the IR (Interventional Radiologist) (is) normally happy to biopsy on aspirin; but that there is a need to confirm with operator prior to sending to biopsy. There then follows an entry by Dr Rowe at 08:55 "Not for liver biopsy today*." [194]

(b) "*There has been no explanation given from anyone involved with Mrs Doherty's care at either hospital as to why aspirin was not withheld from 17 April 2020 (or soon thereafter), the date at which it was decided Mrs*

[194] Paragraph 18 Written Submissions of Doherty Family

Doherty was being considered for a liver biopsy. It appears the first time anyone turned their mind to this topic was the day before the scheduled biopsy." [195]

(c) Aspirin should have been withheld when or shortly after it became known that Mrs Doherty was to be transferred to the RBWH (decision made on 17 April 2020);[196] alternatively

(d) Aspirin should have been withheld upon Mrs Doherty's transfer to RBWH or shortly after.[197]

(e) "*Counsel Assisting submits that it is open to Your Honour to find that it was hypothetically possible (but not certain, and not necessarily likely) Mrs Doherty could have undergone liver biopsy earlier than she did (depending on the restraints of the public hospital system), and that it was hypothetically possible (but not certain, and not necessarily likely) that sodium valproate would have been identified as the culprit before the decision was made to recommence the drug on 29 April 2020. It is submitted it is open to Your Honour to find that both of theses events were likely to have occurred.*

(i) The scheduled biopsy for 23 April 2020 was only cancelled that morning and after consultation with the IR. There is sufficient evidence for Your Honour to find that it was likely that the biopsy would have been performed on 23 April 2020 with earlier cessation of aspirin.

(ii) Likewise, while it took six days for the DILI diagnosis to be indicated from the date of the biopsy of 30 April 2020, there is no evidence about the availability of Prof Clouston at the relevant times. It must be observed that the decision as to whether to recommence the drug would likely have been delayed until the biopsy results were known. It is open for Your Honour to find that it was likely that sodium valproate would have been identified as the culprit before the decision was made to recommence the drug.

(iii) *What flows from those two findings, if they were made, is that a hypothetical benefit would have accrued to Mrs Doherty from having an earlier liver biopsy. That benefit is knowledge and an improved chance of recovery. As the experts and Dr Skoien agreed, the cessation of the culprit drug is the most important step in managing DILI*."[198]

217. Having regard to all of the evidence available, I find as follows:

[195] Paragraph 19 Written Submissions of Doherty Family
[196] Paragraph 3(b)(v) Written Submissions of Doherty Family
[197] Paragraph 3(c)(iii) Written Submissions of Doherty Family
[198] Paragraph 20 Written Submissions of Doherty Family

(a) The decision made on or about 17 April 2020 to transfer Mrs Doherty from the Caboolture Hospital to the RBWH for the purpose of, *inter alia*, giving consideration to her undergoing liver biopsy was appropriate;

(b) For reasons discussed above, it was appropriate that Mrs Doherty remain at Caboolture Hospital over the weekend immediately prior to her transfer to the RBWH on 20 April 2020. It is not the case that she would have been considered for liver biopsy on an urgent basis over the weekend;

(c) In contemplation that Mrs Doherty may require a liver biopsy upon transfer to the RBWH, it would have been appropriate for the medical practitioners at the Caboolture Hospital:

    (i) to cease aspirin at the Caboolture Hospital from the time the decision was made to transfer Mrs Doherty for consideration of biopsy; or

    (ii) alternatively, to consult with medical practitioners at the RBWH, including the hepatology team and/or the interventional radiologists, as to whether cessation of anticoagulant medication (aspirin) was required;

(d) Upon initial review of Mrs Doherty at the RBWH it was noted Mrs Doherty was taking aspirin.[199] Given that one of the two main reasons for the transfer was for consideration of a liver biopsy, it would have been appropriate to cease aspirin from the time of admission to the RBWH if that had not already been ordered by the medical practitioners at the Caboolture Hospital;

(e) Upon learning that Mrs Doherty had been maintained on aspirin throughout her admission to the Caboolture Hospital and that she had also been administered aspirin at the RBWH on 21 and 22 April 2020, and although there appears to be no consensus about the appropriateness of performing percutaneous liver biopsy on aspirin, it was appropriate for Dr Skoien, in consultation with the interventional radiologist who was to perform the biopsy, to postpone the biopsy to allow the aspirin to "*wash out*", and to monitor Mrs Doherty's blood results instead;

(f) With earlier cessation of aspirin at the Caboolture Hospital or the RBWH, it is likely Mrs Doherty could have undergone liver biopsy earlier than she did (depending upon the resourcing constraints of the public hospital system);

(g) In turn, it is likely that sodium valproate would have been identified as the culprit before the decision was made to recommence the drug on 29 April 2020; and

[199] Ex B1.2, page 62 BOE

(h) Otherwise, with sodium valproate having already been ceased as a potential cause for Mrs Doherty's liver injury at the Caboolture Hospital, no other hypothetical benefit would have accrued to Mrs Doherty from having an earlier liver biopsy;

218. Regardless of the likelihood of sodium valproate being revealed as the culprit prior to making the decision to recommence the drug on 29 April 2020, it was, in any event, not appropriate to make the decision to recommence the drug prior to the drug having been excluded as a cause on biopsy. That is, with the inappropriate decision to recommence sodium valproate having been made on 29 April 2020, I find that the "delay" in performing the liver biopsy was of no additional consequence to Mrs Doherty's outcome.

Whether L-carnitine should have been administer to Mrs Doherty

219. Dr Tan made the following observation:[200]

> *I have no personal experience of the use of L-carnitine in valproate-induced hepatotoxicity (I have limited experience with its use in urea cycle disorders and other metabolic conditions, but always under the direction of a metabolic physician). In a registry series of 92 patients with this condition, it is noted that 100% of the 10 patients diagnosed within 5 days of onset and treated with L-carnitine survived without needing transplantation, whereas hepatic survival was 48% in the entire L-carnitine-treated group and only 10% in the group that did not receive L-carnitine…. This should be considered as low-level evidence suggesting that early diagnosis (early cessation of valproate) and treatment with L-carnitine both influence the clinical outcome in this disease.*

220. At the conclusion of his report, Dr Tan states that one of the three measures he considered would have more likely altered the outcome for Mrs Doherty (compared to regular laboratory testing) was the administration of L-carnitine.[201]

221. Dr Sethi agreed that L-carnitine should have been administered to Mrs Doherty from 10 April 2020, with the probability that would have changed the outcome for Mrs Doherty.[202]

222. A/Prof. Majumdar reported:[203]

> *There is some evidence to suggest the L-carnitine may improve the outcome in Valproate induced liver toxicity. This is typically in the settings of Valproate induced hyperammonaemia, overdosage or in the paediatric setting according to published reports. A study of 92 patients (including children) with Valproate induced hepatoxicity found that starting L-carnitine within 5 days of presentation was*

[200] Ex D1, page 7 BOE
[201] Ex D1, page 8 BOE
[202] Ex D3, page 20 BOE
[203] Ex D6, page 4 BOE (references removed)

associated with higher chance of spontaneous survival (in 10 patients), but only 20 of the 42 patients given L-carnitine in the cohort survived. This suggests that even with L-carnitine, Valproate induced liver failure is associated with a poor prognosis. Given the severity of the deceased's liver failure and the relatively benign safety profile of Valproate, L-carnitine could have been considered based on the available evidence once the diagnosis was established. However, the evidence for efficacy is limited and hence it is unclear if it would have altered the eventual outcome in the absence of liver transplantation.

(My underlining)

223. At the Inquest, the issue was taken up with Dr Skoien as follows:[204]

… it's been suggested by some of the experts that it was a therapy that could have been offered to Mrs Doherty once it became clear that she had had an injury caused by the sodium valproate. Do you have any comments about that, which you would like to address?---I have no personal knowledge of the use of L-carnitine in this or any other form of liver injury. I wasn't aware of it at the time. It's a bit hard to become an expert on something that I had no awareness of at the time but my reading now suggests that what little evidence there is for L-carnitine is usually in children and usually immediately upon presentation, in the first few days. No one at the Caboolture Hospital suggested using that. No one at the Royal Brisbane Hospital suggested using that, in fact I think it was the Coroner who first suggested that that could have been used. My personal view of L-carnitine in Mrs Doherty's case is even if it may not have retrieved the situation, when she came to the Royal Brisbane I think she probably should have been offered that because it would have done no harm. In an effort to do as much as possible to help her, it could have been added. Again, my reading of the evidence currently in situations like Mrs Doherty's is that it wouldn't have retrieved her situation when she came to the Royal Brisbane Hospital but, again, it's fairly benign.

Okay. But to be fair to you, you have to know about the purpose – the therapy before it could even be offered?---That's right, yes.

Are you aware of whether it – has it been offered to any other patient in a similar situation at the Royal Brisbane Hospital since, that you're aware of?---This is the first case of severe toxicity due to valproate that I've seen. Obviously I haven't seen it offered to anyone else. I assume it would be available as an agent to be used at the Royal Brisbane Hospital. But I haven't seen it being – I haven't seen it used ever.

[204] T3-22, L34 – T3-23, L10

224. At the Inquest, in response to questions by Ms Robb KC for the MNHHS, Dr Sethi gave the following evidence about the known benefits of L-carnitine, making a number of appropriate concessions:[205]

> *… Do you accept that there's a fairly low level evidence base for the efficacy of L-carnitine in this presentation?---Yes, I do. Yes, I do. This liver – yes, I do.*
>
> *And do you accept, as Dr Skoien says in his letter that you've had access to, or in the letter of Dr Graham – and bear with me, I'm going to have to find the reference to this. I do apologise – that most of the evidence that supports its efficacy relates to its use in children with chronic illness and malnutrition. Would you accept that?---Yes, I do.*
>
> *And would you accept that the greatest benefit is seen when it's administered intravenously within five days of the onset of hepatotoxicity?---Yes.*
>
> *And would you accept that those, to the extent they could be described as optimum circumstances, were not the circumstances in which either hospital could have administered L-carnitine to Mrs Doherty?---Yes.*
>
> *And, in those circumstances, do you still maintain the opinion that it's likely, on the balance of probabilities, the administration of L-carnitine would have changed the outcome?---It's – it would have slightly – it would have given her – it – it may not have saved her life, but it would have likely improved her – her clinical status. It may not have – I accept it may not have – she still may have died, but it would – would have liked – it would have given her a – the best chance of a – best possible chance of a good outcome.*
>
> *Thank you. And the evidence is consistent with that, and certainly Dr Skoien accepted that, on a risk benefit analysis, there would be no harm in administering it and it would have been preferable to do so. But thank you for that reasonable concession….*

225. At the Inquest, A/Prof. Majumdar's evidence was:[206]

> *… All right. I've got one last topic, you'll be happy to hear, from my perspective and that is the question of whether or not a L-carnitine should have been administered after the causative agent of sodium valproate was identified as the most likely cause. And I've just got a few questions about this because you've indicated in your report that it might have been an available therapy or something to consider, but that there's not much data or literatures to suggest that it might have been helpful. Is that a fair summary of your reporting?---That's correct. So, I think the issue with the evidence for L-carnitine is that*

[205] T4-58, L43 – T4-59, L23
[206] T5-32, L50 – T5-33, L 38

it's historical controls, a very heterogeneous group of patients in toxicity with valproate, so it's used in the hyperammonemic – sorry, anaemic state and certainly that's the most common use of it and L-carnitine's major use in urea cycle disorders that produce high ammonia. So it's used for valproate-induced hyperammonemia, which is a – usually an overdose problem, is quite well established. Its role, however, in this situation is controversial, or I won't say controversial, but it's not – it is an established – I should say, it's not well – there's not a definitive amount of research to say that it will help. I guess the study that both myself and I think Dr Tan, the neurologist who provided an opinion as well, we both quoted the same study but I think we had different conclusions from it. One was that in my conclusion was that, you know, in the series of 92 patients, and again this is the matched historical control group, is it wasn't really a very well matched or, you know, statistically valid group to compare to, but their rate of spontaneous survival was lower than that of the contemporaneous group of patients who received L-carnitine. But if you look at the survival rate, it was still less than 50 per cent, so there's 48 per cent of people who survived with L-carnitine out of – in a small group study. So I think, if you're – basically this study was done by following a group of patients who had been given L-carnitine, then finding some patients who hadn't been in a similar situation, and trying to compare the two. So it's definitely an apples and oranges comparison over multiple time cohorts. And time has really been a major factor in the management of acute liver failure in the intensive care unit. So we know that acute liver failure management in the recent decade is far superior to what it was 10 years ago, 15 years ago, 20 years ago, and that's one of the issues with using this type of literature to make valid conclusions. But, that said, L-carnitine is a is a benign drug that has very little side effects and, much in the way that we would use in N-acetyl-cysteine, which is again another fairly benign enzyme, for paracetamol-induced liver toxicity and paracetamol-induced liver failure, we often start that empirically while patients are being worked up for their acute liver failure, if there may be some suggestion of paracetamol in the mix. And so, with L-carnitine, it's more in terms of the risk-benefit profile, although there may not be all that much benefit, the risk of administering it would have been low when the diagnosis was established.

226. Otherwise, at the Inquest Dr Tan made the following concession:[207]

… But the other one that you mentioned in addition to earlier cessation of valproate was the administration of L-carnitine. Now, again I'll ask you, is that something that you would defer to the hepatologists about or is that something that you have some specific expertise about from your own skills and education and experience?---No, I would readily defer to a hepatologist regarding the appropriateness of that treatment.

[207] T6-15, LL 23 - 28

227. Having regard to the very limited support in the literature for the efficacy of L-carnitine in the treatment of sodium valproate hepatoxicity (which is, apparently, limited only to a very short period following the initial onset of hepatoxicity symptoms), and despite the treating team's lack of awareness of the agent's potential benefits in this context, I do not consider it inappropriate that L-carnitine was not administered to Mrs Doherty.

Issue 6

Whether any aspect of the treatment and management provided to the deceased from 1 November 2019 caused or hastened her death?

Issue 7

Whether any failure to provide treatment and management to the deceased from 1 November 2019 caused or hastened her death?

228. It is convenient to address these issues together.

229. Counsel for NOK submits:[208]

(a) There was an unexplained reluctance by various medical practitioners at various times to obtain relevant and further information about Mrs Doherty that was readily available. By failing to consult with practitioners that had previously treated Mrs Doherty and/or failing to obtain documents or information about her prior treatment, multiple opportunities were missed that could have led to an earlier diagnosis and more appropriate treatment;

(b) While an accumulation of conduct or omissions may have contributed to Mrs Doherty's death (outcome changing), there is insufficient evidence to support the finding, to the relevant standard of proof, that any particular aspect of the treatment and management of Mrs Doherty caused or hastened her death; and

(c) Perhaps the most significant failure in the treatment and management of Mrs Doherty, and the one that could have been outcome changing, relates to medication. On admission to both hospitals it was noted that Mrs Doherty was prescribed sodium valproate for migraines. Despite there being consensus that all possible culprit medications should be ceased while trying to diagnose an acute liver injury,3 Mrs Doherty was administered 13 doses of sodium valproate in the three weeks following her admission. Further, at the time it was decided that Mrs Doherty was a candidate for a liver biopsy, no further aspirin should have been administered to her. The Inquest has not received or revealed any clinically valid explanation for these 'medication failures'.

230. Ms Robb KC for MNHHS submits:

[208] Paragraph 3(d) Written Submissions of Doherty Family

"*10. With the benefit of hindsight, the facts and circumstances surrounding Mrs Doherty's death trace a straight line from sodium valproate to the liver injury from which she did not recover.*

11. However, the effect of the evidence of those health practitioners that treated Mrs Doherty, the clinical record, and the expert evidence drawn from several areas of medical specialisation, is that a level of real complexity attended to investigating and establishing the cause of Mrs Doherty's liver injury.

12. While different courses of action could and certainly with the benefit of hindsight would have been taken – including to cease sodium valproate early in the trajectory of Mrs Doherty's injury and to not recommence it – at its highest, the evidence supports the conclusion that while there were prospects of a different outcome it could not be said the outcome would have been different had any different course been taken."

231. I will limit my consideration of whether the outcome would have been any different for Mrs Doherty in the event of the following hypothetical counterfactuals:

    (a) sodium valproate was ceased sooner than was the case on 17 April 2020 (last dose at or about 2000 hours on 16 April 2020); and

    (b) sodium valproate was not recommenced on 29 April 2020.

232. As outlined above, the requisite standard of proof to be applied to these questions is the civil standard but on the sliding *Briginshaw* scale.[209]

233. The issues are most appropriately considered having regard to the expert evidence of the hepatologists.

Sodium valproate was ceased sooner than was the case

234. As I have found above, it would have been appropriate to cease sodium valproate at Mrs Doherty's admission to the Caboolture Hospital on 10 April 2020 (or soon thereafter). The evidence does not establish that it would have been appropriate for a medical practitioner to cease the drug at any earlier time.

235. Dr Sethi opines:

> *It is likely, on the balance of probabilities, that the deceased would have survived with appropriate treatment and management from on or about 10 April 2020. I shall outline my reasoning below. If her treating doctors had reasonably recognised Epilim to be responsible for her severe liver dysfunction, this would have been ceased thereby preventing further liver damage from occurring over the next few*

[209] *Anderson v Blashki* [1993] 2 VR 89 at 96 and *Secretary to the Department of Health and Community Services v Gurvich* [1995] 2 VR 69 at 73

weeks. The drug was continued for a further four days[210] *then recommenced later. Had this not occurred, Ms Doherty would have had the best possible chance of a good outcome.*

(My underlining)

236. At the Inquest, Dr Sethi summarised his opinion as follows:[211]

MR SCHNEIDEWIN: And – so just to be clear about your view as to potential survivorship – [survival], rather, of Mrs Doherty, I'll ask you to assume these things: if, at presentation to the Caboolture hospital on the 10th of April, sodium valproate had been recognised as a potential culprit and ceased; if a biopsy had been arranged in that week that followed, that is, up until, say, the 17th of April at some stage; and if L-carnitine had been administered – or commenced some time during that week, what is your view in terms of whether Mrs Doherty would likely have survived?---My feeling is that Ms Doherty likely would have survived, had all those steps occurred. The only aspect in which my opinion has changed to some extent is just whether the – the utility about the liver function testing by Dr Walsh. Otherwise, no other opinions of mine have – there – I would not have had any other changes of opinion. The only reason the liver function monitoring – if it has changed – because I've now had the benefit of reading the opinion of other experts, which I didn't have before, but otherwise my opinion – to answer your question, I feel that Ms – I think it's on the balance of probabilities, I think Ms Doherty would likely have survived had all those steps you just – you just referenced had occurred.

Is part of the reason for that, in your view, that up until, say, the 17th of April, Mrs Doherty was in –had suffered an acute liver injury, but was not in acute liver failure at that stage? Is that part of your reasoning in terms of the - - -?---That's correct.
- - - outcome?---That is my reasoning, yes, because at that point she was still salvageable. She – she could still potentially have survived, yes.

(my underlining)

237. I make the following observations:

(a) For the reasons canvassed above, I have found that the fact L-carnitine was not administered to Mrs Doherty was not inappropriate;

(b) The evidence suggests that liver biopsy was not indicated until Mrs Doherty progressed to synthetic liver dysfunction (acute liver injury). This was diagnosed when the INR test of 16 April 2020 returned an INR of greater than 1.5.

[210] In fact sodium valproate was continued until 16 April 2020 (for a further 6 days)
[211] T4-41, L33 – T4-42, L10

(c) It is possible Mrs Doherty progressed to synthetic liver dysfunction (acute liver injury) prior to 16 April 2020, but that is indeterminable because INR testing was not performed in the intervening period after 10 April 2020; and

(d) As outlined above, once sodium valproate was ceased on 17 April 2020 (last dose at or about 2000 hours on 16 April 2020) it not likely an earlier biopsy would have altered the course for Mrs Doherty.

238. Considering these observations, the issue is thus reduced to whether cessation of sodium valproate alone at an earlier time in the period 10 April 2020 to 17 April 2020 would have altered the outcome for Mrs Doherty.

239. The opinion of Dr Sethi does not establish, to the requisite standard, that with the hypothetical cessation of sodium valproate at an earlier time in the period 10 April 2020 to 17 April 2020, Mrs Doherty would have survived.

240. A/Prof. Majumdar's evidence is most helpful in considering the second hypothetical counterfactual. For complete understanding of his evidence and the context in which it was given, I extract a lengthy passage from the transcript in the section following. Otherwise, in respect of first hypothetical counterfactual, he opined:[212]

> *…if in the hypothetical scenario the valproate had been ceased at presentation to the Caboolture Hospital on the 10th of April where the patient presented with acute hepatitis, not strictly speaking acute liver injury at that stage, is it more likely than not – sorry, I withdraw that. Are you able to say what Mrs Doherty's prognosis might have been in terms of [survival] if the drug had been ceased at that time?--- That's a very difficult question, especially without any time course really beforehand. I mean the assumption is that it was very acute within, you know, within the limits of the previous consultation with her GP prior to her presentation, which was in the order of two to three weeks. So assuming she was asymptomatic two to three weeks prior to presentation and there was no evidence of liver injury, then I would suggest that the chances of recovery, if valproate had been ceased straight away, you know, would be reasonable, more so than not. But there's no way of understanding exactly what the odds would be, or what the proportion of success would be. The issue is really related to the time course and if the process had been going on for months and months then that would be very hard to turn around, even with cessation of the drug. If it hadn't been doing that and it was all truly acute, then cessation before synthetic destruction would certainly carry a higher chance of spontaneous recovery with cessation of the drug than waiting until acute liver failure had developed.*
>
> (My underlining)

[212] T5-31, LL 26 - 44

241. There is a degree of hesitation evident in A/Prof. Majumdar's response given the difficult nature of the question. This is understandable. Although he appeared to be inclined towards the view that cessation of sodium valproate prior to Mrs Doherty progressing to synthetic liver dysfunction would have given her a reasonable chance of recovery ("*more so than not*"), his response was still qualified by the emphasis that it was difficult to answer the question with any degree of certainty.

242. Given the difficult nature of the hypothetical question and A/Prof. Majumdar's qualified response, it is not open for me to find that his opinion establishes, to the requisite standard, that with the hypothetical cessation of sodium valproate at an earlier time in the period 10 April 2020 to 17 April 2020 Mrs Doherty would have survived.

Sodium valproate was not recommenced on 29 April 2020

243. A/Prof. Majumdar gave the following evidence at the Inquest:[213]

> *Now, I want to ask you some questions about the causative consequences of restarting the valproate on the 27th of April, if I can. And you will recall from the record that I think an additional six doses were given from that date and again ceased after the biopsy – the initial biopsy report was received on the 3rd of May, so in the period 27 April to 3 May, Mrs Doherty received those additional doses of valproate. In that period, the biopsy was performed on the 30th of April, so Mrs Doherty had presumably received two, or possibly three, doses of valproate up to the time the biopsy was performed. Was there any indication on the biopsy that those early additional doses – I'll come back to the ones that were given after the biopsy – but those earlier additional doses contributed in any way to Mrs Doherty's liver injury or liver failure at that point?---Yes, it is really difficult to say often when you get to this situation of severe liver injury and bordering on liver failure at this point that we're talking about in Ms Doherty's course. Sometimes stopping the medication may not stop the process. So what happens in acute liver failure is that, whatever insult causes the initial inflammatory reaction in the liver, often precipitates a severe multi-organ failure type of inflammation, and that's due to the death of liver cells and the subsequent immune reaction. And that is a syndrome that often, by the time liver failure has developed, then even removal of the causative drug may not make a big difference. We also see this in the case, for example, the common thing that we see this in is hepatitis B where you can you put a patient on antivirals, suppress the antiviral or the virus completely, yet the liver failure will develop, the acute liver failure will develop. <u>So it's unclear when that exact point of cessation preventing the ensuing events would be. It's unclear exactly – and I'm sorry to be non-specific about this – but it is the reality of the situation that the extra three to six doses presumably would have made things worse, but in the same token, if you look at the seven days where she'd not received any valproate, her liver tests</u>*

[213] T5-29, L 37 – T5-32, L 48

still worsened. So it's really hard to know if the process had already been irreversibly commenced in the weeks ensuing or whether those extra days did make a direct difference, given that she was already progressing down this acute liver failure pathway. However, on first principles, I'd assume that extra doses when the diagnosis is related to the drug are not a good idea.

All right. I think that you indicated in your report, just if I can point you specifically to it, it starts on the bottom of page 3, and it runs over to the top of the next page. You indicated that the biopsy result was indicative of an older injury from weeks ago. Presumably due to the earlier administration of valproate, but also superimposed with apoptosis, suggestive of more damage associated with the reintroduction of the drug. So, is that objective evidence that there was some additional damage caused by the reintroduction of the drug?---It's really hard to say because, again, if this report was coming from anyone but Professor Clouston, I'd be taking it with a grain of salt. I think this kind of subtlety is really hard to tease out from a liver biopsy. Again, Professor Clouston was giving a second opinion, did have a full clinical record to review at the time, so I think with someone of his level of expertise, this is, you know, definitely a reasonable assumption to make. However, you know, the histological findings are still kind of out of – by histology I mean the biopsy findings – are out of keeping with the degree of liver failure. There wasn't a lot of necrosis, as you'd expect for someone with such severe liver injury with her INR going up. So it is really hard to say the degree, but I would be supportive, as I've mentioned before, that reintroduction of the drug was not helpful. How much could be reversed of the entire process, I can't give you any meaningful answer.
Okay. And just related to that issue, and you touched on it already, but I'll just take you back a step just to be clear, you were talking about whether the cessation of the drug at any point in time might stop the progression of the disease and you've highlighted that in the period of time that Mrs Doherty was not taking the valproate, in fact there was a progression of her disease in that period of time, which is, I think, the point you're making, a bit counterintuitive to the decision to cease. But, earlier on in your report on page 3, you you've made this point:

> *Ceasing the causative drug in many cases of drug-induced liver injury may result in spontaneous resolution. But that is not guaranteed in the case of valproate-induced liver injury due to the mechanism of the injury.*

Is that – are we to understand that valproate causes injury in a peculiar way, which makes it less likely that cessation – – –?---Yes. So, I'll explain that statement. Firstly, the degree of reversibility when stopping a drug depends on the degree of liver injury. So, in the early stages of acute hepatitis, ceasing the drug, you know, most likely will cause recovery or would lead to recover. In acute liver injury where

the INR is raised, then that possibility becomes a little less likely, but certainly by the time it's acute liver failure, the multi-organ failure that ensues, it's very unlikely that removal of the causative drug doesn't – changes the outcome. In terms of valproate, the mechanism of toxicity in the absence of overdose is thought to be related to mitochondria, so mitochondria are energy cells or energy units within cells, and mitochondrial toxicity typically will cause, or at least when there's a hepatitis associated with it, will cause like an inflammatory type reaction. So, it's unclear. And, again, this is a very amorphous type of reaction and a lot of drug injuries don't follow a specific pattern. In the cases have been reported with valproate-induced liver failure, even with cessation of the drug, there has been progressive liver failure and that's perhaps in – it elaborates that well enough in the report, but I think in this situation, as the mechanism isn't a distinctly defined mechanism, or it's not related to a genetic polymorphism or the way someone metabolises a drug, it's really unclear more than a definitive thing about valproate, whether – when you stop the drug and when the liver injury will reverse.

All right. Now, this next series of questions are connected to that observation about, you know, when reversal might be achieved in the context of valproate being the culprit, if I could put it that way. Just for completion, if in the hypothetical scenario the valproate had been ceased at presentation to the Caboolture Hospital on the 10th of April where the patient presented with acute hepatitis, not strictly speaking acute liver injury at that stage, is it more likely than not – sorry, I withdraw that. Are you able to say what Mrs Doherty's prognosis might have been in terms of survivorship if the drug had been ceased at that time?---That's a very difficult question, especially without any time course really beforehand. I mean the assumption is that it was very acute within, you know, within the limits of the previous consultation with her GP prior to her presentation, which was in the order of two to three weeks. So assuming she was asymptomatic two to three weeks prior to presentation and there was no evidence of liver injury, then I would suggest that the chances of recovery, if valproate had been ceased straight away, you know, would be reasonable, more so than not. But there's no way of understanding exactly what the odds would be, or what the proportion of success would be. The issue is really related to the time course and if the process had been going on for months and months then that would be very hard to turn around, even with cessation of the drug. If it hadn't been doing that and it was all truly acute, then cessation before synthetic destruction would certainly carry a higher chance of spontaneous recovery with cessation of the drug than waiting until acute liver failure had developed.

All right. Again, same question but a different point in time and different progressive stage of the disease, if – we know that the drug was ceased on the 17th of April, the last dose being given on the 16th of April, but by that time, diagnostically at least, Mrs Doherty had

developed an acute liver injury. If the drug had not been restarted after it was ceased on the 17th, what would her prognosis look like in terms of survivorship at that point – from that point in time?---Well, I think at that point in time I would be concerned about her prognosis of spontaneous survival with her INR going up, as well as a – the preferred diagnosis at that stage probably was drug-induced liver injury, as valproate was stopped. And, given her age as well, these are all things that are steering her towards meeting the Kings College criteria, which I mentioned in my report. And the Kings College criteria for acute liver failure carry a difficult prognosis without transplantation, so she hasn't met those criteria at that point, but it would be enough to be concerned that there may be a possibility of this being an irreversible drug-induced liver injury at that point.

And would – – –?---But cessation – sorry.

No, you go on?---I was just saying, whether cessation at that point would be – this is the thing that's very unclear in the literature, cessation at that point of acute liver injury with an elevated INR, whether that would have resulted in a similar chance of recovery as before that point, I can't tell you for sure.

Okay. And part of your concern about prognosis at that point, can I suggest, might – sorry. Can I suggest that the fact that Mrs Doherty's liver function generally worsened in that period when she was not on valproate, is that one of the considerations that you had regard to when you say that you would be concerned about a spontaneous recovery from cessation of – on the 17th?---Absolutely. So most of the – as you've talked about, most of the presentations with valproate-induced liver toxicity as a whole is actually related to either overdose or in the paediatric setting where there's a defined genetic polymorphism. And, in the overdose setting, washing out the drug will fix the issue with a high degree of success. In this situation it's very different, it's a standard appropriate dose, so not overdosage, and so what we're dealing with is the ongoing syndrome of acute liver failure with the inflammatory cascade that ensues and then causes this syndrome of multi-organ failure, which unfortunately she succumbed to. So that can develop – all starts developing at a fairly early stage and, if there's no directed treatment, then unfortunately things progress quite rapidly. So, in this situation, it's difficult to really – I mean, I certainly think that the seven days off would have cleared any detectable valproate from her system, given that the half-life is between 10-20 hours so – and so the mechanism of injury is thought to be, as I said, something that's inside the liver cells, the mitochondria, and that reaction would be ongoing and continuing, certainly adding more insults with the rechallenge if the drug isn't, you know, would no doubt influence the situation somehow. But to quantify how much for would be difficult.

So can I put it this way, the chain reaction that leads to acute liver failure may well have already been triggered by the time the decision to cease on the 17th was made, and that would be consistent with the progressive worsening of her condition in the period that she was off sodium valproate, particularly when you have regard to the fact that the drug clears the body relatively quickly in terms of half-life, etcetera, is that a fair proposition?---That's correct, yes. Thank you.

(My underlining)

244. Clearly, A/Prof. Mujumdar would support the proposition that recommencing sodium valproate was not a good idea and may well have caused additional insult (as identified by Prof. Clouston on the biopsy). However, it is not clear that any additional insult suffered as a consequence of restarting sodium valproate caused, or even contributed to Mrs Doherty's death because the cascading inflammatory response triggered by the initial sodium valproate hepatoxicity likely continued and progressed to liver failure regardless of the cessation of the drug. If the re-introduction of the drug did contribute in some way, it is difficult to measure to what extent.

245. Given the degree of uncertainty involved, I do not consider that A/Prof. Majumdar's opinion establishes, to the requisite standard, that Mrs Doherty would have survive if sodium valproate had not been recommenced on 29 April 2020.

Findings pursuant to s.45 *Coroners Act 2003*

246. I make the following findings pursuant to s.45 *Coroners Act 2003*:

(n) The deceased person is Janis Ellen Doherty, born on 29 September 1962;

(o) The deceased died from multi-organ failure due to, or as a consequence of drug induced liver injury caused by sodium valproate hepatotoxicity.

(p) The deceased died on 16 May 2020;

(q) The deceased died at the Royal Brisbane and Women's Hospital in Brisbane, Queensland;

(r) As to what caused the deceased to die:

(i) The deceased was prescribed sodium valproate (Epilim) 400mg nocte for prophylaxis against migraine in the context of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, known as CADASIL syndrome;

(ii) Approximately 5 months after commencing the medication, the deceased developed very rare, relatively late onset acute sodium valproate hepatotoxicity initially causing acute hepatitis, which

progressed to acute liver injury, and ultimately to acute liver failure. This caused multi-organ failure and death; and

(iii) For clarity, any delay in ceasing sodium valproate up to and including 17 April 2020, and the subsequent administration of the drug on 21 April 2020 and during the period 29 April 2020 to 3 May 2020 (inclusive), have not been established, to the requisite standard, as causal factors in the deceased's death.

Recommendations

247. In line with the suggestion of A/Prof. Majumdar, I recommend that MNHHS undertake a review of the risk/benefits of undertaking percutaneous liver biopsy on patients taking aspirin with the view to establishing clear protocols and guidelines relating to the following:

(a) When (if at all) it will be considered safe to proceed with percutaneous liver biopsy where the patient is taking aspirin;

(b) When (if at all) it will be considered unsafe to proceed with percutaneous liver biopsy where the patient is taking aspirin;

(c) When aspirin should be ceased in a patient who:

(i) may require percutaneous liver biopsy;

(ii) is planned to undergo percutaneous liver biopsy; and

(d) the consultation process to be adopted, including which specialist disciplines are to be involved, in making the above decisions and how those decisions are to be documented ad recorded.

I close the inquest.

Stephanie Gallagher
Deputy State Coroner
BRISBANE