Decision 24HDC02377
26 November 2025

HEALTH & DISABILITY COMMISSIONER
TE TOIHAU HAUORA, HAUĀTANGA

Informed consent regarding use of preventive antibiotic in drug trial

1. Ms A, aged 54 years, has refractory[1] multiple myeloma[2] — a type of blood cancer. She was offered a place on a Pfizer[3]-sponsored international drug trial (the trial), which was being overseen by a research trials unit at Health New Zealand | Te Whatu Ora (Health NZ). The trial was a study to evaluate the efficacy and safety of elranatamab[4] in patients with refractory multiple myeloma. As part of the trial, Ms A was prescribed a broad-spectrum antibiotic, levofloxacin,[5] preventively.

2. The trial began on 16 October 2023, with the first dose of levofloxacin taken around 23 October 2023. Ms A said that she developed left shoulder pain in mid-November 2023, which initially she considered to be due to injury.[6] However, when Ms A's right shoulder developed similar pain in February 2024, and this was discussed with her clinicians, a possible connection was made between the shoulder pain and levofloxacin. Ms A was advised to stop using levofloxacin approximately one and a half weeks after this possible connection was made.

3. Subsequently, Ms A was diagnosed with tendinosis[7] and bilateral[8] adhesive capsulitis[9] (aka frozen shoulder). She believes that levofloxacin was the cause of this and raised concerns about:

   (a) whether the use of levofloxacin had been appropriate in her case as well as whether, given its risk profile and that it is an unapproved drug[10] in New Zealand, it should have been used in this trial;

   (b) whether she was consented appropriately to the use of levofloxacin; and

   (c) the timeliness of trial staff identifying the possible causality between levofloxacin and her shoulder issues and subsequently advising that she cease using it.

[1] The cancer does not respond to treatment.
[2] A cancer of plasma cells (mature B-lymphocytes) that usually arises in the bone marrow.
[3] A large international pharmaceutical company.
[4] A medication used to treat refractory multiple myeloma.
[5] Of the fluoroquinolone drug class.
[6] This is supported by an ACC claim made on 4 February 2024 for a shoulder injury reported to have occurred on 7 November 2023 with symptoms beginning a few days afterwards.
[7] Progressive degeneration of a tendon.
[8] Affecting both sides.
[9] A condition characterised by pain and stiffness in the shoulder joint.
[10] It has not been approved by Medsafe to be sold, supplied, distributed, or advertised in New Zealand.

Names have been removed (except Health New Zealand and the clinical advisors on this case) to protect privacy. Identifying letters are assigned in alphabetical order and bear no relationship to the person's actual name.

4. At the outset, I note that it is not my role to establish any causation between the use of levofloxacin and Ms A's shoulder issues. Rather, my role is to assess whether the standard of care provided was appropriate at the time it occurred.

5. To assist in my assessment of this complaint, I sought a clinical steer from my in-house clinical advisor, vocationally registered general practitioner Dr David Maplesden. His advice is enclosed as **Appendix A** of this report.

6. I also sought independent advice from haematologist Dr Nicholas Weber. Dr Weber's advice is enclosed as **Appendix B** of this report.

7. I have relied on the independent clinical advice to assist me in my determination as to whether Ms A's rights were breached.

Responses to provisional opinion

8. Health NZ was given the opportunity to respond to my provisional opinion and provided comments and submissions, which I have considered.

9. Dr B was provided an opportunity to respond to my provisional opinion and had no further comments beyond those already provided.

10. Ms A was given an opportunity to respond to my provisional opinion and made comments that I have considered.

Whether the use of levofloxacin was appropriate in this case — no breach

11. Levofloxacin was prescribed to Ms A as a supportive drug as part of the trial, specifically to reduce the risk of sepsis associated with the trial drug, elranatamab.

12. Ms A told the Health and Disability Commissioner (HDC) that levofloxacin has a well-known adverse event risk profile, particularly regarding musculoskeletal side effects, and that she was at increased risk of tendonitis or tendon rupture from levofloxacin because of her age, activity level, and use of dexamethasone[11] (a corticosteroid) as part of the trial.

13. Health NZ stated that haematologist Dr B[12] considered whether Ms A had any additional risk factors for complications from levofloxacin before prescribing it to her and concluded that she did not.[13] Further, Health NZ stated that it was necessary for the trial participants to be on preventive antibiotic treatment, and the trial protocols recommended the use of levofloxacin or an equivalent antibiotic of the same class, which was not available in New Zealand.

14. My advisor Dr Weber advised that the decision to prescribe levofloxacin was in line with the trial protocol recommendation and accepted clinical practice. He commented that fluoroquinolone antibiotics (which include levofloxacin) are in common usage around the world, and notwithstanding that levofloxacin is not registered in New Zealand, its use in the clinical trial was not dangerous or inappropriate. He said that he could see no convincing

[11] A synthetic corticosteroid used to treat inflammatory conditions.
[12] Ms A's primary haematologist at that time.
[13] Considerations included her clinical history, presenting condition, age, level of activity, and medications.

reason why levofloxacin should have been withheld in Ms A's case. Accordingly, Dr Weber did not identify any departures from the standard of care in this respect.

15. I accept Dr Weber's advice and conclude that the use of levofloxacin in the trial was appropriate. I also conclude that there was an assessment of Ms A's suitability for levofloxacin and accept that there were no specific risk factors for Ms A that would have warranted the withholding of that medication from her. That said, given that levofloxacin had known risks and that it was not registered for general use in New Zealand, it was important to ensure that an appropriate informed consent process took place regarding its use.

Consent for levofloxacin — breach (Health NZ)

16. Rights 6 and 7 of the Code of Health and Disability Services Consumers' Rights (the Code) require that consumers are provided with the information that a reasonable person in that person's circumstances would expect to receive, including the expected risks, side effects, and benefits of the treating option so they can make an informed choice and give informed consent.

17. Ms A is concerned that she was not provided with sufficient information about levofloxacin to have consented to its use properly.

18. Ms A denies being given specific information about levofloxacin and told HDC that the only information she was given about levofloxacin was the information on the pill bottle when it was handed to her on 16 October 2023.[14] She said that she did not receive any information on the possible risks and side effects of levofloxacin. Ms A stated that the first time she was told that levofloxacin might cause significant side effects and might be linked to her shoulder complaint was on 22 February 2024.

19. Ms A was provided with a copy of the Patient Informed Consent Form (PICF) in respect of the trial on 22 August 2023. She was advised to read it and to ask any questions before signing it.

20. Ms A had an appointment with Dr B on 5 September 2023 to screen her for eligibility for the trial and to carry out the consenting process. Dr B stated that Ms A was given printed details of the trial protocol, and he discussed the potential risks and benefits of the trial.

21. The evidence regarding the specific information provided to Ms A about levofloxacin is conflicting.

22. In its initial response to Ms A's complaint dated 26 July 2024 (10 months after the consenting discussion), Health NZ stated that levofloxacin 'as a supportive medication [was] not part of [the] consenting process for the MagnetisMM-5 trial' and that it did not routinely seek consent for supportive medications. In that respect, Health NZ specifically accepted that it had breached Rights 6 and 7 of the Code (the informed consent provisions). I note that Dr B was identified as having participated in the formal review that led to this response.

[14] Information relating to dosage.

23. In a separate response dated 3 February 2025, after HDC had notified Health NZ formally of an investigation into this matter, and 16 months after the consenting process, Dr B stated that he provided verbal information regarding levofloxacin as a supportive medication. He said that he specifically discussed that joint pain could be a potential side effect of levofloxacin. Ms A signed the PICF at this appointment, and Dr B has stated that she gave verbal consent to the supportive medication.

24. I note that the PICF signed by Ms A mentions the use of antibiotics preventively but does not explicitly state the drug name or side effect profile, and the trial protocol does not include any information on potential risks associated with levofloxacin. There is no documentation of what verbal information was provided to Ms A regarding potential risks and benefits of levofloxacin, nor is there any documentation of her having given verbal consent. Further, Ms A (in her response to Dr B's statement) noted that there is a difference between joint pain and tendonitis/tendon rupture, the latter of which is a known side effect of levofloxacin. Ms A (noting that she had been a registered physiotherapist) stated that it is 'inconceivable' that she would have consented to taking levofloxacin had she been advised of the risks of tendonitis or tendon rupture, and she refutes being advised of the risks and benefits.

25. Registered Nurse (RN) C, who was present during the consenting discussion on 5 September 2023, did not identify in her statement (dated 4 February 2025) the content of the discussion but did reference that she provided the levofloxacin to Ms A, informing her that it was an antibiotic to prevent infection, the dosage requirements, and when to commence taking it. No further information was provided at that time.

26. The Medical Council of New Zealand's standards on 'informed consent'[15] and 'managing patient records'[16] state that providers must maintain clear and accurate patient records of what information was discussed during consenting discussions, including any specific risks that were highlighted, and any consent given.

27. Moreover, there are heightened obligations when prescribing unapproved medicines. The Medical Council's 'Good prescribing practice' standard that was in place at the time specifically required consent to the risks, adverse effects, costs, or benefits of such medicines (among other things) as well as provision of the information that the medicine being prescribed was unapproved. This is consistent with Medsafe's guidance on the prescription of unapproved medicines. In addition, my in-house clinical advisor, Dr Maplesden, advised that prescribers have been made aware of the potential risks of fluroquinolone prescribing for some time, particularly regarding connective tissue issues,[17] and such risks should have been discussed with Ms A prior to prescribing.

28. Health NZ's 'Informed Consent' policy[18] also states that, when verbal consent is obtained, it must be documented in the patient's clinical record; and, where a consent form is not

[15] Statement-on-informed-consent.pdf, June 2021.
[16] Maintenance-patient-records.pdf, December 2020.
[17] For example: https://www.medsafe.govt.nz/profs/PUArticles/September2023/Reports-persisting-adverse-reactions-fluoroquinolones.html, https://bpac.org.nz/2021/docs/quinolone.pdf. Accessed 4 November 2024.
[18] Version 9 — Issued 14 March 2019 and reviewed 14 March 2023.

available, the provider must make clear and accurate notes about the consent process, which may include what information was provided to the patient, when, and by whom.

29. I am satisfied, based on the standards and clinical guidance given to my investigation, that explicit consent should have been obtained for the use of levofloxacin – particularly noting that it was an unapproved medication – and that this consent should have been documented in the clinical records. That is, the risks and benefits should have been canvassed with Ms A (including the risks of tendinopathy), together with the fact that the medication was unapproved.

30. Having carefully considered the (at times conflicting) evidence on the content of the consenting conversation on 5 September 2023, I am satisfied on the balance of probabilities that Ms A was not told of the risks of levofloxacin adequately, and, in particular, the risk of tendinopathy. I am also satisfied that she was not told that the medication was unapproved. It is also self-evident from the clinical record that any consenting discussion about supportive medication was not documented.

31. Having reached these conclusions, I find that Ms A did not have all of the information that she needed to make an informed decision and give informed consent to the use of levofloxacin. In the context where the protocol and PICF did not contain information about the supportive medications, and noting Health NZ's more proximate response to the complaint that consent to the supportive medications was not sought routinely for the trial, I consider it appropriate to hold Health NZ (rather than Dr B) to account for the breach of Right 6(2)[19] of the Code, and consequently Right 7(1)[20] of the Code — the right to make an informed choice and give informed consent. That is, expectations and a process to obtain consent to supportive medications was absent for the trial, leading to the failure to obtain consent in this situation.

32. I acknowledge that Dr B and other staff involved in Ms A's care have since spent time reviewing policies and guidelines and agree that written informed consent should have been obtained from Ms A regarding the use of levofloxacin and that Ms A's verbal consent should have been recorded. I also acknowledge the further changes Health NZ is in the process of implementing regarding its clinical trial consenting process and use of unapproved medicines. I remind Dr B of the importance of providing sufficient information, especially for unapproved medicines, and accurate clinical documentation that reflects what was discussed with a patient, particularly in situations concerning informed consent and the use of an unapproved medicine.

[19] Right 6(1): Every consumer has the right to the information that a reasonable consumer, in that consumer's circumstances, would expect to receive.
[20] Right 7: Right to make an informed choice and give informed consent. (1): Services may be provided to a consumer only if that consumer makes an informed choice and gives informed consent, except where any enactment, or the common law, or any other provision of this Code provides otherwise.

Timeliness in identifying possible connection between shoulder symptoms and trial medication, and subsequent ceasing of levofloxacin — no breach

33. Ms A told HDC that she raised concerns about her left shoulder frequently with doctors and nurse coordinators at her fortnightly review appointments, starting in early December 2023.

34. Health NZ stated that staff took reasonable steps to investigate the cause of Ms A's shoulder pain and provide support. Health NZ said that Ms A's left shoulder pain was first reported to trial staff on 25 January 2024 (when it was first documented), and she was advised to stop taking levofloxacin just over a month later, on 5 March 2024.

35. On 22 February 2024, Dr B identified a possible connection between Ms A's shoulder pain and either elranatamab or levofloxacin, as Ms A had begun to experience pain in her right shoulder as well. However, Dr B did not advise Ms A to stop taking levofloxacin at this time as he was concerned that this would expose her to a high risk of infection, and he was not sure whether levofloxacin was the cause of the issue.[21] Dr B wanted Ms A to continue on all the trial medications (including supportive medications) until they had an opinion from an orthopaedic consultant. Dr B also planned to discuss this situation with the haematology team.

36. Following this appointment, Ms A looked into levofloxacin. On or around 4 March 2024, she contacted RN D[22] to ask whether she should cease taking levofloxacin. RN D discussed this with haematologist Dr E,[23] who advised on 5 March 2024 that Ms A should cease taking levofloxacin.

37. Dr Weber advised that the delay in recognising levofloxacin as a possible cause of Ms A's shoulder pain was not excessive or inappropriate and that Dr B fulfilled his duty regarding investigation and management of the shoulder pain. However, Dr Weber also advised that the recognition that levofloxacin may have been the cause of the adhesive capsulitis should have prompted cessation of this on 22 February 2024. Dr Weber said that as it was a preventive drug rather than a therapeutic one, it could have been withheld without jeopardising ongoing trial participation, and alternative antibiotic prophylaxis could have been considered. However, Dr Weber also acknowledged that, given the rarity of adhesive capsulitis and the uncertainty regarding its cause in this case, there would likely be considerable variation in opinion among his peers on whether Dr B should have ceased the levofloxacin on 22 February 2024.

38. I acknowledge Dr Weber's advice. When evaluating an episode of care in relation to Code rights, I am required to consider what is a 'reasonable standard of care', not a gold standard or best practice. In the context of Dr Weber's opinion that there could be varied clinical responses as to whether or not the levofloxacin should have been stopped on 22 February, I am not satisfied that, in this matter, Dr B departed from a reasonable standard of care. Accordingly, I am not critical that the levofloxacin was not stopped on this date. I also note

[21] Dr B stated that he also considered the fact that there was a temporal relationship between the onset of this pain and using filgrastim (a medication that is recognised to cause joint pain) and that Ms A had experienced recurrent multiple joint pain before starting levofloxacin (which Ms A refutes).
[22] The primary clinical nurse coordinator for the trial.
[23] Dr B was on leave.

that Dr B made a considered clinical decision, ensured that there would be further investigation, and recommended appropriate pain relief.

Changes made and recommendations

39. Health NZ has increased awareness with staff around the potential side effects of levofloxacin, the correct processes for gaining informed consent for prescriptions of unapproved medicines (as per Medsafe guidelines), and the importance of keeping accurate, thorough, and clear clinical notes. Health NZ has also acknowledged that all unapproved medicines need to be accompanied by an information sheet with details on possible side effects. It is updating its procedures accordingly and developing a procedure to include written informed consent for all supportive medications for clinical trials.

40. I am satisfied that these changes will assist in preventing a recurrence of the issues detailed in this report. I recommend that Health NZ report back to HDC, within three months of the date of this report, with an update on the procedures currently being developed/updated, as stated above.

Follow-up actions

41. A copy of this report with details identifying the parties removed, except Health NZ and the clinical advisors on this case, will be placed on the Health and Disability Commissioner website, www.hdc.org.nz, for educational purposes.

Morag McDowell
Health and Disability Commissioner

Appendix A: In-house clinical steer to Commissioner

The following in-house clinical steer was obtained from vocationally registered general practitioner, Dr David Maplesden:

'TO	**:**	[…]/INV
FROM	**:**	David Maplesden
CONSUMER	**:**	Ms [A]
PROVIDER	**:**	Te Whatu Ora […] ([a research trials unit])
FILE NUMBER	**:**	C24HDC02377
DATE	**:**	4 November 2024

I have reviewed the information on file.

1. I note levofloxacin was being prescribed as a supportive drug (not specifically required as part of the trial or regarded as a trial drug). It is somewhat concerning to read that the provider did not regard such prescribing as requiring patient informed consent, and it is appropriate they have acknowledged this was inconsistent with accepted practice and have changed their processes in this regard. Prescribers have been made aware of the potential risks of fluroquinolone prescribing for some time, particularly in regard to connective tissue issues,[24] and such risks should have been discussed with the consumer prior to prescribing, as should the 'off-label' nature of the prescribing.[25]

2. Given the main issue in this case is prescribing of levofloxacin (not a trial drug), albeit such prescribing was undertaken to reduce the risk of sepsis associated with the trial drug elranatamab-bcmm, I think it is reasonable to seek external expert advice from a haematologist (preferably tertiary hospital). With the issue of lack of informed consent being acknowledged, expert advice is most likely required regarding the following issues:

- Was prescribing of levofloxacin clinically indicated?
- Were there any contraindications or specific precautions regarding the prescribing of levofloxacin in this case?
- Was there adequate monitoring for potential adverse effects of levofloxacin?
- Was there an appropriate and timely response to Ms [A]'s repeated reporting of potential connective tissue issues (shoulder pain) in relation to the prescribing of levofloxacin?
- Any additional comments?

[24] For example: https://www.medsafe.govt.nz/profs/PUArticles/September2023/Reports-persisting-adverse-reactions-fluoroquinolones.html, https://bpac.org.nz/2021/docs/quinolone.pdf Accessed 4 November 2024
[25] https://bpac.org.nz/bpj/2013/march/unapproved-medicines.aspx Accessed 4 November 2024

3. Areas that should probably be outside the scope of expert comment are causation (not possible to make a definitive comment and probably irrelevant in that any suspicion [rather than confirmation] of a fluroquinolone-related adverse event should probably have resulted in prompt review of use of the drug) and ongoing national and international use of the drug (still appropriate to use in selected cases and with appropriate precautions). I note Ms [A]'s reference to compensation, and I wonder if she has investigated lodging an ACC treatment injury claim with respect to her connective tissue issues being a possible unexpected outcome of levofloxacin use.'

Appendix B: Independent clinical advice to Commissioner

The following independent advice was obtained from haematologist Dr Nicholas Weber:

Complaint:	
Our ref:	**24HDC02377**
Independent advisor:	**Dr Nicholas Weber**

I have been asked to provide clinical advice to HDC on case number 24HDC02377. I have read and agree to follow HDC's Guidelines for Independent Advisors.
I am not aware of any personal or professional conflicts of interest with any of the parties involved in this complaint.
I am aware that my report should use simple and clear language and explain complex or technical medical terms.

Qualifications, training and experience relevant to the area of expertise involved:	I am a clinical haematologist in full-time practice at the Royal Brisbane and Women's Hospital in Queensland, Australia. I have been a medical practitioner since 2007 and a consultant haematologist since 2015. My practice includes all aspects of haemato-oncology, with a special interest in multiple myeloma and lymphoma.
Documents provided by HDC:	1. Letter of complaint to HDC date 22 August 2024 (5 pages) 2. Patient complaint letter to (with attachments) dated 05 June 2024 (35 pages) 3. Medical Director response dated 26 July 2024 (5 pages) 4. Patient correspondence to dated 29 July 2024 (8 pages) 5. Health NZ's response via lawyers dated 18 February 2025 (9 pages) 6. Patient correspondence to HDC regarding Health NZ response (undated, 15 pages) 7. Additional patient response to HDC dated 04 March 2025 (9 pages) 8. Additional documents in zip folder labelled 'Combined documents'
Referral instructions from HDC:	Health NZ Te Whatu Ora 1. Whether the prescribing of levofloxacin was clinically indicated. 2. If there were any contraindications or specific precautions regarding the prescribing of levofloxacin in this case. 3. Whether there was adequate monitoring for potential adverse effects of levofloxacin. 4. If there was an appropriate and timely response to Ms reporting of potential connective tissue issues (shoulder pain) in relation to the prescribing of levofloxacin.

	5. The adequacy of the changes subsequent to this event. 6. The extent of the accepted departures from accepted practice regarding informed consent (see cover letter). 7. Any additional comments.

Factual summary of clinical care provided complaint:

Brief summary of clinical events:	Ms was prescribed levofloxacin antibiotic prophylaxis during a clinical trial for relapsed multiple myeloma. On this treatment she developed bilateral shoulder adhesive capsulitis that she believes was caused by levofloxacin. Ms complaint states that her healthcare rights were breached as a) she was not appropriately consented for this drug, and b) the drug was not ceased immediately once clinical suspicion was raised that it may have been the cause of her symptoms.

Question 1: Whether the prescribing of levofloxacin was clinically indicated.	
List any sources of information reviewed other than the documents provided by HDC:	none
Advisor's opinion:	Three months of antibiotic prophylaxis with a fluoroquinolone (levofloxacin or equivalent) was recommended on this trial for all participants at 'high risk' of infections. A definition of high risk was not provided in the protocol, but examples provided were a) patients with a history of pneumonia or b) grade 4 neutropenia. Extended prophylaxis was left to the discretion of the investigator but was recommended for patients with prolonged neutropenia (<1000/microlitre). In my opinion there was sound rationale for this recommendation given the recognised increased risk of infection with the medicine under investigation (elranatamab). Ms could be considered at increased risk of infection given her grade 2 neutropenia at study entry which could be expected to worsen once she commenced elranatamab. Indeed she continued to experience neutropenia requiring filgrastim growth factor support during the trial and hence the decision to prescribe levofloxacin was in line with the protocol recommendation and accepted clinical practice.

What was the standard of care/accepted practice at the time of events? Please refer to relevant standards/material.	From my experience it is common practice for patients to receive levofloxacin or other fluoroquinolone prophylaxis on clinical trials with anti-BCMA agents such as elranatamab. This practice is endorsed in international guidelines (*Lancet Oncology* 2024;25:e205-216, *Blood Cancer Journal* 2023;13:116). Early experience with these agents has shown high rates of infectious morbidity and mortality, and there is consensus among prescribers that aggressive antimicrobial prophylaxis should be employed. Fluoroquinolone antibiotics are in common usage around the world, and I do not agree with Ms claim that because levofloxacin is not registered in New Zealand that its use in the clinical trial was dangerous or inappropriate.
Was there a departure from the standard of care or accepted practice? • *No departure;* • *Mild departure;* • *Moderate departure; or* • *Severe departure.*	No departure
How would the care provided be viewed by your peers? Please reference the views of any peers who were consulted.	Acceptable
Please outline any factors that may limit your assessment of the events.	None
Recommendations for improvement that may help to prevent a similar occurrence in future.	n/a

Question 2: If there were any contraindications or specific precautions regarding the prescribing of levofloxacin in this case.	
List any sources of information reviewed other than the documents provided by HDC:	1. *Australian Prescriber* (2021); 44:161-4 2. *European Journal of Clinical Pharmacology* (2019); 75:1431–1443
Advisor's opinion:	From reviewing the information provided to me, I see no convincing reason why levofloxacin should have been withheld in Ms case.

	With respect to specific side effects of special interest to the patient, tendinopathy (inflammation or rupture of the tendon), chiefly involving the Achilles tendon, is a well-recognised but nonetheless uncommon complication of fluoroquinolone therapy with an estimated incidence of 2% (1). Tendinopathy at other sites (such as the shoulder) is even less common. Whilst age >65 and corticosteroid use have been identified as significant risk factors for Achilles tendon inflammation and rupture, this effect is less pronounced at other tendon sites (2). Therefore, I would consider the coadministration of dexamethasone to be a precaution, but not a contraindication, to the use of levofloxacin. Dexamethasone use is almost universal in the treatment of myeloma and so the fact that Ms was prescribed levofloxacin in addition to dexamethasone is not inconsistent with standard care.
What was the standard of care/accepted practice at the time of events? Please refer to relevant standards/material.	Recommendations for supportive care during clinical trial therapy are usually stipulated in the trial protocol which is approved by local institutional ethics committee before study activation. In accordance with ICH Guideline for Good Clinical Practice E6(R2), the clinical trial investigator (ie the physician responsible for the patient's care during trial participation) is ultimately responsible for deciding whether or not it is safe for the patient to receive treatments provided on the trial. There are several instances where a clinical investigator may decline to prescribe a supportive care medication that has been recommended in a clinical trial protocol. Examples include: a) the patient has a history of allergy/hypersensitivity/intolerance to that or related agents, or b) there are unacceptable interactions with co-prescribed essential medications, or c) there are concerns about therapeutic index in the setting of altered drug handling (such as kidney or liver dysfunction)

Was there a departure from the standard of care or accepted practice? • *No departure;* • *Mild departure;* • *Moderate departure; or* • *Severe departure.*	No departure
How would the care provided be viewed by your peers? Please reference the views of any peers who were consulted.	Acceptable
Please outline any factors that may limit your assessment of the events.	none
Recommendations for improvement that may help to prevent a similar occurrence in future.	n/a

Question 3: Whether there was adequate monitoring for potential adverse effects of levofloxacin.	
List any sources of information reviewed other than the documents provided by HDC:	none
Advisor's opinion:	Regular monitoring for treatment side effects is mandated on clinical trials. Patients are scheduled for frequent reviews with the trial investigator to assess new or ongoing symptoms, their severity and likely causality. Ms was attending clinic fortnightly for treatment visits and was maintaining regular contact with the haematology doctors and clinical trial staff. I can see no evidence that leads me to believe that she was not being monitored for adverse effects of any of her treatments.
What was the standard of care/accepted practice at the time of events? Please refer to relevant standards/material.	Adverse event monitoring and reporting is required under ICH Guideline for Good Clinical Practice E6(R2) section 4.11.
Was there a departure from the standard of care or accepted practice? • *No departure;* • *Mild departure;* • *Moderate departure; or*	No departure

• *Severe departure.*	
How would the care provided be viewed by your peers? Please reference the views of any peers who were consulted.	Acceptable
Please outline any factors that may limit your assessment of the events.	None
Recommendations for improvement that may help to prevent a similar occurrence in future.	n/a

Question 4: If there was an appropriate and timely response to Ms reporting of potential connective tissue issues (shoulder pain) in relation to the prescribing of levofloxacin.	
List any sources of information reviewed other than the documents provided by HDC:	none
Advisor's opinion:	***Regarding time to diagnosis:*** According to the information provided to me, Ms symptoms were first reported in late December 2023 and were first recorded in the medical notes in January 2024. The symptoms were initially unilateral and appeared to have an insidious onset. The symptoms were acknowledged by treating staff and not unreasonably presumed to be related to injury while gardening. Given the patient had previously reported arthralgias with filgrastim and Privigen treatment, these agents were also considered as possible causes. The patient took an active role in the investigation and management of these symptoms, and sought her own physiotherapy advice and ultrasound investigation. The possible relationship to levofloxacin was first considered on 22 February 2024 by which time her symptoms had worsened and begun to affect the contralateral shoulder. An ultrasonographic diagnosis of adhesive capsulitis had been made by this time. Given the evolving nature of the symptoms and the uncommon nature of the complication I do not believe the delay in recognising levofloxacin as a possible cause was excessive or inappropriate.

	Regarding time to cessation of levofloxacin: Whilst the levofloxacin was considered as a potential culprit, Dr made a considered decision not to cease this agent based on concerns about ongoing infection risk and uncertainty about the causative role of the drug. His decision to await a specialist opinion about the cause of the adhesive capsulitis, given the atypical presentation for levofloxacin toxicity, was reasonable. In my opinion, however, the recognition that levofloxacin may have been the cause of the adhesive capsulitis should have prompted cessation of this drug. As a prophylactic, rather than a therapeutic intervention, levofloxacin could have been withheld without jeopardising ongoing trial participation and alternative antibiotic prophylaxis could have been considered. Nonetheless it is doubtful that immediate cessation of the drug would have altered the outcome given the natural history of adhesive capsulitis, a condition in which recovery can take months to years and for which there is no definitive treatment. ***Regarding further investigation and management of the adverse event:*** As the clinical investigator Dr had a duty of care to recommend further investigation and management of any adverse event that arises in the course of the trial. I believe he fulfilled this duty by recommending symptom relief (anti-inflammatory medication), and by recommending to the patient's GP, and subsequently to the patient, to arrange an orthopaedic opinion. I note that during this time the patient had already self-initiated some treatment and investigation of her symptoms including an intraarticular steroid injection.
What was the standard of care/accepted practice at the time of events? Please refer to relevant standards/material.	Assessment of adverse event causality is difficult in a complex disease such as myeloma where the patient is receiving numerous concurrent medications, including novel agents for which clinical experience is limited. For symptoms that are considered to be non-life threatening it would be common practice to adopt a observant approach while offering symptom relief for

	patient comfort. Regular review of symptoms and refinement of the differential diagnosis, including reconsideration of potential drug causes, would constitute good clinical practice. According to ICH Guideline for Good Clinical Practice E6(R2) section 4.3.2: During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.
Was there a departure from the standard of care or accepted practice? • *No departure;* • *Mild departure;* • *Moderate departure; or* • *Severe departure.*	Mild departure
How would the care provided be viewed by your peers? Please reference the views of any peers who were consulted.	Given the rarity of adhesive capsulitis and uncertainty regarding its aetiology, I think there would be considerable variation in opinion regarding whether Dr should have ceased the levofloxacin when he first considered this as a possible cause on 22 Feb 2024.
Please outline any factors that may limit your assessment of the events.	None
Recommendations for improvement that may help to prevent a similar occurrence in future.	My reading of the responses provided by Health NZ indicates that they have reviewed their policy on levofloxacin use and have taken steps to prevent similar occurrence in future.

Question 5: The adequacy of the changes made subsequent to this event.	
List any sources of information reviewed other than the documents provided by HDC:	none
Advisor's opinion:	I take this to mean the adequacy of the DHB response to this incident.

	I believe the response from the DHB was detailed and appropriate. In line with GCP they reviewed their trial processes and the safety of the other trial patients. The undertaking to review the clinical trial consent process and pharmacy procedures will address the patient's concerns about inadequate consent. I do not consider any of the nursing or medical staff to have displayed an inadequate standard of care. As suggested by Dr this incident is a valuable learning point for staff to be reminded about the risks of levofloxacin.
What was the standard of care/accepted practice at the time of events? Please refer to relevant standards/material.	n/a
Was there a departure from the standard of care or accepted practice? • *No departure;* • *Mild departure;* • *Moderate departure; or* • *Severe departure.*	n/a
How would the care provided be viewed by your peers? Please reference the views of any peers who were consulted.	n/a
Please outline any factors that may limit your assessment of the events.	none
Recommendations for improvement that may help to prevent a similar occurrence in future.	none

Question 6: The extent of the accepted departures from accepted practice regarding informed consent (see cover letter).	
List any sources of information reviewed other than the documents provided by HDC:	none
Advisor's opinion:	I note the inconsistencies between Ms and Health NZ's accounts in relation to what level of detail was provided regarding specific risks of levofloxacin during the clinical trial consent process.

	The consent form signed by the patient mentions the use of antibiotic prophylaxis but does not explicitly state the drug name or side effect profile. Statements from her treating team suggest that she was informed that levofloxacin is an antibiotic, and that arthralgia was a generic side effect of the study treatment. Based on Ms responses, and her background in healthcare and evident health literacy, it seems implausible that she would have continued the levofloxacin despite her worsening symptoms, had she been informed of the specific risk of tendinopathy. In this respect I support her assertion that she was not appropriately consented for this drug and I agree that she should have been provided with verbal or written information about this side effect before the drug was supplied.
What was the standard of care/accepted practice at the time of events? Please refer to relevant standards/material.	It is accepted practice that physicians should follow an informed consent process when prescribing medications that fall outside usual standard of care, including off-label or unregistered medications. Verbal consent documented in the medical record is generally considered adequate. For patients on clinical trials, a dedicated written consent form that covers all trial therapies is an essential part of Good Clinical Practice. It is the responsibility of the physician to provide information that is both general, as well as specific to the patient's circumstances, as part of this consent process.
Was there a departure from the standard of care or accepted practice? • *No departure;* • *Mild departure;* • *Moderate departure; or* • *Severe departure.*	Moderate departure
How would the care provided be viewed by your peers? Please reference the views of any peers who were consulted.	Levofloxacin is not commonly used in Australia, but the related drug ciprofloxacin, which is in routine usage, carries the same risk of tendinopathy. My peers would consider a brief discussion of this risk to form a necessary part of the informed consent discussion for the clinical trial.
Please outline any factors that may limit your assessment of the events.	none

Recommendations for improvement that may help to prevent a similar occurrence in future.	My reading of the responses provided by Health NZ indicates that they have reviewed their policy on informed consent and have taken steps to prevent similar occurrence in future.

By signing this report, I agree to HDC correcting any formatting, spelling, or grammar issues on the proviso that the substance of the report and any quoted material remains unchanged.
 Signature:
Name: Dr Nicholas Weber
Date of Advice: 24 March 2025