04/08/210

21 March 2005

Pat Chainey
Ethics Committee
PO Box 92 522
Wellesley Street
AUCKLAND

Dear Pat

Ref: ***AKY/04/08/210***
A Case Control Study to Evaluate the Post Licensure Effectiveness of 3 Doses of the New Zealand Meningococcal B OMV Vaccine (MeNZB) Against the New Zealand Meningoooocal Epidemic Strain Administered to Children under 5 years of age.

I have written to Tim Dare, Chair of the Committee, as requested by John France. I will be available to attend the next meeting of the Ethics Committee which I believe is on 6th April to discuss these matters urgently.

The matter is urgent as the evaluation of vaccine efficacy is dependent on the contract associated with this Ethics application and vaccine is already being delivered in the Auckland area where the study should have commenced.

Yours sincerely

Diana Lennon

Diana Lennon
Principal Investigator Meningococcal B Case Control Study of Vaccine Efficacy

21 March 2005

Tim Dare
Ministry of Health - Ethics Committee
PO Box 92 522
Wellesley Street
AUCKLAND

cc: John France
Pat Chainey
Peter Smith – Dean,
School of Medical & Health Sciences

Dear Tim

Re: Clinical Trials of Meningococcal B Vaccine Run by the University of Auckland, Research Team led by Principal Investigator Professor Diana Lennon (AKY/02/00/198, AKY/02/00369, AKX03/02/049 & AKY/03/11/291)

I am writing to you at the suggestion of John France, Deputy Chair, Ministry of Health Auckland Ethics Committee, after discussions relating to these trials. I seek the opinion of the Ethics Committee re access to raw electronic datasets from these immunogenicity studies.

New Zealand has run a unique set of clinical trials (Principal Investigator Diana Lennon) to assess the reactogenicity and efficacy of the New Zealand strain vaccine in different age groups of the New Zealand population. These trials have not been duplicated elsewhere and to date have been exclusively analysed by the vaccine company Chiron Corporation with a summary to the Principal Investigator of paper only copy of the Clinical Study Report for each trial. In two of the four trials paper datasets have been signed off by the Principal Investigator prior to submission to Medsafe to allow licensure of this vaccine for epidemic control. However two of the Clinical Study reports have been viewed by the Principal Investigator some time after licensure. In no case has an electronic dataset been available to the Investigator and Statistician to verify the company's results. This is in the face of a publicly declared partnership between the University of Auckland, Chiron Vaccines and the Ministry of Health for the production of clinical trial data by the University of Auckland for the licensure of the vaccine and epidemic control. We understand the Ministry of Health as co-sponsor does not yet have an electronic dataset for these trials.

This is also in contra-distinction to the process with the first clinical trial of the New Zealand Meningococcal B vaccine in adults where the raw data was available in electronic form before sign off of the Clinical Study Report.

Publication of clinical trial results in a peer reviewed journal requires the Principal Investigator as guarantor to certify to the validity of the work, which would not be possible while the analysis and hence interpretation of the data can not be verified.

In view of the unique situation that New Zealand has found itself in the absence of other sites performing the same experiments and the eventual aim to vaccinate all New Zealand children, we feel that you the Ethics Committee should be aware of the situation and we seek guidance.

– who should publish?

Yours sincerely

Diana Lennon.

Diana Lennon
Principal Investigator – Meningococcal B Vaccine Trials

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missing

13.3 "The data from the study will be kept for 15 years and the Principal Investigator or their deputy will be responsible for its safekeeping"

13.4 "Access will be limited to those described in the Informed Consent form, being the study staff, or regulatory authorities as required" (please see letter to Pat Chainey 9th March 2005 clarifying "regulatory authorities": this was to infer an auditing process)

Operations Manual Study Team Version sent 7th March 2005 – Section 5.5.1 Data Safety & Security

"All completed questionnaires for cases and controls will be photocopied. The original form will remain with the Auckland Regional Public Health Service and will stored in a locked cupboard. A copy will be sent to the Principal Investigator at the University of Auckland School of Population Health for secure storage as required by Ethics approval. Limited time exclusive use, data entry and data analysis will be negotiated with the Ministry of Health by the University of Auckland separately."

Operations Manual **Amended Copy from the Ministry of Health received 10th March 2005** – Section 5.5.1 Data Safety & Security

"All completed questionnaires for cases and controls will be stored in a locked cupboard by the Ministry at the end of the study."

2. Question: The responsibility of the **Principal Investigator** is as the guarantor of a study. Reputable journals require a statement to this effect. The role of **guarantor(s)** (page 2 reference 1) is defined as a person(s) who takes responsibility for the integrity of the work as a whole, from inception to published article, and publishes that information. To maintain the integrity of this study we believe:
   1. the Operations Manual should guarantee the right of the Study Team to analyse the data.
   2. the Manual should specify that the Study Team has an exclusive right to publish.
   3. a data set could be made available for independent analysis.

   Is this reasonable?

   Ethics Application:

   The Ethics application is silent on this, though in the family information sheet the Principal Investigator is cited as Diana Lennon and "the study is being done by the University of Auckland, Auckland Regional Public Health Service and the Ministry of Health". There is no statement assuring the subjects that their data once anonymised will be appropriately analysed and disseminated though data for research is collected in good faith subject to appropriate use as guided by the Principal Investigator. In the Ethics application Section 7.3: Dissemination of Results, states "submission for publication in peer reviewed medical journals".

   Operations Manual Study Team version sent 7th March 2005 – 5.4 Data Analysis and Interpretation: Authorship of publications

   "The criteria of the International Committee of Medical Editors will be applied for authorship.

Data analysis (in the event of the study running the full length) will be carried out by the Study Team within the University of Auckland with a 6 month period of exclusive use of the data. This will generate a report to Medsafe and papers for submission to scientific journals.

The Study Team will have the right to publish the results of the Case Control Study and any information relating thereto. Before publishing, however, copies of any manuscript proposed for publication or presentations will be submitted to the Ministry of Health at least thirty days in advance of submission of such publication or presentation to a publisher or third party."

Operations Manual Version Supplied by the Ministry of Health 10th March 2005 - 5.4 Data Analysis and Interpretation: Authorship of publications
"The criteria of the International Committee of Medical Editors will be applied for authorship.

The contract between the Ministry and Auckland District Health Board makes it clear that the Ministry is committed to a timely analysis of the results of the Case Control Study and that the Study Team and the Implementation Team have the right to be part of a group (subject to the authorship criteria referred to above) which will eventually publish such data.

Operations Manual **Modified Version acceptable to the Study Team – yet to be forwarded to the Ministry of Health** – 5.4 Data Analysis and Interpretation: Authorship of publications
"The criteria of the International Committee of Medical Editors will be applied for authorship.

The contract between the Ministry and Auckland District Health Board makes it clear that the Ministry is committed to a timely analysis of the results of the Case Control Study and that the Study Team **at the end point of the study (14 July 2007)** have the right to **analyse the data and to be** part of a group **led by the Principal Investigator** (subject to the authorship criteria referred to above) which will eventually publish such data."

Although a contract for the third phase of this study has not been negotiated we believe statements of intent as above are required to allow this study to proceed ethically.

3. Your advice please: To ensure open and ethical reasons for terminating this study should the epidemic cease naturally (as judged by cases outside of Auckland prior to vaccination), we recommend an Independent Data Monitoring Board. The Operations Manual has been modified by the Ministry of Health to state – **"The decision to cease the study prematurely will be that of the Ministry of Health. The Ministry will seek independent academic advice before making such a decision. The Ministry has agreed to consult with the Principal Investigator amongst other experts as to who could give such independent advice."**

We seek your advice on these three areas.

Yours sincerely

Diana Lennon
Principal Investigator
Meningococcal B Clinical Trials & Vaccine Effectiveness
Professor of Population Child & Youth Health

Reference:
International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. http://www.icmje.org/index.html. Updated October 2004, accessed 18 March 2005