

Ethics committees and guardianship legislation

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TO THE EDITOR: In addition to a complicated ethical approval process, new privacy laws have presented challenges for multicentre research studies.¹ In Victoria, an amendment to the *Guardianship and Administration Act 1986* came into effect on 1 January 2003. We wish to highlight its unanticipated ramifications.

We proposed to conduct a pilot study on the feasibility of ascertaining cases of Murray Valley encephalitis (MVE) in Victorian hospitals. Currently, there is no routine human surveillance for MVE, and we intended to perform diagnostic tests for several encephalitis aetiological agents on routinely collected samples. A study protocol was developed and submitted in November 2002 to five Human Research Ethics Committees (HRECs), one at the Department of Human Services and four at hospitals where the study was to be conducted. The case definition for encephalitis included the criterion that the patient had an "altered conscious state", and could not therefore give informed consent.

Informed consent was to be provided by the patient's next-of-kin, but, in late December, an HREC representative alerted us to an imminent amendment to the Act which stipulated that only a guardian appointed by the Victorian Civil and Administrative Tribunal (VCAT) could provide consent to participate in "any procedure carried out for the purposes of medical research" on behalf of a disabled patient (in this instance, a patient with an altered conscious state). The Act does not further define medical research. Surveillance involves no intervention, and it is unclear to us (and some ethics committees) whether surveillance was considered a "procedure". We indicated our uncertainty in a letter to VCAT in January 2003.

If an application to VCAT were required for each patient we wished to enrol, then the study became unworkable. Under legislative requirements,

VCAT is only obliged to "commence to hear" an application within 30 days of its receipt, which would prevent surveillance being conducted in a timely manner.

Awareness of the legislative amendment differed between HRECs. In December 2002, two committees gave full approval for the study without reference to the amendment, while the remainder gave conditional approval, subject to complying with the amended Act. VCAT wrote to HRECs in February 2003 to clarify the amendment, and directly indicated to us that it did not apply to our proposed study. In May, despite the correspondence from VCAT, one HREC reaffirmed its position that applications must be made to VCAT for consent for studies such as this one.

Despite attempts at clarification, a legislative amendment in Victoria has created ongoing confusion about obtaining consent on behalf of disabled patients. Researchers planning studies involving invasive procedures (eg, blood chemistry or seroprevalence studies) need to be aware of the amendment's potential impact. Differences in interpretation of the amendment by the tribunal and various ethics committees highlight the need for further clarification of the Act, as well as for centralised and consistent assessment of HREC applications.

1. Carapetis JR, Passmore JW, O'Grady K. Privacy legislation and research. *Med J Aust* 2002; 177: 523. □

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COMMENT: Fielding and Heath raise two issues. The first is the increasing barriers to the conduct of research as the law and Human Research Ethics Committees (HRECs) quite rightly ensure the safety of participants in human research. In the words of Cicero, *salus populi suprema est lex* ("the welfare of the people is the highest law"),¹ but the law is not immutable. The confusion uncovered by Fielding and Heath over the implications of the amendment to the *Guardianship and Administration Act 1986* may prompt legislators to re-examine the purpose of the Act in the

context of research involving patients with "altered conscious state".

The second issue raised is more general. The plurality of HRECs' interpretations of the amendment may be difficult to fathom by ordered scientific minds: data are data, so why the differences in HRECs' opinions? These frustrating differences are the bane of researchers involved in multicentre research.^{2,3} The 1999 *National statement on ethical conduct in research involving humans*⁴ empowers HRECs to minimise duplication and allows for ethical and scientific assessments made by one HREC to be accepted by others.⁵ Nevertheless, HRECs value their independence and are unlikely to relinquish it to others easily.⁶ Various states are considering the feasibility of centralised ethical bodies,⁵ but bureaucracy moves cautiously and change is always slow.

1. Cicero. De legibus.
2. Jamrozik K, Kolybaba M. Are ethics committees retarding the improvement of health services in Australia? *Med J Aust* 1999; 170: 26-28.
3. Loblay RH, Chalmers CRC. Ethics committees: is reform in order [editorial]? *Med J Aust* 1999; 170: 9-10.
4. National Health and Medical Research Council. National statement on ethical conduct in research involving humans. Canberra: NHMRC, 1999. Available at: www.nhmrc.gov.au/publications/pdf/e35.pdf (accessed Sep 2003).
5. Breen KJ, Hacker SM. Privacy legislation and research [letter]. *Med J Aust* 2002; 177: 523-524.
6. Pearn JH. The realities of ethical review of research in Australia. *Med J Aust* 1999; 171: 38-39. □

Acute liver failure associated with the use of herbal preparations containing black cohosh

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TO THE EDITOR: We wish to report a case of acute liver failure associated with the use of a herbal preparation that contained several ingredients, including *Cimicifuga racemosa* (black cohosh).

In January 2003, a 52-year-old woman was referred to our unit with acute liver failure. She had taken a herbal preparation for three months (for severe tinnitus), but ceased four weeks before admission. The preparation was made and provided by a pharmacist. The preparation was supplied in a

200 mL bottle and contained a mixture of the fluid extracts of *Nepeta hederacea* (ground ivy) 80 mL, *Hydrastis canadensis* (golden seal) 20 mL, *Ginkgo biloba* (ginkgo) 40 mL, *Avena sativa* (oats seed) 40 mL and *Cimicifuga racemosa* (black cohosh) 20 mL. According to the information supplied by the pharmacist, one gram of herb was contained in each 1 mL of extract, with the exception of golden seal, for which 0.5 g of herb was contained in each millilitre. The oats seed fluid extract was supplied by Southern Cross Herbal School (Gosford, NSW), and all other fluid extracts were supplied by the Herbal Extract Company of Australia (Sydney, NSW). The patient took a total of 600 mL over the 3-month period (7.5 mL bd orally as required). Before developing symptoms of liver failure, the patient had taken no other medications and had no risk factors for the acquisition of viral hepatitis.

On arrival, she was deeply jaundiced but not encephalopathic. Liver span was reduced and there were no signs of chronic liver disease. The international normalised ratio was 3.0 (normal, 1.0–1.2), and she had serum concentrations of albumin, 26 g/L (normal, 35–50 g/L); bilirubin, 368 $\mu\text{mol/L}$ (normal, < 18 $\mu\text{mol/L}$); alkaline phosphatase, 230 U/L (normal, 35–104 U/L); alanine aminotransferase, 1380 U/L (normal, < 55 U/L); and γ glutamyl-transpeptidase, 134 U/L (normal, < 45 U/L). Extensive investigation excluded other recognised causes of acute liver failure.

Her condition deteriorated over the following week, with the development of hepatic encephalopathy and hepatorenal failure. She underwent liver transplantation in early February 2003, and had an uneventful postoperative course. Examination of the explanted liver revealed massive hepatic necrosis.

Following transplantation, the pharmacist supplied samples of the individual extracts to the Therapeutic Goods Administration (Canberra) for analysis. The analysis revealed no undeclared pharmaceutical drugs. Assay of the individual extracts of golden seal, ginkgo and black cohosh revealed the listed ingredients to be present. The presence of ground ivy and oats seed in the extracts has not yet been confirmed owing to the lack of a suitable reference standard.

It is not possible to determine the individual ingredient, or mixture of ingredients, that resulted in acute liver failure in this patient. However, this is the third case of acute liver failure associated with black cohosh ingestion to be reported recently in Australia.¹ In this instance, liver failure progressed despite cessation of the herbal therapy, and transplantation was required, suggesting that a process of irreversible liver injury had been initiated before treatment was ceased. It should be noted that ground ivy contains pulegone, a known hepatotoxin. However, the concentration of pulegone in ground ivy is accepted to be vastly less than in pennyroyal, where pulegone-induced hepatotoxicity has been reported.² To our knowledge, there are no reports of golden seal, oats seed or ginkgo causing hepatotoxicity.

The popularity of herbal therapies is due in part to their perceived lack of side effects. It is important for the medical and broader community to be aware of the potential toxicity of these preparations. In any patient presenting with unexplained hepatitis it is essential to determine if there has been exposure to herbal therapies, since early cessation of treatment may be life saving.

1. Whiting PW, Clouston A, Kerlin P. Black cohosh and other herbal remedies associated with acute hepatitis. *Med J Aust* 2002; 177: 440-443.

2. Barnes J, Anderson LA, Phillipson JD. Herbal medicines. A guide for healthcare professionals. 2nd ed. Pharmaceutical Press, 2002. □

Hormone replacement therapy: to use or not to use?

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TO THE EDITOR: The randomised controlled trial associated with the Women's Health Initiative (WHI) found that long-term hormone replacement therapy (HRT) with combined oestrogen-progestin causes net harm.¹ Both the article by Baber and colleagues on HRT² and a previous editorial by Patel and colleagues³ imply that the method used to calculate the confidence intervals in the WHI report is questionable. Baber et al suggest that "a trial such as this, with multiple endpoints, should use adjusted rather than nominal confidence intervals to test individual end-

points for significance".² It is important that this issue is clarified.

In the WHI report in *JAMA*, Table 2 shows both nominal and adjusted confidence intervals for the primary and secondary outcomes.¹ Nominal confidence intervals are appropriate for the preselected primary outcomes of the trial — breast cancer, coronary heart disease and the composite global-index score.⁴ Confidence intervals adjusted for multiple comparisons are possibly appropriate for the multiple secondary endpoints in the study, but are not advocated by all statisticians.⁵ In any case, the decision of Baber and colleagues to concentrate on adjusted confidence intervals for the preselected primary outcomes is not valid.⁴

The purpose of confidence intervals is to assess the effects of random variation or chance. It is not sensible to suggest that the extra harm that occurred in the combined HRT arm of the WHI study could be due to chance. Moreover, 42% of women in the HRT group stopped taking the drug, and 11% of women in the placebo group started taking it.¹ Therefore, the reported findings of the intention-to-treat analysis underestimated the true harm to individual women taking long-term HRT. Also, if duration of treatment is important (as appears the case with breast cancer risk), and because compliance decreased over time, 5-year results underestimated longer-term treatment harm.⁴

The aim of the WHI trial was to assess whether long-term HRT is a useful preventive intervention for postmenopausal women. It did not assess the short-term use of HRT to relieve severe hot flashes. As Sackett points out, curative and preventive medicine are absolutely and fundamentally different in their obligations and implied promises to the individuals whose lives they hope to modify.⁶ As a long-term preventive intervention, HRT causes more harm than good. Although the absolute risks were small, millions of women were prescribed this treatment worldwide, causing harm to thousands. Billions of dollars were spent on an ineffective preventive intervention.⁶ The thousands of Australian women who stopped taking HRT on learning the results of the WHI trial made a sensible decision.