Ethics

The death of a healthy volunteer in a human research project: implications for Australian clinical research

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A healthy 19-year-old United States college student volunteer in a clinical research program underwent a bronchoscopy and died as a result of acute lignocaine toxicity. The major contributing factor in the tragedy was that the research protocol failed to specify an upper dose limit for lignocaine spray, although previous versions of the protocol had done so. We look at the implications of this case for Australian institutional ethics committees. ***(MJA 1998; 168: 449-451)***

In early 1996, in New York state, a healthy young woman volunteer in a clinical research program died (see Box). The New York State Department of Health conducted an investigation of the incident.

Case summary

A healthy 19-year-old female university student underwent a bronchoscopy at University of Rochester Medical Center, Rochester, New York, in early 1996 as part of a research investigation into the function of lung cells. Topical lignocaine was sprayed on her upper and lower respiratory tract, as is usual to allow passage of the bronchoscope, but she required considerable amounts of spray to decrease discomfort. She was discharged from the centre after a 60-minute observation period, although she complained of chest discomfort. Fifteen minutes later, her boyfriend noted that she was very uncomfortable and could barely talk. He left her at his apartment so that she could have a nap, but when he returned an hour later she was having an epileptic fit. On admission to the emergency department, she was in cardiac arrest, and she died two days later. There was a large out-of-court settlement (perhaps approaching US$100 million) between the University Medical Center and the family.[1]

Why did she die?

The proximate cause of death was considered to be a toxic lignocaine blood concentration, although this must remain somewhat speculative. The lignocaine level in the emergency department blood sample was 12.9 mg/L (56 μmol/L); the maximum safe concentration is less than 5–6 mg/L (22–26 μmol/L).[2] This concentration was measured about three hours after the bronchoscopy, and a back-extrapolation suggests a possible maximal lignocaine blood level of about 36 mg/L (155 μmol/L). It was calculated she had been administered about 1200 mg.

The study protocol did not specify an upper dose limit (nor did professional guidelines for the bronchoscopy procedure[3]), although the original study protocol of 1981 had specified a maximum dose of 300 mg. Between 1981 and 1995, the study protocol had been amended a number of times — on many occasions with Institutional Ethics Committee (IEC) and National Institute of Environmental Health approval — but the deletion of the upper dose limit of lignocaine had not been submitted specifically as an amendment. It was presumed[1] that the researchers did not consider that deleting the upper dose limit had safety implications, reflecting contemporary practice and guidelines.[3]

This procedure for protocol alteration was in keeping with the university's clinical research regulations (ie, minor alterations without safety implications did not require formal approval by the IEC). However, epileptic fitting and severe cardiac arrhythmias are well known serious adverse effects of excessive blood concentrations of lignocaine, knowledge that appeared to have become less influential or compelling up to the time of this incident.[2]

There was no record of the dose of lignocaine spray administered, although Medical Center officials noted that this could be an estimate only given the expected removal by suction of the drug from the airways during the procedure.

The young woman had been discharged 60 minutes after the procedure, although she complained of chest pain. There was no record of her being reviewed before discharge by a physician, although her routine observations were presumably satisfactory.

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What other issues were identified?[1]

The consent form. The three-page consent form was explicit about possible adverse events, but did not mention the possibility of death. Consent forms rarely note this possibility. Although the consent form made it clear that subjects could withdraw at any stage without prejudice to their medical care, it was not clear whether the honorarium (US $150) would be paid in this event, creating a potentially powerful inducement to a student to continue despite possible adverse events.

The IEC. Although the IEC had discharged all its statutory obligations, it had not performed an "in-depth" or "complete" re-review of the protocol and its alterations over the protocol's 14-year life.[1]

The protocol. Protocol violations were discovered during the NY State Department of Health investigation of the incident and the IEC's procedures.[1] The lignocaine solution used was a higher concentration than that specified in the protocol, and 28 "bronchial brushings" were done, whereas the protocol specified "about 10". It was contended by the university that this latter violation could be classed as "minor". Yet, apart from indicating a level of researcher non-compliance, these violations also illustrated that the IEC had not reviewed the procedural aspects of the study closely. However, annual reports had been submitted by the researchers to the IEC, appropriately fulfilling the university's statutory "review" obligations.

Some New York State Department of Health recommendations for IECs[1]

Institutional ethics committees should pay particular attention to long-running research programs (ie, those that run over a number of years) with multiple research protocols and amendments. Periodic "fresh" review of the complete protocols is warranted, particularly in regard to the safety of research subjects.

IECs should foster a better-informed clinical research community that is more sensitive to subject risk. Regular education is needed about protocol alterations, the minimising of risk to subjects, the methodology for obtaining informed consent, the recognition and reporting of adverse events, and the question of honorariums. These issues need to be discussed frequently by the research community.

Research project annual reports would be improved by incorporating all protocol amendments and procedural alterations, plus comments on how these might impinge on subject safety.

All protocol amendments need to be reviewed and approved by IECs (this is generally the case in Australia).

Could such an unfortunate event happen in Australia?

The death of a healthy volunteer in the course of human research raises questions relevant to the Australian system of clinical research review by our IECs. We explore these questions in the light of the 1996 review of the role and functioning of IECs.[4]

Payments to volunteers

There are long-standing concerns about payments to volunteers for participation in human research. The National Health and Medical Research Council (NHMRC) *Statement on human experimentation*[5] requires that an IEC be satisfied that the consent of a research subject is not influenced by any financial inducement (or by any other improper pressure).

Payments to research subjects may affect consent and the validity of the results. Paul Dansker, a partner in the US law firm representing the family of the student who died, suggests that such payments may also lead to a contemptuous attitude to the research participant,[1] suggesting that "investigators simply don't care as much about the wellbeing of volunteers as they would if the subjects were actual patients and there existed a true physician–patient relationship". He also contends that "when a facility is paying a volunteer, a certain casualness can creep into the investigator's regard for the subject's welfare, leading in extreme cases to lack of compassion or even cold-bloodedness" — an attitude of "we're paying them so what's a little discomfort?". This remark brings into stark focus concerns about payments to research subjects and the difficult job an IEC has in determining whether payments are in keeping with NHMRC principles.

Monitoring clinical research

Should IECs be more vigilant in their review, re-review and ongoing monitoring of protocols? Under current NHMRC guidelines, all IECs are obligated to ensure appropriate monitoring of research projects until their completion.[5] The guidelines establish minimum requirements, but an IEC may introduce further procedures when considered necessary.[5] However, in practice, most Australian IECs comply with the minimum requirements set out in the monitoring guidelines by relying on the principal investigator's written reports and notification of any adverse or unforeseen consequences of the project.[6] Very few IECs have any systematic methods for monitoring, and only a handful report the use of site visits.[6] This reflects, in large part, the lack of resources available to IECs to undertake more monitoring work.

The Australian clinical research and IEC community recognises the importance of monitoring, noting that it "... is essential if there are to be any teeth to the public watchdog role [of an IEC]".[4] The 1996 review of the role and functioning of IECs recommended that an IEC has the responsibility when approving a research protocol to ensure that appropriate and adequate monitoring arrangements are in place consistent with the level of risk involved in the project to research subjects, are in place before the commencement of the project and that the annual compliance information form tabled by IECs with the Australian Health Ethics Committee (AHEC) includes confirmation of due monitoring procedures in place and any problems encountered.[4]

This increased monitoring will place further strain on resources, a fact recognised by the review.

However, monitoring by an IEC is only one aspect of the

overall strategy to ensure protection of research subjects' interests. Peer review of research proposals and protocols, institutional supervision, researchers' individual professional ethical standards, education of researchers about ethical issues, and effective information and complaints mechanisms all promote the earliest possible detection of potential harm in research projects. Again, these activities require considerable commitment, organisation and resources.

Expertise of IEC members

The importance of appropriate pharmacological and procedural expertise in clinical research teams and IEC review organisations is self-evident, but the competence of members of an IEC to understand the risk in some projects is by no means assured in even some of our most active research institutions. The review committee recommended that training should be introduced for IEC members in regard to the work, responsibilities and procedures of the IEC. This recognises the diverse backgrounds and experience of IEC members and the otherwise daunting task faced by prospective members of developing the competence to contribute effectively to IEC deliberations.

However, the tragic death discussed may not have been avoided by even the most competent IEC.

Can we assure Australians that such an event could not happen here?

Our most troublesome question is: is it possible to assure the public that the circumstances that led to the death of this volunteer in a research project could not occur in Australia? The answer must be no, on the basis that all activities involve some level of risk, but continuing improvement of our IEC system reduces that risk.

Review of the role and functioning of (Australian) IECs (1996)[4]

The review report made a number of recommendations aimed at improving and standardising the procedures of IECs to reduce the risks to volunteers:

- The adoption of meeting procedures on the lines of those developed by the Royal College of Physicians in the United Kingdom.[7] These working procedures include details about required quorums, adverse decisions, confidentiality, and declaration of interest.
- The production of an Australian manual of procedures based on existing manuals used by major Australian institutional IECs. Manuals of procedures for IECs have been developed overseas — for example, in the United Kingdom, by the Department of Health.[8,9]
- Setting up formal complaints mechanisms to replace existing mechanisms and to complement formal, independent health complaint handling bodies set up under the Medicare Agreement.[10]
- The review committee considered that the minimum required membership of an IEC should be increased to seven members, with eight members for hospital IECs, with the proviso that when additional members are appointed an appropriate balance between institutional/non-institutional and medical/non-medical must be maintained. Not less than half the committee should consist of non-institutional, non-medical members.
- The AHEC was advised to revise its current compliance information form to collect more detailed information so that it could meet its statutory accountability responsibility. For example, greater detail will be required on the actual documenting procedures of an IEC, the type of research considered by the IEC, and how complaints are handled.
- The NHMRC *Statement on human experimentation*[5] needs substantial revision to apply to "research involving humans" rather than experimentation, and to be substantially more prescriptive and detailed.

These recommendations are aimed at improving IEC procedures and reporting to reduce the risk of similar events occurring in Australia.

Conclusion

Careful review by IECs of research protocols, protocol amendments and research reports, as well as strict adherence to protocols by researchers, all of which are enhanced by the recommendations of the review,[4] are the activities most likely to lower the (admittedly very small) risk of a similar event occurring in Australia. Vigorous and continued attention to improving the quality, safety and ethical standard of clinical research and the IEC system in Australia is needed to earn and maintain public confidence in and support of clinical research, which in itself is vital to the quality of healthcare.

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