The ethics of placebo use in vaccine trials

By Dr Nikki Turner
Director of the Immunisation Advisory Centre at the University of Auckland

Superficially, *Primum Non Nocere* seems to be a simple principle. However, when applied to the ethics of placebo use in vaccine trials, it is not so straightforward.

Vaccines are delivered in every country in the world via national vaccination programmes, mostly to large population groups of healthy children. For reasons of safety, community acceptability, and resource management it is important to know the vaccine profile as accurately as possible before widespread usage. Vaccines that have been in use for many years were less likely to have undergone large randomised trials, which are the gold standard today. This means that for some products, such as the inactivated trivalent influenza vaccines, there is little data comparing the biological agent with a placebo. For the introduction of any new vaccine the standard requirement is a randomised controlled trial, ideally using an inert placebo (usually saline) delivered to a control group.

Is it acceptable to give an inert substance to the control group in a vaccine randomised controlled trial (RCT)? Guideline 11 of *The International Ethical Guidelines for Biomedical Research* [1], states that it is acceptable to use a placebo with a control group if the use of a placebo would not add ‘any risk of serious or irreversible harm’.

RCTs clearly have an important role to play in establishing baseline data for a new vaccine and therefore the use of a placebo is generally seen as acceptable, recognising there are small risks, including the use of unnecessary injections, pain/distress, and family inconvenience. In the case of a new vaccine with the potential to reduce significant morbidity and mortality and with no existing effective intervention, the small risk is generally acceptable, so long as harm is minimised with appropriate informed consent and quality control measures in place in a well-run clinical trial. Many trials also incorporate other aspects of prevention for the control group, such as education and promotion, as seen in HIV vaccine trials [2]. Other trial designs include the use of an alternative vaccine that provides protection against an unrelated infection in the control group, or add-on vaccine approaches which offer some gain to the control arm participants. This has to be weighed up against the risk of a different vaccine in the control group creating immunological action that may bias the outcome.

However, the international world of vaccine availability is currently very inequitable: excellent new vaccines such as conjugate pneumococcal and rotavirus vaccines are well used in wealthier countries but much less so in more resource-poor countries who carry a much greater burden of the disease in their populations. The major barrier to vaccine introduction is funding and the high costs of the more recently licensed vaccines. Newer vaccines are continually being developed that are cheaper, therefore offering options to countries unable to purchase existing vaccines. Should an existing vaccine be used as a comparator every time a country or area wishes to trial a different vaccine that may be a more viable option? This may be the gold standard approach but such studies would be more resource intensive than using placebos. Because disease is likely to be prevented in both treatment groups the trial may need to be very large to be adequately powered. This approach may often delay the introduction of effective vaccines.

*(Continued on page 2)*
Another challenge is that vaccines with established efficacy in one population may not be as effective in different populations: the epidemiology, demographics, host response, and environmental effects may differ altering the vaccine performance. Therefore, further trials may be needed to assess the relevance of the established licensed vaccine.

An example given by Brian Greenwood in a commentary article for The Lancet is that of malaria vaccines [3]. There is now a licensed anti-malaria vaccine (RTS,S/AS01) that is of mediocre effectiveness at about 30 per cent [4]. Will future malaria vaccines need to be compared head to head with this one, or is it ethical to continue with placebo-controlled RCTs?

With all these challenges there is significant variability across national ethics committees as to what is seen as acceptable.

In January 2013 the World Health Organization convened a group to provide recommendations on the ethical issues associated with vaccine trials [5]. This expert panel concluded that, where the epidemiology of an infection is expected to be substantially different from the communities where the pivotal trial that led to licensure was undertaken, then placebo controlled trials can be justified.

They considered five situations where it was justified to use placebo-controlled trials instead of a comparator. The first is where the licensed vaccine is not expected to be introduced in the foreseeable future due to resource constraints. An example was using a novel protein-based pneumococcal vaccine in Bangladesh [6] where pneumococcal conjugate vaccines are not used due to cost. The next four situations were around scientific constraints; the need to establish efficacy and safety in different settings; variability with local epidemiological and demographic data making the existing licensed vaccines scientifically inappropriate as a comparator, such as seen with rotavirus disease; uncertainty around the public health significance of the vaccine introduction; and local population acceptability about the licensed vaccine, such as concerns with vaccines containing porcine gelatine or other ingredients.

The greatest ethical dilemma today with vaccines is the inequitable availability to those communities who stand to benefit the most. If requirements are too stringent or too resource heavy then needed vaccines may not become available to the populations that would benefit the most. However, this does not automatically give the right of clinical trials to potentially cause harm to individuals through the use of placebos in control groups when a valid comparator vaccine or other study design offering benefit to the control group is readily available.

There remains a difficult balance between protecting individual research participants from unjustifiable risks versus the potential for significant reductions in morbidity and mortality across large populations. Where at all possible it is preferable to use an existing vaccine as a comparator. However there are situations where placebos may be ethically acceptable, even with the existence of an efficacious vaccine. Ethical acceptance of a trial must include the ability for the vaccine to be made available to the population on completion of the trial if it is proven to be efficacious. If a placebo-controlled trial is the chosen design, the risks in using a placebo need to be ‘minimal, preventable or reversible’ [5].

Consent and the legality of research

Research involving human individuals requires their informed consent to participate. However, vulnerable groups, such as children, intensive-care patients, and people with an intellectual disability may not be able to provide such consent. Should they be excluded from participating in research? Is it legal to include someone who lacks the competence to consent in the study? In recent months there has been discussions and media interest about the consent and legality of research involving incompetent participants. In this issue of Ethics Notes we have included two commentary pieces about this matter, one from Bruce Northey, General Counsel at the Auckland District Health Board (ADHB), and another from Colin McArthur, Clinical Advisor for Research at the ADHB.

Health and Disability Ethics Committees and the law

By Bruce Northey
General Counsel, Auckland District Health Board

Health and Disability Ethics Committees (HDECs) are created and resourced to confirm on behalf of the public that a study meets generally accepted ethical standards. This is clearly set out in the Standard Operating Procedures for HDECs (SOP):

What HDECs do
8. HDECs check that proposed health and disability research meets established ethical standards that aim to protect participants. These ethical standards are set out in guidelines authored by the National Ethics Advisory Committee (NEAC),

Despite this unequivocal statement, Ministry of Health Legal advised all Health and Disability Ethics Committees (HDEC), via a letter dated 7 April 2014, that "Investigators must satisfy the committee that the proposed research is lawful before a committee approves an application". Following that letter, the Ministry of Health reissued in August 2014 the SOP, without consultation with stakeholders, redrafting the section headed “What HDECs do not do” to include a new responsibility that HDECs must do (?!):

HDECs do not provide legal advice.

15. Researchers and sponsors are responsible for ensuring that their health and disability research is conducted lawfully. HDECs need to be satisfied that any research approved by the Committee is consistent with New Zealand law. An HDEC may not approve an application that is inconsistent with New Zealand law, even if that application is consistent with ethical guidelines.

16. The New Zealand Bill of Rights Act 1990 (NZBORA) applies to acts done by HDECs. Approval by an HDEC of research that breaches the NZBORA may result in the approval being found to be unlawful if judicially reviewed by the courts.

18. Where an HDEC suspects that a research proposal is not lawful, it should advise the applicant of its concerns, and may suggest that they seek formal legal advice. However, HDECs are not themselves responsible for providing such legal advice. HDECs may seek independent legal advice if they are unclear as to the lawfulness of proposed research.

Rather unhelpfully, the Ministry of Health has not provided any guidelines or interpretation of relevant New Zealand law for HDECs when contemplating this new obligation, thus raising the spectre that each HDEC will apply both a different approach and a different interpretation of the relevant law.

How might HDECs approach the issue of lawfulness of research when it is generally accepted, including by lawyers, that ethics and law are as similar as oil and water?

(Continued on page 4)
Law, ethics, and research in critical illness

By Dr Colin McArthur
Clinical Advisor for Research, Auckland District Health Board
Chair, Australia and New Zealand Intensive Care Society Clinical Trials Group

“Drugs tested on critically ill coma patients” ran the front-page headline. “Thousands of critically ill or unconscious patients have been enrolled without their consent...” The implication was that this was a convenient study population who could not object to trials of experimental therapies which offered little or no benefit to the individual, but might be good for ‘Big Pharma’. Great for selling newspapers, perhaps, but the truth was rather different.

Since 2001 over 7000 patients in New Zealand intensive care units have been enrolled into interventional studies. Due to the nature of their illness or the effects of treatment, most of the participants were unable to consent for themselves at the time of enrolment. Following the principles outlined by the National Ethics Advisory Committee¹, New Zealand’s research ethics committees approved these studies with deferred consent.

Consistent with international ethical guidelines such as the Declaration of Helsinki² and those of the World...
Health Organization, in very specific circumstances it is ethical to enrol participants into clinical trials without their prior consent. These include the requirements that the study cannot reasonably be conducted in a population that can consent, that any additional risk conferred by participation is balanced by potential benefit to the individual and/or to the patient group to which the individual belongs, and that the consent of a substitute decision-maker is gained. However, under current New Zealand law (and in contrast to many other jurisdictions), in most cases no-one can legally consent to research involving an incompetent adult. Therefore, as an ethically equivalent alternative, prior ‘assent’ (agreement) is sought from family/whānau member(s) in a manner equivalent to consent.

In all cases family assent to continued participation must be sought as soon as reasonably practical after enrolment, and the deferred consent from participants for any future study procedures and use of data is sought if/when participants regain competence.

What then of the thousands of patients? A review of studies approved by New Zealand research ethics committees between 2001 and 2014, with a provision for some or all participants to be included when they were unable to consent, found 40 examples of which 32 were investigator-initiated. Seven were observational studies but included measurements or assessments beyond those required for clinical care. Of these, five were able to gain prior agreement for the additional assessments from the patient or their family and the other two required time-critical laboratory samples for which delayed consent for subsequent analysis and use of data was obtained.

In the 33 interventional studies, participants were randomly allocated to one of two different treatment options. Twenty-one were “comparative effectiveness” studies of two approaches to treatment that were within the range of standard acceptable practice, and therefore were treatments that patients would be given randomly by individual clinician choice outside of the study. These offered no greater risk than usual treatment, and account for over 97 per cent of patients enrolled without their prior consent. In all these studies, the participant’s family and the patient if/when competent were approached for assent or consent (or provided with information and the option to opt-out) to ongoing participation as soon as reasonably practical.

The other 12 interventional studies included a treatment not currently in clinical practice, and where some or all of the participants were expected to be incompetent. In eight of these studies, prospective prior assent was obtained from the patient’s family or consent from the patient if they were competent. If initial participation had been agreed by the participant’s family, then delayed consent to ongoing participation was obtained from patients if/when they became competent.

The final four studies, including a non-standard treatment arm where delayed assent to ongoing participation was sought from families (and later consent to continue in the study from surviving competent patients), were all studies of emergency treatment for brain injury causing coma. None involved pharmaceutical products. For all these studies, the ethics committees considered that there was little or no additional risk to participants compared to standard care, that there was evidence that the study intervention was potentially beneficial, and that there was no other way of appropriately assessing the treatment with prior assent from families or consent from participants.

Is this an acceptable approach? We have good evidence from some of the more major studies that delayed consent in these circumstances is supported by patients and families. The overall proportion of families or patients who declined delayed consent after they or their relative had been enrolled in an interventional study comparing two approaches to standard care was as follows: SAFE (albumin vs saline resuscitation fluid) 0.8 per cent; NICE-SUGAR (blood glucose control target) 2.0 per cent; RENAL (high vs low dose renal replacement therapy) 2.6 per cent; CHEST (hydroxyethyl starch vs saline resuscitation fluid) 3.6 per cent. This shows that over 95 per cent of families and participants do not decline delayed consent, which is strong support for the approach taken by researchers and ethics committees in New Zealand over the past 15 years.

Although the ethical position is reasonably clear, the same cannot be said for the legality of research involving participants who are unable to consent. The Code of Rights section 7(4) allows for legal surrogates.

(Continued on page 6)
Research misconduct

By Dr Greg Pringle

“...his meteoric rise in the ... scientific establishment had left behind a trail of ruined careers and shredded egos, and he was equally loathed and admired by his colleagues... It had not gone unnoticed in certain circles that much of his success had come from the shameless stealing of other people’s research and the ruthless undermining and intellectual carpet-bombing of anyone he perceived as a rival.”

So wrote Quinn Berentson in his recent book ‘Moa: The Life and Death of New Zealand’s Legendary Bird’ (Craig Potton Publishing, 2013), referring to a renowned UK anatomist Professor Richard Owen on his career to 1839. Such behaviour would still be immoral today, and the ‘stealing of other people’s research’ is surely misconduct. But has anything changed since 1839, considering the global research community has expanded by several orders of magnitude? Evidence would suggest that it has not.

Drivers of behaviour

For those with lofty career aspirations, it is not surprising that there are...
personal incentives to maximise one’s publication record in a competitive environment with a bias towards the weight of publication. The Performance Based Research Fund has undoubtedly increased the pressure for publication across a range of academic positions in New Zealand universities. This is tied directly to a major funding mechanism and is thus of interest to the researcher’s institution. There is no evidence to date that this has resulted in a lowering of publication ethics in New Zealand.

There are also personal incentives for publishing first in some of the more fast-moving disciplines, and this may lead to quality issues, self-plagiarism, ‘salam’ publishing (splitting one paper into several to increase the count) and duplication.

**Grades of irresponsible practice**

At the extreme, there are many examples overseas of health researchers fabricating and falsifying data, and of plagiarism (collectively labelled ‘FFP’). These acts are deliberate – there is an intent to deceive. The world record for this would have to be recent revelations of a Japanese anaesthesiologist fabricating data for 172 papers (Akst, 2012). These and other examples often require the public retraction of the offending articles (http://retractionwatch.wordpress.com) and through their journals, of which there were over 500 in 2013. We would be naive to think that irresponsible research practices are totally absent in New Zealand. Not all retractions are the result of misconduct or bad science – a recent retraction involving New Zealand researchers was due to the subsequent discovery of equipment effects, and was rightly retracted quickly and in the correct manner, leaving reputations intact and a professional service to the research community.

**Of lesser evil are questionable research practices (QRPs), which while not deliberate, are ‘ sloppy ’ behaviours and may be claimed to be more prevalent. Deleting the data outlier from analysis, inappropriate authorship (inclusion or exclusion), insufficient acknowledgement, lack of citation (or improper citation), inadequate research design, and biased or inappropriate conclusions from the data fall into this category. In the relatively small research community we have in New Zealand, conflicts of interest in peer review are almost unavoidable, with differences of academic opinion at times irresolvable and potentially damaging for the applicant. True confidentiality (of concepts and commercial end-points) is also hard to achieve in a community such as ours.

End-users of reported research also have obligations. The researcher’s moral rights need to be respected – acknowledging their contribution correctly and appropriately, ensuring the integrity of the work (without alteration, distortion or mutilation), respecting any request for anonymity, and the avoidance of false attribution. These requirements are easily manifest in the research contract between the research provider and the sponsor. Clauses that mandate the need for researcher vetting of sponsor report alterations or communications based on the research, naming the researchers and their organisations, work hand-in-hand with the researcher’s obligations to acknowledge the contributions of the sponsor or funder of the research.

Surveys of the incidence of FFP have revealed rates of up to 2 per cent for FFP and 72 per cent for QRPs. Rates have been increasing markedly in recent years, due in part to the exposure of research misconduct is having internationally, systems being put in place within the science community, and an increased ability to detect such behaviour.

**Exposure, review, sanctions and consequences**

Retractions can be made years after the original publication. The concern here is for the research of others who have relied on the original (mis)information, and possible consequences for follow-on research, clinical practice or commercial activity. The retraction of a paper by an Australian-headquartered company late last year resulted in a fall in their share price from 95c to 60c. More spectacular examples have resulted in the collapse of companies founded on bad science, at the expense of investors.

A common theme in cases of proven misconduct is that close colleagues were often aware of questionable practices. Their willingness or ability to challenge false findings may be diminished by internal power relationships, dogma or the pressure to publish, and perhaps by a quiescent authority within the institution. A public challenge is enough to bring the misconduct to light, such as happened in the National Women’s cervical cancer work of the 1960s when colleagues were exasperated enough to publish a challenge to Dr Green’s findings in 1984. As a result of similar incidents, protection of the whistleblower is enshrined in some overseas guidelines but must be exercised with caution, as there is the opportunity for malicious or frivolous challenges.

Such practices could draw disciplinary action through employment provisions in the researcher’s institution. Ethics committees may be an initial port of call for investigations of ethically-approved research, but they should not necessarily be the arbiters of irresponsible behaviour or misconduct.

---

Ethics Summer Studentships

Four students were awarded HRC Ethics Summer Studentships in 2013/2014. The purpose of the studentship is to enable a student to train with a research team during the summer break and have the opportunity to explore ethical issues that face New Zealand. Here we feature brief reports of the students’ projects.

Colleen Bain, AUT University
Supervisor – Professor Louise Longdin
Ethics implications arising from the delivery of New Zealand health services via mobile device applications

Many health providers are now turning to mobile device technology to deliver health services through the use of smartphone applications, known as mHealth. The functionality spectrum of mHealth services ranges from low-level appointment reminders and reference resources for searching symptoms, to registered medical devices allowing, for example, real-time monitoring of an embedded device. This research identified and analysed key issues raised by mHealth that differed from those encountered in traditional delivery models, focusing on concerns about privacy and information security as well as specific problems thrown up by the remote interaction existing between providers and consumers. It considered the ways in which each of these areas represents a potential risk to the cornerstone principles of autonomy, beneficence, non-maleficence and justice. The research detailed how providers who may be fully meeting their legal obligations to consumers under New Zealand law, may still fall short of satisfying important ethical obligations incumbent on them as professionals under their respective code of ethics.

Charlotte Stockwell, the University of Auckland
Supervisor – Professor Rosalind Hurthouse
Abortion, virtue ethics and the role of the state

Virtue ethics is a theory of normative ethics which tries to look at the bigger picture of a person’s life as a whole, rather than only at individual actions. It encourages us to view ethical issues in context. Political issues such as abortion need to be viewed both in the wider socio-political context (education and health care in general, for example), and in the context(s) of the great variety of individual circumstance. It stresses the need for individual eudaimonia (flourishing, living well, or “the good life”), as well as emphasising the role of the state in enabling and promoting the flourishing of its people. The researcher argued that at its very core, virtue ethics provides an excellent basis for comprehensive sex education; virtues such as responsibility, love, kindness, justice, and honesty, tied together by phronesis (practical wisdom), lie at the core of what New Zealand students need to learn, both in regards to sex, and life in general. This study tried to demonstrate that flourishing can best be promoted by reducing the numbers of unwanted pregnancies. To achieve this, the study suggested providing comprehensive sex education to students, starting before they reach 13 years of age, and by making contraception as readily available as possible.

Bonnie White, University of Otago
Supervisors – Professor Jennie Connor and Dr Simon Walker
Freedom as responsibility: Rethinking the ethics of alcohol policy in New Zealand

Alcoholic drinks have an established place in most societies (Law Commission Report 114, 2010) and are often consumed in dangerously large amounts (Rehm et al., 1999 and 2003). Given the responsibility of the state to promote the overall health of society, there is a need to review the current national policies related to alcohol consumption. The researcher considered the ethical basis of reforms that were proposed in a 2010 Law Commission report (Law Commission Report 114, 2010), and responded to the claim that such policies constitute an unjustified restriction of autonomy. The researcher argued that policies that effectively enable safe alcohol consumption enhance autonomy by allowing rationalised decision-making and promoting self-determination.
The HRC Ethics Committee (HRC EC) welcomes Professor Lesley McCowan, ONZM, MBChB, FRANZCOG, MD, CMFM as a new member of the committee. Professor McCowan replaces Professor Sue Stott who finished her term with the HRC EC in December 2013. The HRC EC would like to thank Professor Stott for her valuable contribution over the past six years.

Professor Lesley McCowan is head of the Academic Department of Obstetrics and Gynaecology at the University of Auckland. She is a sub-specialist in maternal-fetal medicine at National Women’s Health, and her main clinical interests are in managing high-risk pregnancies, especially those with fetal growth restriction and pre-eclampsia. She has chaired the perinatal mortality review process at National Women’s for many years and was a founding member of the national Perinatal and Maternal Mortality Review Committee, which reviews deaths of babies and mothers nationally.
Similarly, ‘naming and shaming’ isn’t in the ethos of the New Zealand research community. The process of review of an allegation should be very discrete, as premature disclosure may be sufficient to cause irreversible reputation damage to an innocent person. In overseas jurisdictions, guilty parties have been excluded from the ability to apply for research grants, have had close supervision imposed, or been excluded from acting in any advisory capacity for such processes. The greatest damage though is to the researcher’s reputation, as well as that of the laboratory and institution, and is thus a serious limitation to career progression.

**Prevention is better than cure**

Awareness and education are precursors for good research practice. This must begin during undergraduate and postgraduate researcher education, and extend across the ‘value chain’ of early career researcher induction to a new research environment, funding agencies, journals and professional bodies.

In Australia, the need for a research integrity governance framework is tied to the university’s key funding agencies (ARC and NHMRC), effectively ‘forcing’ compliance and behaviour. This compliance has come at a cost of both the need for infrastructure (Research Integrity Officers) and in-kind time input (all staff). New Zealand would benefit from the softer approach of awareness and education. Regulation is not a preferred option at this point, but educational resources and training opportunities are largely missing. The Royal Society of New Zealand does publish a code of conduct, but it is enforceable only for its members and does not cover the full range of research conduct in sufficient detail. Such codes of conduct refer to unethical behaviour, but as we all know, there are behaviours that would be considered unprofessional but not unethical – such as the example mentioned at the start of this article. In the continuum of professional behaviour, it would be impossible to regulate this cleanly.

---


---

### Upcoming meeting dates

**HRC Data Monitoring Core Committee (HRC DMCC)**
- 21 and 22 April 2015
- 20 and 21 October 2015

**HRC Ethics Committee (HRC EC)**
- 18 February 2015
- 13 May 2015
- 19 August 2015
- 11 November 2015

Please note: Any submissions to the HRC EC need to be sent to Lana Lon, at llon@hrc.govt.nz three weeks before the meeting.