Health and disability research involving adult participants who are unable to provide informed consent

Auckland Women's Health Council Submission

Note:

Case Study A: Observational study measuring clearance of antibiotics during dialysis

Dr A wants to study how quickly antibiotics used to treat septic patients in Intensive Care Units (ICUs) are removed by dialysis. It is already known that most antibiotics are removed by dialysis to some extent, but the rate can vary. Consumers with severe sepsis often require dialysis therapy due to acute kidney injury. A special form of dialysis is used for these consumers in the ICU, but currently there is no information available regarding the rate at which that form of dialysis removes the antibiotics used to treat sepsis. If antibiotics are cleared by dialysis at a faster rate than expected, the sepsis could be undertreated.

Dr A proposes a study involving acutely unwell septic patients in the ICU, who are unlikely to be able to provide informed consent owing to the impact of the sepsis. Dr A will not amend the treatment provided to the study participants — they would be provided with antibiotics and dialysis in the same way as they would outside of the study. However, Dr A would enrol the participants in his research and measure the changes in antibiotic concentrations during the participants' dialysis sessions. Changes would be measured by a number of tests, including urine and blood tests that would not otherwise be performed.

Information from the study would not affect the clinical management of the participants, and they would not benefit from the research. However, Dr A believes the data gathered may lead to more accurate dosing of antibiotics for other septic patients in ICUs in the future.

Case Study A questions

A.1: If you were a patient with sepsis and unable to consent, would you want the research to go ahead with you as a participant?

Yes/**No**/Unsure

A.2: Please give the reasons you formed this view.

The AWHC would like to make clear from the outset their philosophical opposition to conducting medical experiments, including within the auspices of clinical trials, on any New Zealanders without their fully informed consent, and these concerns apply to all case studies provided. That vulnerable groups of consumers can, and are, being exploited for research gain under the current law goes against the principles of the Nuremberg Code (1947), the founding document that gave rise to modern medical research ethics. It is clear that the law as it stands is sufficiently weak and uncertain as to allow "studies to proceed in relation to participants who are unable to consent if participation in the research is in their "best interests""* where the researcher is able to make the decision as to what constitutes in the patients "best interests".

The AWHC believes that absolutely no incapacitated/incompetent adults should be enrolled for medical experiments/clinical trials/research until there are sufficient protections and safeguards established in law that first and foremost protect their rights and interests, health and well-being.

The Nuremberg Code (1947) on medical experimentation on human subjects was followed by the Geneva Convention and then the Declaration of Helsinki formulated by the World Medical Association, of which the New Zealand Medical association was and is a member. The Declaration of Helsinki clearly states that:

- "while the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects";
- "some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm… All vulnerable groups and individuals should receive specifically considered protection."
- "participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees."

Yet despite these existing protections, which New Zealand's Medical Association ratified, medical experimentation on competent women at National Women's Hospital occurred without their knowledge or consent in the 1960s and 70s.

Our Code of Health and Disability Services Consumers' Rights, while a step in the right direction, still allows for research on adults not capable of providing informed consent on the basis that the researcher decides it is in the consumer/patient's best interests. The AWHC does not believe that researchers are capable of making an unbiased decision that is truly in the best interests of the consumer/patient. In addition, it is the AWHC's view that the current Health and Disability Ethics Committees (HDEC) do not prioritise the protection of research subjects.**

Once an adequate ethical and legal framework is in place (including specific definitions of terms such as "minimal risk/burden", "benefits", "best interests", and who constitutes an authorised legal representative) further nationwide discussion involving all stakeholders, including patient and consumer advocates, should revisit the circumstances, if any, in which research involving vulnerable groups such as incapacitated/incompetent adults might be permitted.

If an adequate ethical and legal framework was established that provided sufficient protections for incapacitated/incompetent research subjects, including a Special Ethics Committee to oversee approval to such research proposals (see Consultation Question 9), the AWHC might take the following view on a research proposal such as described in Case Study A:

The research is relatively non-invasive in that it does not involve varying the treatment protocol, and there is very low level of risk involved. It involves the collection of data from urine obtained through dialysis that is already occurring. However, the case study text infers that further blood tests would be taken to provide data on antibiotic concentrations in the blood; blood tests that would otherwise not be performed. The knowledge gained could improve treatment for future patients, and it seems that significant benefit to future patients may result. Informed consent must be obtained from next of kin or anyone holding Enduring Power of Attorney (EPOA) and the patient's informed consent when competence is regained. However, if the patient, upon reaching competence, withholds consent, data collected from that patient must be withdrawn from the study and destroyed.

* *Health and disability research involving adult participants who are unable to provide informed consent* consultation document.

** AWHC members have attended HDEC meetings over the last eight years, and three current Council members have been sitting members of various ethics committees.

Case Study B: Clinical trial comparing two products used following neurosurgery

Dr B wants to compare the safety and effectiveness of two products used to achieve a watertight closure of patients' brain membranes following neurosurgery. Both products have already been clinically approved and are commonly used by surgeons. The current evidence does not indicate that either product is safer or more effective than the other, but no research has been conducted that directly compares the two products.

Dr B proposes to conduct a study on consumers undergoing neurosurgery, who would be randomly allocated to receive one of the two products. Dr B would then collect data about the safety and effectiveness of each product.

The consumers are mostly having surgery in relation to brain tumours and are likely to have reduced capacity to make decisions. Some of the potential participants may have brain injuries, cognitive impairments, intellectual disabilities, mental illnesses or be in intensive care. While some of the proposed participants may be able to provide informed consent, others will not have the capacity to do so. Dr B believes that both groups need to be included in the research in order to gather useful data that can be generalised to other consumers in the future.

Dr B intends to include consumers who are unable to give consent, and then seek "delayed consent" from any consumers who regain the capacity to consent after the trial. If any of those consumers refuse consent after regaining capacity, their data will be removed from the study.

B.1: If you were having this surgery and unable to consent, would you want the research to go ahead with you as a participant?

Yes/**No**/Unsure

B.2: Please give the reasons you formed this view.

There is insufficient information provided in this case study; however, it appears that the same information could be obtained through enrolling competent consenting patients undergoing elective surgery (refer to Schiariti A.; Surg Neurol Int. 2014; 5: 171.), in which case clinical trials on incapacitated/incompetent patients should not be considered.

Randomising patients without their consent is unethical because, in many patients, there could be a necessary variance from what is best practice care for the surgeon involved. It is unclear from the information provided if the researcher, Dr B, is the surgeon who will perform the surgeries involved in the study. There are several reasons why any given surgeon chooses to use particular products and those reasons may impact upon outcomes in different patients operated on by different surgeons. If patients are to be randomised a surgeon may end up using a product s/he was less familiar with or had less confidence in and this could introduce an outcome bias.

It is clear from other similar research that this research could be undertaken in patients who are competent before surgery and as a starting point Dr B should undertake fully consented research on competent patients.

There are insufficient clear benefits to incapacitated/incompetent patients that outweigh their right to provide informed consent.

B.3: What are your views about "delayed consent"?

There can be no such thing as "delayed consent"; it is effectively an oxymoron. Asking for consent after the fact is like a child asking a parent for a biscuit after having eaten one; if the answer is no what happens? You can't change what has already occurred.

In observational studies it is possible to remove a subject's data from the results of the study, but in interventional research the outcomes of treatment will be the same. Where treatment or procedures in a study (particularly a randomised study) might vary from what would have happened in a non-study situation, once it has happened it can't be reversed. There may well be compelling reasons why a person would not have consented; they opposed randomisation or had a personal preference for a specific procedure or product to be used; there were ethical issues that concerned them about the manufacturer/suppler or manufacturing process or materials used… or simply did not want to take part in research for personal or cultural reasons. It goes without saying that if "delayed consent" is sought, then a subject's information and any data obtained must be removed, and if the follow-up is long term (beyond the regaining of competence) the subject should be withdrawn. The inclusion of people not competent to consent prior to the research should never be justified on the basis that "retrospective consent" can be sought.

In reality, the only consent that can be obtained in retrospect from a previously incapacitated or incompetent research subject is consent to remain in the research. It is simply disingenuous semantics to suggest that patients could provide delayed or retrospective consent.

Case Study C: Trial regarding care provided to consumers with severe dementia

Dr C wants to study the care provided to rest home residents with severe dementia. Dr C believes that conventional care for such consumers is task-focused, concerned primarily with the consumer's physical needs and daily activities. Dr C thinks conventional care may be neglecting consumers' psychosocial needs, meaning that many consumers with dementia are spending many hours alone and emotionally distressed. Dr C thinks that part of the problem may be that a dementia diagnosis is treated as diminishing a consumer's personhood, leading staff to reduce their efforts to establish and maintain relationships with the consumer.

Dr C proposes a study that would randomly allocate consumers with severe dementia into two groups, each group receiving a different type of care. Group 1 would receive conventional care, which focuses on physical task-oriented practices and physical needs. Group 2 would receive "interactive care", an alternative to conventional care that is intended to maintain personhood as dementia progresses. "Interactive care" includes a greater focus on the psychosocial needs of the consumer. At this stage, there is very little evidence about the benefits or risks associated with "interactive care". However, Dr C believes that the proposed study could supply evidence that would lead to improvements in the care provided to consumers with dementia.

It is not known whether the research would be in the participants' best interests. They would have to undergo additional assessments as part of the research, but the additional assessments could benefit the participants if the increased contact with the researchers was beneficial to them, or changes in their condition were picked up that would not otherwise have been noticed. On the other hand, there is a risk that some participants may find the additional contact distressing.

The proposed trial would take place over four months. Researchers would assess the participants' agitation levels, psychiatric symptoms and quality of life before and directly after the trial period, and then again four months after the conclusion of the trial.

The fact that a consumer has dementia does not necessarily mean that he or she is unable to provide informed consent. Some may be capable of providing informed consent with appropriate support, or they may have intermittent periods when they are able to provide consent to participate in the research. Dr C also proposes to include in the study consumers who are not able to consent.

C.1: If you were a person with dementia and unable to consent, would you want to be a participant in this research?

Yes/**No**/Unsure

C.2: Please give the reasons you formed this view.

The research should start with a pilot study among those patients capable of providing consent. Dr C is clear that "there is very little evidence about the benefits or risks associated with 'interactive care' " and dementia patients are a very vulnerable group. A pilot study among consenting patients would give Dr C sufficient information to assess levels of distress among participants in the "interactive care" group as well as any benefits that such care might ultimately afford the patients.

A well designed study undertaken with sufficient advance notice should be able to provide enough information to answer the question as to the benefits and risks of the intervention without including patients unable to provide informed consent.

In a situation in which there is a strong legal and ethical legislative framework that offers sufficient protections and safeguards for vulnerable groups, results from a cohort of participants able to provide consent ***might*** then form the basis for further research in which informed consent from next of kin or those with EPOA might be a valid approach to understanding the benefits and risks of intervention for those unable to consent. However, the results of a pilot study might deliver data that rules out intervention on the basis of risk versus benefit, in which case a highly vulnerable incapacitated/incompetent cohort would never need to be subjected to research of little or no benefit to them.

A further consideration is that frequent assessments in themselves might raise levels of frustration, anxiety or emotional distress in this highly vulnerable group of patients and it's clear that the researchers can't say that the research is in any way in the "best interests" of the patients.

Case Study D: Clinical trial regarding use of adrenaline

Dr D wants to study the use of adrenaline in the treatment of cardiac arrest. Adrenaline has been used as a routine treatment for cardiac arrest for over 50 years, but its safety and efficacy have not been tested fully. Several previous studies suggest that while adrenaline may help to restart the heart initially, it may also lower overall survival rates and increase brain damage. While these studies have led to significant concerns about whether adrenaline could be harming consumers, the body of evidence is not yet strong enough to change current practice.

Dr D proposes a large clinical trial to gather further information. The trial would be randomised, double-blind and placebo-controlled. This means that some of the participants would receive adrenaline and some would receive a placebo (in this case, salt water). During the trial, neither the participants nor the paramedics would know who was being given adrenaline and who was being given salt water.

No consumer undergoing treatment for cardiac arrest would be able to provide informed consent to participate in the study, so Dr D proposes to enrol consumers in the trial without obtaining consent. She considers that the research is important to ensure the best outcomes for consumers who have cardiac arrests in the future, and that it cannot be conducted on consumers who are able to provide consent.

To deal with this issue, Dr D suggests an "opt-out" process for consent. Consumers not wishing to be enrolled in the study would be able to opt out by requesting a bracelet with "NO STUDY" engraved on it. Awareness of the study would be raised through a public information campaign.

Case Study D questions

D.1: If you suffered a cardiac arrest, would you want to be part of the study?

Yes/**No**/Unsure

D.2: Please state the reasons you formed this view.

It is totally unethical to withhold a standard or best practice treatment from patients without their consent and, in particular, in a life or death situation, such as when a patient's heart has stopped beating. While the issue of whether or not the use of adrenaline leads to overall lower survival rates and increase in brain damage is an important one to research, there is insufficient information provided on the effects of not using adrenaline and using a placebo (which by definition is a non-therapeutic substance or treatment) instead. This research has absolutely no benefit for the subjects involved in the research and can only possibly benefit future patients. The threshold for benefit versus risk, in the case where consent cannot be obtained, must necessarily differ if those provided a treatment cannot weigh up the pros and cons and make an informed decision. In this case the benefits for the subjects are too low and the risks potentially too high.

AWHC objects in the strongest possible terms to this type of research in which subjects unable to consent may be randomised to not receive best practice care in a life threatening situation. It is hard to imagine any scenario in which such research could be considered ethical. In addition, as a double blind trial, the attending physicians would not know whether adrenaline or placebo had been given and will therefore have no idea the exact cause if the patient fails to respond to the treatment.

D.3: What are your views about the proposed "opt out" process?

An "opt out" process, in virtually any medical scenario, is highly problematic and is in no way a valid or ethical alternative to the provision of fully informed consent. It is predicated on the idea that 100% of the population that may be at risk of sudden cardiac arrest will be made sufficiently aware of their choices that they will be able to, and motivated to, make an informed decision to "opt out" or, by definition, choose to actively "opt in" by doing nothing. Given the known apathy of populations to exercise their mandated right to do such things as vote (a far less personally risky action than to choose to participate in research in a life-or-death situation), it is extremely unlikely that anything close to 100% of the "at risk" population would be reached in a public information campaign. Therefore, the probable low level of active decisions to "opt out" cannot be taken as tacit consent to participation in a medical experiment by the remaining (quite likely majority) of the "at risk" population.

Additionally, many of the at risk population simply do not know that they are at risk until they have such a medical event. People ignorant of their risk status would not be easily communicated with via a public campaign.

A further stumbling block to this proposal is that it would seem likely that few people would want or would be bothered to consistently wear an "opt out" bracelet.

The "opt out" idea is a highly disingenuous way of abrogating responsibility for the need to obtain informed consent from patients involved in potentially risky medical research. It has been acknowledged that it would be difficult if not completely impossible to obtain informed consent in the described scenario and the "opt out" solution is an unethical attempt to get around deservedly stringent regulations regarding the participation of human subjects in medical experiments.

Case Study E: Clinical trial of drug for people with Down syndrome

Dr E wants to investigate whether a particular drug will improve the cognitive and learning abilities of people with Down syndrome. He proposes a randomised, double-blind, placebo-controlled study. This means that some of the participants would receive the study drug and some would receive a placebo (for example, a sugar pill). During the trial, neither the participants nor the researchers would know who was receiving the drug. Participants would be required to undergo regular six-hour assessment visits to check their progress.

The study drug has already been tested on people without Down syndrome. That research provided some information about the possible risks and side-effects of the drug, including that, for some participants, it increased the incidence of contemplating suicide. However, there may be other risks or side-effects that have not yet been discovered. In particular, the effects of the drug on people without Down syndrome may be different from those on people with Down syndrome.

It is not known whether the drug will have the desired effect on cognition or learning (or any other beneficial effects). However, it is likely that even if the drug did lead to an improvement in cognition for the research participants, the effect would be temporary because the drug would not be available to participants after the conclusion of the trial.

Some adults with Down syndrome may be capable of providing consent if given appropriate support and information. Those consumers could then be enrolled in the study in accordance with ordinary consent principles. Dr E proposes also to enrol participants who are not able to give consent because the effects of the drug on those participants may be different. Dr E proposes to consult with family/whānau/caregivers and, if they express objections, those participants will not be enrolled.

Case Study E questions

E.1: Do you think people with Down syndrome who are unable to give informed consent should be part of this research?

Yes/**No**/Unsure

E.2: Please state the reasons you formed this view.

The risks are significant in a group of already highly vulnerable people, with limited or no benefit. It is clear that the benefits are not well understood and that if there were any, they would likely be short lived – what would be the effects on the adults with Down syndrome if they enjoyed improvements in cognition and learning ability only for those effects to dissipate once the drug was no longer administered? This surely amounts to a cruel punishment, and if the subjects are not competent enough to provide informed consent, how will they cope with an improvement and followed by a decline in their abilities? Given that clearly little is known about the adverse effects of the drug, and that many Down syndrome people have other physical health problems, such as poor immune function, congenital heart defect and epilepsy, it would be unethical to risk side-effects that would further compromise their quality of life without their informed consent.

It is entirely unethical to involve anyone without their fully informed consent, and a full and conscious knowledge of the risks and benefits, in research that may raise their risk of contemplating suicide. It is hard to imagine that any transient and short-lived cognitive benefit to Down syndrome adults could be perceived as balancing the risk of self-harm or even thoughts of self-harm.

E.3: Do you think the proposed consultation with family/whānau/caregivers gives sufficient protection for participants who are unable to give consent?

Yes/**No**/Unsure

E.4: Please state the reasons you formed this view.

Some of the issues that are raised in E2 above apply here: if the subjects are not competent enough to provide informed consent, how will they cope psychologically with the impacts of the research and administration then withdrawal of the drug (e.g. an improvement and followed by a decline in their abilities; or significant risks to their health and quality of life, such as increased thoughts of suicide) if another person sees fit to consent on their behalf?

The family/whānau of vulnerable patients/consumers are subject to potential coercion and duress. Most want what is best for their loved ones, but may not be best placed to make important decisions regarding research of which they may have little understanding, in particular when they harbour hope that improvement is possible when the prognosis is poor.

In this case study, while family/whānau may be swayed by thoughts of possible improvements to cognitive and learning abilities, the risks are still significant and the benefits insubstantial and ephemeral. While people with Down syndrome have a reduced mental capacity, many lead happy, productive, quality lives and this vulnerable group should not be viewed as experimental subjects by anyone and only they should have the right to provide informed consent for medical research.

Consultation Question 1

1.1 Do you believe research should ever be allowed to proceed with adult participants who are unable to provide informed consent?

If yes, please state the reasons why.

If no, please state the reasons why not.

As stated at the outset of this submission, the AWHC holds a philosophical opposition to conducting medical experiments, including within the auspices of clinical trials, on any New Zealanders without their fully informed consent. That vulnerable groups of consumers can, and are, being exploited for research gain under the current law* goes against the principles of the Nuremberg Code (1947), the founding document that gave rise to modern medical research ethics. It is clear that the law as it stands is sufficiently weak and uncertain as to allow "studies to proceed in relation to participants who are unable to consent if participation in the research is in their "best interests"" where the researcher is able to make the decision as to what constitutes 'in the patients best interests'.

The AWHC believes that absolutely no incapacitated/incompetent adults should be enrolled for medical experiments/clinical trials/research until there are sufficient protections and safeguards established in law that first and foremost protect their rights and interests, health and well-being.

* Johnston, M.: Consent for drug trials on coma patients to be reviewed, New Zealand Herald, 15 December 2014.

1.2 If you think such research should be allowed, please make any general comments about the circumstances/restrictions that you think should apply.

In the event that sufficient protections and safeguards are established in law – legislation that first and foremost protect their rights and interests, health and well-being – in some limited and very strictly controlled circumstances, research involving incapacitated/incompetent adults might be permitted to proceed. If there is a direct benefit to the incapacitated/incompetent adult/s, and without research there would be no other opportunity for the incapacitated/incompetent adult/s to benefit (e.g. a new drug specifically for the condition that relates or contributes to their lack of ability to consent), and if the risks are significantly outweighed by the benefits, research might be allowed to proceed. However the most stringent safeguards must be applied and each case (research proposal) should be assessed on an individual basis. Observational studies are of lesser concern as such studies do not require any variation on best practice treatment of the research subjects; rather the collection and analysis of data that would can be routinely collected in the normal course of care and treatment for their health condition/s.

However, even observational studies raise issues of consent and whether or not it is culturally appropriate and sensitive for some patients to be included without their consent when they might hold different values and views around the collection, storage and use of personal data and human material such as blood, urine and tissue.

Where there is no direct benefit to the incapacitated/incompetent adult/s but to future patients in the same or similar situation, research might be allowed to proceed under strict ethical control (see Question 6.2) where there is also very limited or no risk involved, such as in the case of observational studies without variance from best practice care of the subjects, and where sufficient other safeguards (e.g. next of kin/EPOA consent and "retrospective consent" is obtained, notwithstanding submissions made in Question B3 above and 3.2 below) are in force. However, as discussed in Question A2, it is critical that clear definitions of terms such as "minimal risk", "burden", benefit" and "best interests" should be set out with no room for interpretation. Additionally, the person/s able to make an "in the patient's best interests" decision must be clearly defined, including that that person cannot be associated with the research, or directly benefit from the research, and should have knowledge of the patient, and their condition.

Specifically, research should only involve incapacitated/incompetent adults in the following circumstances:

1. That the research is observational and does not involve invasive procedures and does not involve any deviation from best practice care of the patients; that data will be collected in the course of the normal best practise care provided.
2. That the same research cannot be undertaken with adults capable of providing informed consent;

And/or

Research has already been undertaken in competent, consenting adults, and further research involving incapacitated/incompetent adults would significantly add to the body of knowledge AND benefit those patients or future patients with the same condition (subject to 3 below).

3. That the research is directly related to the condition/s that the incapacitated/incompetent adults have, and/or directly relates to the reasons they are incapable of providing informed consent.
4. That there is direct benefit for the research subjects and negligible risk, or that the benefit to the research subjects is significantly outweighed by the risks; that a research subject will benefit as much from being included in the research as not being included;

Or

There is no expected benefit for the research subjects but that there will be a significant benefit for future patients with the same condition, and the risk to the research subjects is negligible.

5. That the research does not involve "non-inferiority" research, and that benefits to the subjects are more than inclusion benefits.
6. That all proposed research is subject to approval by a "special ethics committee". This committee would have a core membership including entirely independent medical ethicists, patient advocates, lay persons and medical/health/disability representatives, and for each proposal would include co-opted members such as entirely independent lay representatives and patient advocates with a special interest in the vulnerable group to be involved in the research, lay persons or ex-patients of a similar medical demographic to the proposed subjects (where possible), and medical/health practitioners with expertise in the vulnerable group to be involved in the research.
7. That, notwithstanding the submission made in Question 3.1 below, in all cases where "retrospective" or "delayed" consent from the incapacitated/incompetent adult is obtainable upon regaining competence, that consent is sought under the existing code (i.e. without coercion, duress, discrimination, harassment, or exploitation).
8. That all efforts are made through discussions with next of kin, EPOA or the patient's regular health professional (e.g. GP, counsellor, etc.) to ascertain the incapacitated/incompetent adult's attitude to participation in research or clinical trials, such that it may have been discussed explicitly or otherwise at a time when the subject was competent, to understand the views that the now incapacitated/incompetent adult may hold were they in a position to provide consent.

9. That any indication that the research subject does not consent, or appears to object, or shows signs of resistance before, during or after the research, they must immediately be withdrawn from the research.
10. That especially vulnerable groups of incapacitated/incompetent adults, such as those with permanently reduced mental capacity (e.g. Down Syndrome, dementia patients) with no likelihood of being able to ever provide consent are never to be involved in anything more than strictly observational studies in which there is no deviation from best practice care and no physical intervention.

The Code provisions relate to health and disability research conducted only by a health care or disability services provider. Research relating to health and disability issues is also conducted by non-providers, for example, some academic research. Given that such research is outside the jurisdiction of the Commissioner:

1.3 Do you think the same laws should apply to all health and disability related research?

Yes/No/Unsure

1.4 Please make any general comments you have about question 1.3.

The circumstances, role, employer or title of the person or group undertaking the research do not in any way at all alter the vulnerability of adults who are unable to provide fully informed consent to participate in experimental research. There should no difference in the application of any code of rights, legislation or safeguards regarding the recruiting and involvement of incapacitated/incompetent adults in any and all research and the foremost consideration should be the safety and well-being of the subjects/proposed subjects of the research. The same laws should apply to all research involving adults unable to provide informed consent!

Dissent

Some people who are unable to make an informed choice to participate in research may be able to express dissent or refuse the procedures involved, for example, by way of facial expressions indicating pain or fear.

Consultation Question 2

2.1 Should the law state expressly that irrespective of the person's level of competence any expression of dissent or refusal to participate in research must be respected?

Yes /No/Unsure

2.2 Please give reasons for your answer.

If there is any doubt whatsoever about the willingness of any research subject to participate or continue participating, the decision must err on the side of caution and the subject must never be enrolled in or must be withdrawn from the research.

When considering such vulnerable groups of adults, the threshold for participation must be especially high in order to ensure all such adults are protected to the fullest extent possible. In order to protect all potential research subjects, it may be that some who may have consented had they had the competence to do so are ruled out, but this is necessary to ensure that no person is included in research that would not have consented had they been competent to do so.

It is widely reported by health professionals working in the field, that unconscious patients can still have some awareness of what goes on around them, in particular through the sense of hearing. Likewise, conscious but impaired people, such as dementia patients or intellectually disabled people have many ways of expressing their dissent even if they are unable to verbalise it with the same degree of articulateness that a fully competent adult might. It cannot be assumed that a patient who cannot provide clear, audible or visible responses in the way that fully competent patients can, cannot express themselves in any manner at all or that they are entirely unaware of what is happening. To ignore subtle signs of distress or resistance risks refusing the patient the opportunity to express their lack of consent in the only way that is possible.

Delayed consent

In some jurisdictions, researchers may be permitted to carry out research on a person who is temporarily unable to give informed consent provided that the researcher obtains delayed (retrospective) consent from the participants after they regain the ability to consent. Delayed consent is not permitted under New Zealand law.

Consultation Question 3

3.1 Do you think the law should be changed to allow researchers to obtain delayed or retrospective consent to research after incompetent participants regain competence to consent?

Yes/**No**/Unsure

3.2 Please give reasons for your answer.

Although in earlier questions in this submission the AWHC has indicated that this should be sought and the decision respected and abided by, in general we have a philosophical objection to the concept of "delayed" or "retrospective" consent.

It is simply not possible to provide ***informed*** consent after the fact.

As stated in Question B3, there can be no such thing as "delayed consent" or "retrospective consent"; it is effectively an oxymoron. The consultation document states that "In New Zealand, delayed consent is not a legally valid form of informed consent. It is not possible to provide informed consent retrospectively, because the events have already taken place, even if the consumer, upon regaining capacity, does not have an objection to having been included in the research."

There needs to be an alternative term that more accurately describes the situation where patients, on regaining competence, are informed that they have been participating in research without their consent and that they can withdraw and have their data withdrawn from the study.

In a few very limited cases the obtaining of this type of "retrospective" consent may be sufficient to right an incorrect assumption that the subject would have given consent had they been able to prior to the commencement of research. In a practical sense, if the research is entirely observational and the data can be removed from the study if the adult, once competent, withholds consent, that might seem to remedy the situation entirely. However, in some cultures the collection of data may represent a breach of their beliefs and the removal of data from the study insufficient to remedy the wrong.

The inclusion of people not competent to consent prior to the research should never be justified on the basis that retrospective consent can be sought. Only in life or death situations, where lack of action or treatment would likely lead to the death or serious further disability of a patient, should action be taken prior to obtaining consent, and research in itself is not a life or death situation.

It is also absurd to assume that all patients have some degree of altruism and would happily consent on the basis of contributing to the "the greater good". There are constant examples of the lack of altruism among many citizens, and those citizens are as likely to find themselves in situations in which they are

incapacitated /incompetent as any citizen whose altruism is demonstrated. In addition, one person's altruism may not extend to happily consenting to research that may bring no direct benefit plus known or unknown risks, and unless consent is acquired while they are competent it is all but impossible for anyone else to know if that person would consent on the basis of "the greater good".

Alternative participants

The NEAC guidelines require that studies should not be performed with vulnerable groups if the studies can be performed adequately with other groups. However, this ethical standard is not a legal requirement.

Consultation Question 4

4.1 Do you think that there should be a legal requirement that, before research on incompetent persons is permitted, the researcher must show that research of a similar nature cannot be carried out on competent persons?

Yes/No/Unsure

4.2 Please make any further comments you have about question 4.1.

It is imperative that if research involving incapacitated/incompetent adults is proposed, and considered, that absolute proof be provided by the applicant that:

- they have exhausted all possible means of obtaining the required data from enrolling competent participants;
- it is critical to undertake research in a specified group of incapacitated/incompetent adults in order to benefit the specific cohort of incompetent adults with the particular conditions associated with their inability to provide informed consent; and
- adequate preliminary studies have been undertaken in competent and consenting adults in order to establish the probable risks and benefits prior to any research involving incapacitated/incompetent adults being proposed.

The AWHC also believe that such an ethical standard be made a legal requirement. There seems little point in having ethical standards that have no legal support, cannot be enforced and rely entirely on researcher compliance.

It may be that, in some cases, obtaining informed consent from competent patients prior to the situation in which their condition or impairment renders them incapacitated/incompetent slows down the progress of the research. In this case research must be delayed in order to amass sufficient consenting subjects to undertake the research rather than rely on incapacitated/incompetent subjects. The primary concern here is, and must always be, the welfare, health and well-being and rights of the research subjects, not the convenience of the researcher or expediting his or her research.

Changes to the Standard Operating Procedures of the HDECs in 2012 has resulted in a shift away from protection of consumers and proposed research subjects towards expediting research. Issues of concern were raised in an open letter to then Minister of Health, Tony Ryall, by five bioethicists. Their concerns included a reduction in ECs from seven to four, leading to a reduced level of scrutiny of clinical trials, expeditious review by the chair, and some research not being reviewed at all in order to cope with the

increased workload. As a result of the changes, research protocols for clinical trials that are categorised as low risk, also receive only expedited review by a committee chair.

There must be a shift back to making the welfare, health and well-being and rights of proposed research subjects the foremost issue for consideration in the HDEC approval process.

Interests of others to be taken into account

There are different possible criteria about the people who might benefit from research conducted with other people as participants. Examples of such criteria are requirements that the research:

- be permitted only if it may benefit others who have the same or a similar condition to the participant
- be connected to the impairing condition that prevents the participants from being able to provide consent
- be intended to provide knowledge of the causes or treatment of the impairing condition that prevents the participants from being able to provide informed consent
- be intended to contribute to significant improvement in scientific understanding of the incapacity suffered by the participants.

Given that in most research on incapacitated/incompetent participants any benefits for participants are uncertain, but the outcomes may benefit others:

Consultation Question 5

5.1 Should research on an incompetent participant be permitted if the research may or may not benefit the individual participant, but may benefit other people?

Yes/No/**Unsure**

5.2 Please give reasons for your answer.

As previously stated in this submission, the AWHC believes that absolutely no incapacitated/ incompetent adults should be enrolled for medical experiments/clinical trials/research until there are sufficient protections and safeguards established in law that first and foremost protect their rights and interests, health and well-being.

Even in the event that such legislation is enacted, insufficient information is provided in this document to adequately and definitively answer this question. Whether such research should be permitted would depend entirely on the nature of the research. As AWHC stated in question 1.2 above, the only research that we believe should be permitted in incapacitated/incompetent adults is that of an observational nature, in which there is no deviation from best practice care of the specific cohort of patients. It is accepted that such research is unlikely to benefit the research cohort, but may benefit future adults with the same impairing conditions.

If the requirement that only observational studies are permitted in incapacitated/incompetent adults is met then the answer to Question 5.1 might be yes.

However, if the proposed research goes beyond the observational and involves intervention, variation to best practice treatment, randomised controlled trials, non-inferiority trials, etc. and there is no benefit to the research subjects or the benefit is only an “inclusion” benefit, and inherently, because the research is interventional, some level of risk must be involved, then the answer is a categorical NO.

If the answer to question 5.1 is yes:

5.3 If the proposed research may or may not benefit the incompetent participants, but may benefit others, should there be criteria about the group of people that it is intended to benefit?

Yes/No/Unsure

5.4 If the answer to 5.3 is yes, please indicate the criteria that you think should apply and indicate the order of importance of the criteria with 1. being the most important and 5. being the least important.

1. The group that the research is intended to benefit have the same or a very similar condition to the research subjects.

2. That the research is directly related to the impairing condition that prevents the participants from being able to provide consent.

3. That the results of the research is intended to provide knowledge of the causes or treatment of the impairing condition that prevents the participants from being able to provide informed consent.

The AWHC holds serious concerns that any regulation that allows research on one particular group of vulnerable patients to be involved in research in order to ultimately benefit any future patients would be subject to regulatory creep. It is unacceptable and unethical to undertake research on one group of subjects in order to subsequently benefit an entirely different demographic group; for example, undertaking research on cognitive improvement in Down syndrome adults that is then used to benefit dementia patients instead, effectively treating the Down syndrome adults as a group of lesser importance or value – effectively as guinea pigs!

Any others?

Ethics committee approval

An option for change would be to make ethics committee approval mandatory in all cases where the research involves adult consumers who are unable to provide informed consent. This requirement could be introduced independently, or in addition to other criteria.

Consultation Question 6

6.1 Do you think researchers should be required by law to obtain ethics committee approval before conducting health and disability research with adult participants who are unable to give consent?

Yes/No/Unsure

6.2 Please give reasons for your answer.

Absolutely, ethics committee approval must be obtained! It is unconscionable that research involving incapacitated/incompetent adults not be subject to the same rigors of ethical approval to which any other research involving competent consenting adults is subject. While it might currently be possible for medical, health and disability research to go ahead without ethics committee approval because the researcher is not a health and/or disability services provider and is, for example, an academic, it is imperative that ethics committee approval be mandatory no matter the researcher or setting in which the research is to be carried out.

The AWHC believes that the ethical threshold for research involving incapacitated/incompetent adult research subjects must be much higher than that required for competent adults. Such vulnerable sectors of

the community must be afforded greater protections than those groups of competent adults who can make decisions for themselves and be their own advocates.

The AWHC believes that the current Code of Rights and HDECs do not provide sufficient protection for vulnerable adults incapable of providing informed consent.

Right 7(4) of the Code explicitly applies to the provision of health and disability services, not research, although right 9 does say that all rights in the code extend to research. However, greater clarity regarding rights of incompetent/incapacitated adults within the code should be addressed irrespective of any other legislative provisions for the protection of incompetent/incapacitated adults.

The AWHC requests that a separate and independent special ethics committee (separate and independent from the existing HDECs) be set up solely to consider research in these vulnerable incapacitated/incompetent adult cohorts. This committee would have a core membership, including entirely independent medical ethicists, patient advocates, lay persons and medical/health/disability representatives, and for each individual research proposal would include co-opted members, such as entirely independent lay representatives and patient advocates with a special interest in the vulnerable group to be involved in the research, lay persons or ex-patients of a similar medical demographic to the proposed subjects (where possible), and medical/health practitioners with expertise in the vulnerable group to be involved in the research.

Ways to assess the advantages and disadvantages of participation by incompetent consumers in research

Consultation Question 7

7.1 Do you think the current best interests test, which requires that the consumer would be better off participating in the research than not participating, strikes an appropriate balance between protecting the rights of consumers who are unable to give consent and allowing research to proceed?

Yes/**No**/Unsure

If you answered "No" to question 7.1, please answer question 7.2.

7.2 If research were to be permitted to proceed without the consent of adult incompetent participants, what criteria/tests do you believe should be used to assess the advantage and disadvantage to the participants?

As AWHC has already stated, its view is that only observational, non-interventional and non-invasive research should be permitted in incapacitated/incompetent adults.

The AWHC opposes the "best interests" test because the term "best interests" is ill-defined and open to significant variations in interpretation depending upon who is making the decision that a particular course of action is in the "best interests" of an incompetent/incapacitated patient.

In particular, this assessment should never be left to the researcher. The AWHC does not believe that researchers are capable of making an unbiased decision that is truly in the best interests of the consumer/patient. Researchers necessarily have a conflict of interest and should never be the ones to determine the "best interests" of a proposed research subject.

In addition, the concept of "minimal" or "negligible" risk or burden is also ill-defined, and a relative concept that may vary significantly depending on who is making the assessment, and the range of adverse effects or events or the degree of burden that may be suffered by the research subjects. It is also entirely possible for

completely unforeseen adverse effects to be suffered by research patients, for example, the phase I trials of TGN1412 which "caused a near fatal systemic inflammatory response in all six healthy trial volunteers" (Eastwood, D.; Br J Clin Pharmacol. 2013 Aug; 76(2): 299–315.). AWHC oppose all first in man trials in incompetent/incapacitated adults for this reason (see Question 9). However, even phase II and III trials can be subject to unforeseen and potentially catastrophic adverse events, as evidenced by Case Study E in this consultation document in which there was an increased incidence of suicidal thoughts in previous trials. In another example, in a 1993 phase II clinical trial of Fialuridine, out of 15 patients in the trial, five died and two required liver transplants despite a pilot study of 43 of shorter duration revealing no serious adverse effects (Honkoop P., Drug Saf. 1997 Jul;17(1):1-7; and Attarwala H., J Young Pharm. 2010 Jul-Sep; 2(3): 332–336).

In the event that sufficient protections and safeguards are provided, and in the circumstances of the limited research that AWHC considers might be permitted (as set out previously in this submission) the decision regarding whether or not participation in the proposed research is in the "best interests" of the proposed subject should be made by an EPOA or authorised representative, and, an independent physician (not involved in the research) who has knowledge of the condition or impairment the subject has. As is set out in the Australian guidelines, if consent is provided by an EPOA or authorised representative that consent should be "witnessed by a person who has the capacity to understand the merits, risks and procedures of the research and is independent of the research team, and who knows the person and is familiar with his or her condition."

AWHC is of the view that there are no circumstances in which it is acceptable to impose risk or burden upon a research subject who has no opportunity or ability to weigh up the benefits and risks of their involvement in medical experimentation. Likewise, it is not acceptable to assume that a person is or would be sufficiently altruistically motivated to accept risk and burden of pain, discomfort or adverse effects of research with little or no benefit to themselves, 'for the greater good', unless this view has been explicitly expressed prior to their loss of competence to provide informed consent.

However, in the case of observational studies where it is argued that there are no risks or burden, the very least that is owed the incapacitated/incompetent subject is that people with sufficient knowledge of the patient and the proposed research including its risk, benefits and likely outcomes make that decision on their behalf.

In summary, the criteria should be that the proposed research causes no disadvantage, discomfit, pain or adverse effect on the research subjects. In effect there should be no disadvantage to the patient notwithstanding the potential for breaching cultural beliefs as commented upon in Question 3.2 above; this is the only way in which it can be assured that an incompetent adult is not subject to harm that s/he has no ability to consent or object to.

With regard to benefit, inclusion benefit – that the research subject will receive better care and monitoring if they take part in the research than if they did not – should never be used in any risk:benefit assessment and never used as any form of justification for inclusion in the research.

7.3 Please state the reasons you formed this view.

Determining whether or not an incompetent/incapacitated patient should participate in research should never come down to a mathematical formula: that if perceived or expected benefit exceeds the expected risk or burden the patient should be included. The value placed on any benefit or degree of harm from burden, or an adverse event or outcome, is a qualitative as well as quantitative assessment that competent adults make when making an informed decision and it varies according to each individual's values, circumstances and beliefs.

Who decides?

Consultation Question 8

8.1 Do you think there should be any change made to New Zealand law regarding who decides whether an incompetent consumer will be enrolled in a study?

Yes/No/Unsure

8.2 Do you think there should be any change made to the roles played by the various possible decision-makers under current New Zealand law?

Yes/No/Unsure

Despite what researchers might believe about themselves, all manner of biases are reported in the medical literature and few if any medical researchers could be said to be entirely unbiased. Many biases are sub-conscious and to place the burden of decision making about what is or is not in the best interests of patients in the hands of a single, interested researcher leaves both the researcher and their research subjects open to harm. Dependent on the nature of the proposed research, a range of people, preferably with complete independence from the research and researcher, should be involved in the decision to involve incapacitated/incompetent adults in research.

Similarly, the decision should not be solely made by the family/whānau of the proposed research subject. In some circumstances, the proposal to enrol an incapacitated/incompetent adult in research may be because their condition or impairment is life threatening. In such situations the family/whānau will be under stress and may not be capable of making objective decisions; may not be in a position to ask the questions that the proposed subject might ask were s/he competent. Such stress may constitute being asked to consent under duress, in particular, if the prognosis for their loved one is poor.

8.3 If you answered "Yes" to question 8.1 and/or 8.2, please complete the table below about possible decision-makers and the roles you believe they should play in decision-making. Please note that you may consider that a combination of decision-makers is appropriate (either to play different roles in the decision-making process or to make decisions in different circumstances).

Person who could have a role in decision-making (X)	Should X ever have a part to play in deciding whether an incompetent consumer is enrolled in a study?	If yes, in what circumstances should X be involved in decision-making? i.e., a) In all cases where X is available? b) Only when particular criteria are met (e.g., that the study is to be conducted for the purpose of saving the consumer's life or preventing serious damage to the consumer's health)? c) Only when other possible decision-makers (please specify which decision-makers) are unavailable? d) Only where the circumstances require that an urgent decision is needed (see, e.g., Case Study D)? e) Other? *Please choose the letter(s) for any of the options above that you think should apply, or provide comment if you prefer.*	Where X is involved in decision-making, what role should he or she have? i.e., a) Consulted by decision-maker? b) Power to veto* consumer's participation in the research? c) Provide or withhold consent on behalf of the consumer? d) Other? *Please choose the letter(s) for any of the options above that you think should apply, or provide comment if you prefer.* *A veto means the right to refuse or reject permission for an incompetent consumer's participation in research.
EPOAs and welfare guardians	**Yes/No/Unsure**		
Family/ whānau	**Yes/No/Unsure**		
Provider not involved in the research (e.g., consumer's responsible clinician or GP)	**Yes/No/Unsure**		
Researcher	**Yes/No/Unsure**		
Other (please name):	**Yes/No/Unsure**		

AWHC finds the table in Q 8.3 above overly prescriptive and it does not allow sufficient flexibility for vastly differing circumstances of incompetent individuals that might be considered for inclusion in research. The decision making process should be necessarily more complicated than these questions allow for; decisions for individuals need to be made on a case by case basis rather than according to some algorithm.

8.4 Who do you think should be the final decision-maker when making a decision as to whether to enrol an incompetent person in a research project? Set out below are some options.

- **EPOA or welfare guardian**
- **Family/whānau**
- **Provider not involved in the research (e.g., the consumer's responsible clinician or GP)**
- **Researcher**
- **Other**

Please rank the decision-makers you chose in order of preference from 1. being your most preferred to 5. being your least preferred. If you prefer a decision-maker other than those listed, please indicate the decision-maker.

1. EPOA or welfare guardian
2. Independent patient advocate, perhaps appointed in the absence of an EPOA and/or where there is no competent next of kin
3. Family/whānau
4. Provider not involved in the research (e.g., the consumer's responsible clinician or GP)
5. Special ethics committee in exceptional circumstances (see question 6.2)

8.5 Please provide any other comments you wish to make about the decision-makers.

The AWHC opposes the veto option for deciding upon whether or not an incapacitated/incompetent adult is enrolled in research. Notwithstanding the AWHC's philosophical opposition to research involving incapacitated/incompetent adults, if there is to be such research there should be a specific responsibility placed on a person or people to provide consent. A veto is akin to an "opt out" option (see Question D3), and the gravity of such a decision to involve an incapacitated/ incompetent adult in research deserves more serious consideration by those involved in the decision making.

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9. Please add any final comments or suggestions you wish to make.

The AWHC has specific concerns about the involvement of incapacitated/incompetent adults in medical experimentation. While we understand the potential benefits of increasing knowledge on the conditions suffered by incompetent adults and the impairments that lead them to be in the position of being incapable of providing consent, the overriding concern must be for the health and welfare of the patient, not the acquisition of knowledge no matter how well intentioned that might be.

While it has reservations about even the least invasive observational research, the AWHC categorically rejects permitting the following types of research on incapacitated/incompetent adults:

- 1st in man or phase I clinical trials of any type;
- non-therapeutic trials, e.g. non-inferiority trials;
- any research in which known or expected adverse effects could possibly exceed any potential benefit to the research subjects;
- any research in which known or expected adverse effects may include death, permanent disability or impairment, or a worsening of the existing condition or impairment.
- any interventional research where the only or most likely benefit to the incompetent adult is an "inclusion benefit".

It is the AWHC's view that HDEC approval is insufficient protection for vulnerable research participants such as incapacitated/incompetent adults, and that a Special Ethics Committee (see question 6.2) must be set up to specifically consider research proposals that seek to involve such subjects. The AWHC notes that the current law does not require research carried out in New Zealand to have HDEC approval (although lack of approval does impose some limitations on research such as an inability to publish results) and that low risk

studies do not require approval. However, the threshold for what constitutes low risk must necessarily be much, much higher when considering research in such vulnerable groups as incapacitated/incompetent adults who cannot weight the risks and benefits for themselves and make informed decisions or advocate for themselves if and when anything goes wrong, and cannot withdraw their consent and withdraw from the research at will.

It must be accepted that, because of the unique vulnerabilities of incapacitated/incompetent adults and the need to protect them, the timeframes for approval or otherwise of research proposals must necessarily be different from research that involves competent participants. Longer lead-in times must be accepted (by researchers, sponsors such as pharmaceutical companies, and ethics committees) and timelines established to benefit and protect the research subjects rather than research being expedited for the convenience and benefit of the researcher/s.

In addition, the AWHC protests in the strongest possible terms the lack of real consultation with the community and patient advocates with regard to proposed softening of the laws and regulations to allow the enrolment of incapacitated/incompetent patients in medical research. In a letter to the AWHC by HD Commissioner, Anthony Hill, dated 7 November 2016, he stated that "it is likely that, in addition to inviting written submissions, my Office will organise and focus groups and/or public meetings to facilitate discussion of the issues raised by the consultation document. The exact details of the consultation process will be released concurrently with the consultation document". Despite this undertaking the AWHC has not seen any further evidence of the intention to do so.

Any proposal to involve vulnerable people in medical experiments without their explicit and informed consent contravenes the Nuremberg Code. Although the Declaration of Helsinki and our own Code of Health and Disability Services Consumers' Rights are watered down versions of the Nuremberg Code, they still protect the rights of incapacitated/incompetent adults, albeit with wording that is at times vague and open to interpretation. Any change that would allow or sanction medical experimentation on New Zealanders, especially our most vulnerable citizens, requires more than submissions on a consultation document that has had little media coverage. It is entirely likely that significant portions of the potentially affected sectors of our community and their family/whānau, and the health professionals who care for them, are entirely unaware of the existence of the consultation paper or the proposed changes to the Code.

The AWHC requests that further consultation, in particular something of the nature of a nationwide road show, public meetings and/or focus groups, be considered to elicit greater community comment and involvement in any changes to the Code and that any changes not be expedited at the expense of our most vulnerable citizens.