Participant injury in clinical trials conducted in New Zealand for the benefit of manufacturers: an unfair system?
Mark J Bolland

ABSTRACT
A patient with a long-standing medical condition was enrolled in a clinical trial, deemed as conducted for the benefit of the manufacturer. The patient entered the trial and, shortly afterward, developed a severe illness that left him with a significant permanent disability. Clinical investigators and clinicians not involved in the trial believed the illness was related to trial participation. Because the trial was for the manufacturer’s benefit, the participant was not eligible for compensation from the Accident Compensation Corporation (ACC). Discussions with the trial sponsor took many years to resolve. This case highlights the numerous barriers faced by patients seeking compensation from trial sponsors for adverse events probably resulting from trial participation. Legal changes are required to resolve this situation. Without such changes, potential participants and researchers should consider carefully whether to participate and invite people to participate in trials conducted for the benefit of a manufacturer, as there may be little support available should a trial-related illness occur.

In New Zealand, participants in clinical trials that are deemed as being conducted for the benefit of the manufacturer are not eligible for Accident Compensation Corporation (ACC) coverage if they suffer an injury from participating in the trial. At ethics committee submission, investigators indicate whether the trial is conducted for the benefit of the manufacturer, and the ethics committee confirms that they are in agreement with that view during the approval process. Here I outline a case that highlights many problems with the current process and discuss potential solutions.

Case details
A middle-aged man was referred for a specialist review to help control a long-standing medical condition. Before that review, he was approached to participate in a clinical trial. He agreed, entered the trial, received the study medication, but unfortunately suffered a significant illness that led to him being withdrawn from the trial. The physicians involved believed the illness was related to participating in the trial, and he was referred to a medical outpatient clinic for ongoing management.

The illness had an enormous impact. Although he made a slow initial recovery, his health never returned to baseline levels and he remained severely affected and persistently disabled over the next several years. He required time off work, changed his job, reduced his work hours, but ultimately was no longer able to work. He could no longer drive a car, had to move to a house more suitable for his poorer physical condition, and was unable to carry out the usual daily and leisure activities he previously undertook. There was a large amount of emotional stress and financial pressure, both for him and for his extended family. Family members moved cities to live nearby and provide support. Collectively, there was a substantial reduction in quality of life and a restriction of lifestyle.
Support and compensation

The clinical trial was deemed as being conducted for the benefit of the manufacturer, and therefore participants were not eligible for ACC coverage if they were to suffer an injury that resulted from participating in the trial. Because the clinicians involved had assessed his injury as being related to trial participation, he was ineligible for ACC coverage. The patient was therefore advised to seek support and compensation from the trial sponsor. The ineligibility for ACC coverage is not a criticism of ACC or its processes. The case was not reviewed by ACC (and therefore was not declined for coverage by ACC) because it was felt that the relationship of the injury to the trial participation precluded him from ACC coverage.

A claim was lodged with the trial sponsor. There was disagreement with the assessments of the treating clinicians and the sponsor denied liability and rejected the claim. Subsequent discussions with the sponsor were prolonged, lasting more than six years. While the discussions took place, the participant did not receive any support or assistance with his illness or subsequent disability from the trial sponsor.

The participant required legal support for these discussions, which he could not afford. The precise details of the case and the discussions with the trial sponsor remain strictly confidential and are unable to be discussed in greater detail for legal reasons. Nevertheless, the details provided illustrate problems with the compensation process for trial participants. Table 1 highlights some of these issues and other barriers faced by trial participants attempting to seek support or compensation if they are ineligible for ACC coverage.

Informed consent?

Table 2 shows the relevant sections of the information sheet and consent form signed by the participant. The information provided to the participant about treatment and compensation for injury is clearly inconsistent with the subsequent events. For example, there is the clear undertaking, albeit not legally binding, that if an injury is related to the trial, compensation comparable to ACC coverage will be provided. Furthermore, there is no suggestion that the participant would be required to prove an illness was causally related to the trial medication, as the trial sponsor has required. Given the marked inconsistency between the information provided in the consent form about injury and the participant’s experience, it is reasonable to conclude that the information provided was inadequate, and therefore truly informed consent was not obtained.

The text used for this information sheet was the standard text provided by the New Zealand ethics committees at the time for use in all clinical trials deemed to be conducted for the benefit of the manufacturer. Subsequently, the text was updated in 2015 and 2018. Table 2 shows that the 2015 text was considerably briefer and again inconsistent with the trial participant’s experience. The 2018 text is considerably more detailed and more cautious. However, parts are still confusing: initially the text states that New Zealand guidelines require compensation to be at least ACC equivalent, but later contradicts this statement by saying industry guidelines may not provide ACC-equivalent compensation. It seems unlikely that potential participants would truly understand the significance of the text or that, if they were to be injured during the trial, they may face as daunting a process as the one outlined in this article.

Law, ethics and compensation in commercial trials

Professor Jo Manning has recently conducted detailed reviews of the ethical and legal aspects of compensation in clinical trials conducted in New Zealand. Some of the key points and conclusions from these reviews are summarised here (for details and references see Manning J1 and Manning JM2).

Research participants were covered by ACC until 1992, when legislation was passed that excluded participants in commercial trials from ACC coverage. The rationale was that, because commercial companies profit from medicines trialled, they should meet the costs of compensation for injuries during the trials rather than the ACC-levy payers. However, this left a gap in compensation coverage for participants in commercial...
Table 1: Problems in the process of seeking compensation from the trial sponsor.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of equity</td>
<td>Denied access to standard care, support and compensation that other trial participants receive from ACC.</td>
</tr>
<tr>
<td></td>
<td>Rehabilitation and support may not be offered by the trial sponsor immediately after the illness, which is when support is needed (and as would normally be available through ACC).</td>
</tr>
<tr>
<td>Unreasonable delays</td>
<td>Process is prolonged. In this case, it took over six years to resolve.</td>
</tr>
<tr>
<td>Unreasonably high requirements for proof of causality</td>
<td>Processes place burden of proof on participants to prove their illness is causally related to trial participation, without similar a requirement for trial sponsors to provide proof of the corollary—that the illness would have occurred if the patient had not participated in the trial.</td>
</tr>
<tr>
<td>Lack of suitable resources</td>
<td>Trial participants have few independent experienced resources to assist them: in this case the Health and Disability Commissioner declined to assist; it was unclear where else to turn.</td>
</tr>
<tr>
<td>Lack of experienced assistance in New Zealand</td>
<td>Because ACC coverage extends both to complications of treatments that are not a “necessary or ordinary consequence” of the treatment and trials not done for the manufacturer’s benefit, few practitioners have experience of such cases. In this case, numerous specialists declined to provide expert opinions.</td>
</tr>
<tr>
<td>Reliance on legal opinion</td>
<td>Legal counsel is rarely required in New Zealand healthcare, but mediation with legal assistance from an early stage is a central component of the process.</td>
</tr>
<tr>
<td>Financial burdens</td>
<td>Legal counsel is very expensive and, in this case, was unaffordable in the context of an illness that had already placed a huge financial burden on the trial participant.</td>
</tr>
<tr>
<td>Unfair mediation process</td>
<td>Any result from a mediation process is non-binding, according to the industry guidelines that pharmaceutically sponsored clinical trials are conducted under.</td>
</tr>
<tr>
<td>Inequity in resources</td>
<td>The process is adversarial, with a single trial participant placed against a multinational company that has greater financial resources and access to expert witnesses and legal representation.</td>
</tr>
<tr>
<td>Process inconsistent with Medicines New Zealand guidelines</td>
<td>Medicines New Zealand “favours a simple and expeditious procedure in relation to the provision of compensation for injury caused by participation in clinical trials.” The case demonstrates the process is neither simple nor expeditious.</td>
</tr>
<tr>
<td>Confidential agreements</td>
<td>Potential trial participants and researchers can be unaware of issues related to seeking compensation or how commonly these difficulties arise.</td>
</tr>
</tbody>
</table>
Table 2: Relevant sections of trial information sheet and consent form and templates from the New Zealand Health and Disability Ethics Committees.

<table>
<thead>
<tr>
<th>Text from information sheet and consent form signed by participant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment and Compensation for Injury</strong></td>
</tr>
<tr>
<td>The Ethics Committee has certified that this clinical trial is being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which this trial is being carried out. This means that if you suffer injury as a result of your participation, you will not be eligible for cover under accident compensation legislation. However, if you follow the directions of the doctors in charge of this study and you are physically injured due to any substance or procedure given to you in accordance with the plan for this study, [the trial Sponsor] will pay the medical expenses for the treatment of that injury which are not covered by your medical insurance or by any other third party in accordance with the “New Zealand Researched Medicines Industry Guidelines on Clinical Trials- Compensation for injury resulting from participation in Industry Sponsored Clinical Trials”. Those guidelines say that compensation should be no less than would be awarded under the accident compensation scheme.</td>
</tr>
<tr>
<td>These RMI Guidelines are only guidelines and until your claim is assessed by the insurers of [trial Sponsor] and Company (NZ) Limited, it cannot be said with any certainty exactly what type or amount of compensation you will receive if you suffer injury as a result of your participation, or what sort of injury will be covered. The guidelines require that compensation must be provided by [trial Sponsor], where the injury you suffer is serious and not just temporary and is one caused by the trial medicine or item or where you would not have suffered injury but for your inclusion in this trial. The guidelines also require that the compensation you receive must be appropriate to the nature, severity and persistence of your injury. This means that you may not receive compensation from [trial Sponsor] if your injury is minor or temporary. Further, you may not receive compensation from [trial Sponsor] if your injury was caused by the investigators, if there is a deviation from the proposed plan of research, or if your injury was caused solely by you.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suggested text from consent form template 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you were injured as a result of treatment given as part of this study, which is unlikely, you won’t be eligible for compensation from ACC. However, compensation would be available from the study’s sponsor, [x], in line with industry guidelines. We can give you a copy of these guidelines if you wish. You would be able to take action through the courts if you disagreed with the amount of compensation provided.</td>
</tr>
<tr>
<td>If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.</td>
</tr>
</tbody>
</table>
Table 2: Relevant sections of trial information sheet and consent form and templates from the New Zealand Health and Disability Ethics Committees (continued).

**Suggested text from consent form template 2018**

As this research study is for the principal benefit of its commercial sponsor [insert name], if you are injured as a result of taking part in this study you won’t be eligible for compensation from ACC.

However, [insert name] has satisfied the [insert name] Health and Disability Ethics Committee that approved this study that it has up-to-date insurance for providing participants with compensation if they are injured as a result of taking part in this study.

New Zealand ethical guidelines for intervention studies require compensation for injury to be at least ACC equivalent. Compensation should be appropriate to the nature, severity and persistence of your injury and should be no less than would be awarded for similar injuries by New Zealand’s ACC scheme.

Some sponsors voluntarily commit to providing compensation in accordance with guidelines that they have agreed between themselves, called the Medicines New Zealand Guidelines (Industry Guidelines). These are often referred to for information on compensation for commercial clinical trials. There are some important points to know about the Industry Guidelines:

On their own they are not legally enforceable, and may not provide ACC equivalent compensation.

There are limitations on when compensation is available, for example compensation may be available for more serious, enduring injuries, and not for temporary pain or discomfort or less serious or curable complaints.

Unlike ACC, the guidelines do not provide compensation on a no-fault basis:

The Sponsor may not accept the compensation claim if:

Your injury was caused by the investigators, or;

There was a deviation from the proposed research plan, or;

Your injury was caused solely by you.

The injury was caused by <<NAME OF COMPARATOR DRUG>> (include only if holds true for specific study)

An initial decision whether to compensate you would be made the by the sponsor and/or its insurers. If they decide not to compensate you, you may be able to take action through the Courts for compensation, but it could be expensive and lengthy, and you might require legal representation. You would need to be able to show that your injury was caused by participation in the trial.

You are strongly advised to read the Industry Guidelines and ask questions if you are unsure about what they mean for you.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.
trials. An industry body, the Researched Medicines Industry (now known as Medicines New Zealand (MNZ)), adapted UK guidelines for compensation, which were then adopted for use in New Zealand.³

The key drawback of these guidelines is that a sponsor’s obligation to pay compensation for research-related injury is expressly stated to be ‘without legal commitment’ (ie, legally unenforceable by the injured participant). There have been repeated calls to repeal the section of the Accident Compensation Corporation Act 2001 (the ACC Act) that excludes commercial trial participants from coverage. In 2007, the chairs of the ethics committees, and in 2010 and 2014 the National Ethics Advisory Committees, called for repeal or review of this provision, but this was not acted on by the Government in 2015 after consideration by the Minister for ACC and the Minister of Health.

There is general agreement that no-fault compensation is the best ethical response to research-related injury. The alternative, adversarial approach presents formidable barriers to trial participants, who are usually required to prove both negligence, which is unlikely to have occurred, and a causal link between the injury and the treatment received, which is difficult to establish.

The MNZ guidelines have been criticised for a number of reasons. Not all trial sponsors are members of MNZ and use these guidelines. And even when used, the guidelines are not legally enforceable, lack specific details about the quantum of compensation (other than a broad statement that they should be at least ACC-equivalent), lack details of the time frame within which claims should be resolved and contain numerous exceptions when compensation will not be paid. If there is disagreement between the injured participant and the trial sponsor, mediation at the sponsor’s expense is offered but the results are non-binding. Overall, these industry-developed and industry-sponsored guidelines are considered to be heavily weighted in favour of trial sponsors.

On the basis of these extensive reviews,¹² Manning concluded that these compensation arrangements for trials deemed as being conducted for the benefit of a manufacturer fall below ethical expectations. In particular, the main issues are that the compensation process followed is only a ‘guideline’; there is no legal obligation on the sponsor to pay compensation; the process of obtaining compensation is weighted against the participant and will be insurmountable for the majority of participants; and information sheets provided to participants do not provide adequate information, such that injured participants will only find out the true situation when they come to submit a claim.

A possible solution?

An alternative to the current process is that all injury in all trials should fall under ACC coverage, regardless of whether the trial is conducted for the benefit of the manufacturer. In practice, one potential approach would be that prospective trials are assessed by ACC (at sponsors’ expense), and that a levy is charged according to the risk of the trial and number of participants. Potential cases of injury would then be handled through existing ACC protocols. Claims would be directly submitted to ACC and resolved between ACC and the trial participant. The trial sponsor would be informed by ACC of the outcome. This approach would address many of the problems identified in Table 1 and provide trial participants with the confidence they will be dealing with ACC, a respected New Zealand Crown entity, rather than facing potentially adversarial dealings with a multinational company.

Another approach could be that, instead of charging a levy, ACC assesses injuries through existing processes, and if an injury meets criteria for ACC support and/or compensation, it would be provided by ACC and the costs passed directly to the trial sponsor.

Manning reviewed possible improvements to the current system and the legal issues related to such solutions, concluding that the best and simplest legal option is repeal of the relevant section (32 (6)) of the ACC Act that excludes personal injury suffered by a participant in a commercially sponsored trial. This would mean that all trial participants are covered by ACC, as outlined in the previous paragraph. The advantage for trial participants is fairer access to superior compensation than the current system offers. The main concern for trial sponsors is that this would set a worldwide precedent for managing possible trial-related injury, but this is unlikely given the unique nature...
of the ACC scheme. The main concern for regulators is that this approach may shift the risks and costs of trials from the trial sponsor on to ACC, leading to riskier trials and greater costs for ACC. In practice, this seems unlikely to occur, because if an ACC levy were charged at market rates, the levy would probably be similar to or higher than the insurance premiums that trial sponsors are currently required to pay.

Manning also considered other alternatives, such as participants making a legal claim against the company, providing better informed consent, requiring ethics committees to refuse to provide approval unless appropriate compensation processes are in place, or requiring sponsors to purchase ACC coverage for the trial. However, Manning considered that none of these options were as simple, timely or likely to be as effective as repealing the provision in the ACC Act that excludes commercial trial participants from coverage.\(^1,2\)

Returning to the case. If the trial had been publicly funded or if commercial trials fell under ACC coverage as proposed, the participant would almost certainly have been covered and compensated by ACC because injuries that are not a necessary or ordinary consequences of the treatment being trialled are covered; compensation is payable without proof of fault by the sponsor or researchers; and ACC does not require the high level of proof of the causal link between trial product and personal injury that sponsors do under the current guidelines for compensation.

**Recommendations**

Patients who are participating, or considering participating, in existing trials conducted for the manufacturer’s benefit should be informed that they are explicitly excluded from ACC coverage. They should be told in plain language that if a serious injury or illness occurs during the trial, it may be extremely challenging to obtain any compensation or support from the sponsor; that there are few independent experienced resources available for affected trial participants; that expensive legal representation may be necessary; and that if compensation or support is forthcoming, it is likely to take considerable time for this to occur.

Table 2 shows that this information has not been stated on participant information sheets until recently. Even with the latest, most cautious information sheet provided by the ethics committees, it is doubtful that potential participants will truly understand the situation they may face if an injury occurs. Updated draft guidance for ethical committees in New Zealand is unchanged from previously,\(^4\) even though cases such as this one have been discussed at the highest level within the ethics committees, the Ministry of Health and ACC,\(^5\) so this situation is unlikely to change in the foreseeable future. There is a need for a political will to resolve this inequity for participants in trials conducted for manufacturers.

Given these concerns, people should consider very carefully whether they wish to participate in a trial being conducted for the manufacturer’s benefit. Researchers and treating clinicians should also consider very carefully whether they wish to be involved with such trials, including inviting people to participate. The process for receiving support and compensation for a trial participant injured during a trial conducted for the benefit of a manufacturer is fraught with difficulties. At the simplest level, the current process seems unfairly stacked against the trial participant.
Competing interests:
Dr Bolland reports: I have no financial conflicts to declare. The views expressed in the article represent my own opinion: the manuscript has not been written on behalf of any of my employers, nor does it represent the views of any of my employers.

Acknowledgements:
I wish to thank Professor Jo Manning for her advice and comments on the manuscript. The trial participant gave consent for clinical details of the case to be published.

Author information:
Mark J Bolland: MBChB, PhD, Associate Professor of Medicine, Department of Medicine, University of Auckland; Department of Endocrinology, Auckland District Health Board.

Corresponding author:
Mark J Bolland, MBChB, PhD, Associate Professor of Medicine, Department of Medicine, University of Auckland; Department of Endocrinology, Auckland District Health Board m.bolland@auckland.ac.nz

URL:

REFERENCES