Better treatments...
Better lives.

Mr Tim Vines
Manager, Therapeutics
Strategy, Policy and Legislation
Ministry of Health
New Zealand

3 March 2023

Dear Mr Vines

RE: Therapeutic and Natural Health Products Regulation – Considerations for Cabinet regarding the Therapeutics Products Bill to Parliament

The Australasian Leukaemia and Lymphoma (ALLG) is a not-for-profit clinical trial organisation that Sponsors Investigator Initiated clinical trials. ALLG is New Zealand's only cooperative clinical trial group offering investigator-initiated trials across multiple hospital sites for patients with haematological malignancies.

The ALLG membership represents more than 800 haematologists, scientists, and clinical trial research staff across Australia and New Zealand. ALLG has a strong track record in the conduct of investigator-initiated trials with 160 clinical trials over 50 years. In FY22 the ALLG had 25 clinical trials open to recruitment, recruited more than 900 patients in the year to clinical trials and registry projects, published 12 trials in peer reviewed journals and supported its members to participate in 16 presentations of their clinical trial findings at local and international conferences.

We welcome the ability to contribute to Cabinet's decision regarding the Therapeutic Products Bill New Zealand. The new bill proposes greater regulation of medicines imported for clinical trials (regulated by a new business unit). **The bill proposes that these regulatory costs are met through fees/levies, which would presumably fall to whoever is running the trial to cover.** The bill provides no indication as to who will be subjected to these fees nor how much these fees will be; we remain concerned that the introduction of new fees, (and potentially high fees) will be detrimental to academic, investigator lead cooperative group trials. **What is proposed is a significant process change that will now, in our view, significantly increase the cost of conducting trials.**

In the field of cancer, it is increasingly common to subset malignancies according to specific genetic alterations, and to personalise therapies accordingly. These personalised therapies are increasingly assessed in 'platform trials', in which a large number of new medicines are assessed, each in the small number of patients who are most likely to benefit from them. Such niche medicines, such as kinase inhibitors or immunotherapies, are often manufactured by smaller pharmaceutical companies that do not have representation in NZ. These 'platform trials' are often run by international co-operative, non-profit organisations such as the Australasian Leukaemia & Lymphoma Group and the UK Medical Research Council group. We remain concerned that the new requirement for a "local sponsor" of a new pharmaceutical makes it cost-prohibitive to run trials of targeted therapies for niche indications (e.g. IDH1 and IDH2 inhibitors in AML), where only a few patients in this country would receive the drugs, and where the drugs are made by a smaller pharmaceutical company that does not have a NZ base already.

ALLG have considered the Act and contribute the following comments:

1. **The new bill could significantly add to the logistical burden of running international cooperative group trials in NZ.**

Australasian Leukaemia & Lymphoma Group (ALLG)
Business & Central Trial Office
Ground Floor, 35 Elizabeth Street, Richmond, VIC 3121
F +61 3 9429 8277 | www.allg.org.au

In haemato-oncology, this might particularly affect AML and MDS (Myelodysplastic syndrome) trials, and especially platform trials that involve a number of new medicines. We note that clinical trials are already highly regulated and are assessed for risks and benefits by ethics committees and by the Standing Committee on Therapeutic Trials (SCOTT) or The Gene Technology Advisory Committee (GTAC) where new medicines or gene therapies are involved. We recommend that this is explored in further detail before the change in bill is considered.

2. The new bill could significantly add to the financial burden of running cooperative group trials in NZ.

We are concerned that the requirement for a new regulatory body, with unspecified fees and levies, to regulate medicines imported for clinical trials, plus the need for a 'local sponsor' of a medicine used in a clinical trial, will add major financial and logistical burdens to important platform trials of personalised cancer therapies. These risks could preclude NZ participation in future international co-operative group cancer trials, as not for profit co-operative groups do not have the resources to support extensive regulatory processes and costs for a large number of new medicines for a small number of NZ patients. This would have a chilling effect on the NZ clinical trial environment in the field of cancer.

3. Rare conditions need alternative considerations for access to medicines:

We recommend an exemption mechanism, or an abbreviated regulatory process is provided for clinical trials that involve treatment of a small number of people (e.g. < 60 NZ patients/year) with life-threatening conditions (such as advanced cancers), particularly where the medicines involved have already been through an assessment by competent authorities (e.g. in Australia, Europe, USA). **We also recommend that** the new regulator provides **fee exemptions for public good clinical trials** (e.g. co-operative group trials or those funded by the Health Research Council or Cancer Society), as opposed to trials run principally for the benefit of a pharmaceutical company. Additionally, the small size of the market and Pharmac hurdles mean that some companies already refuse to provide medicines for NZ patients in collaborative trials as the potential commercial return is deemed to low; this is a logistic and financial hurdles and likely to become worse under the new Act.

4. Three areas that might have particular implications for blood cancer patients:

1. No more self-importation of unregistered medicines. Patients will no longer be able to self-import medicines directly (e.g. no self-importation of unregistered ibrutinib brands), unless they bring them in their own luggage (too expensive for many, impossible during a pandemic). We understand that a pharmacist can register to import unauthorised medicines (for individual patients on prescription), but this will presumably incur additional costs for the pharmacist (and therefore the patient), and for rarer drugs, it may be difficult to find a pharmacist willing to arrange this. This briefing paper notes this issue, and notes that it has not yet been consulted on: https://www.health.govt.nz/system/files/documents/pages/impact-summary-personal-imports-dec18.pdf

2. Possibility of increase in fees for NZ clinical trials that involve new medicines**.** There may be greater regulation of medicines imported for clinical trials (involving a new business unit), and it is proposed that these costs are met through fees/levies. There is no clear idea how much these fees will be, but they could be high – and if so, might have a chilling effect on cooperative group studies (e.g. AML trials). We might also find that the need for a local sponsor of a new pharmaceutical makes it cost-prohibitive to run trials of targeted therapies for niche indications (e.g. IDH inhibitors), where only a few patients in this country would receive them. With national and internationally lead cooperative trials it will be important that some sort of exemption mechanism is included for public good trials – see this regulatory impact paper: https://www.health.govt.nz/system/files/documents/information-release/publication_-_regulatory_impact_statement_therapeutic_and_natural_health_products_regulation_-_supplementary_analysis_2022_no._2_1.pdf

3. Big changes to regulation of cell therapies, impacting stem cell transplants (including e.g. stem cells for transplantation, virus-specific T-cells, CAR T-cells etc). As cell products are typically 'unregistered' by Medsafe, if these might now require a pharmacist to import them. This adds further complexity and delays should the new Act come into effect. The impact paper here: https://www.health.govt.nz/about-ministry/information-releases/regulatory-impact-statements/therapeutic-products-regulation-replacement-medicines-act-1981-and-medicines-regulations-1984-new-0

Quality evidence from trials informs decision making, and to that point we believe that clinical trials provide the best evidence base for access to new novel therapies, including small-scale trials in rare diseases. Lack of access to clinical trials in New Zealand is a major barrier to patients being able to access new procedures, tests, and medications. There is a fully recognised need for trials that generate data that is fit-for-purpose for technology assessment in the New Zealand context for both therapeutics and diagnostics. Pivotal questions often remain such as: should a new expensive therapy continue life-long (and if so, at what cost), or is the therapeutic intervention effective to use for a shorter time limited period only? New Zealand's **investment in public good trials is key to advancing the evidence associated with novel technologies and the use of novel therapies**.

A major benefit of investment in public good trials is greater involvement by patients and the community. Transparent conduct of trials relevant to unmet needs in the New Zealand community will encourage more equitable access to unsubsidised medicines and more consumer involvement in trial design and result dissemination.

New Zealand should:

1. Accelerate funding to activities that enable and encourage clinical trials, specifically funding for hospitals in support of their participation.
2. Specifically fund trials that address cost-effectiveness, and fund real-world data analyses designed to inform drug and technology assessments.
3. Offer research funding grants for clinical trial research that assesses all elements (e.g. QOL, economic evaluations, and care pathways for follow-up initiatives beyond immediate clinical trial treatment) that are relevant to both subsidy decisions and implementation in standard practice.
4. Fund a program that supports access to drugs in a data-generating fashion to better inform subsidy decisions.
5. Offer a scheme that specifically supports research centres participating in public good trials; funding to assist with core staff or protected time for public good trial work requirements in New Zealand new drugs can be accessed via clinical trials.

National academic trials such as those conducted by the ALLG are designed to answer key clinical questions relevant to patient care in New Zealand; unlike pharmaceutical trials where it is always a commercial motivation. Policy makers, in ensuring their obligations to cancer patients, should look to better support the New Zealand clinical trial environment, as the key provider for access to evidence-based research for New Zealanders.

There remains a need to support research careers within the priorities of building capacity and collaborative research. While regulators rightly require high standards of evidence to support public subsidy, increasingly public private partnerships may be needed to support a more coordinated approach to clinical research, trials, and evidence development where patient populations are small. To be and remain at the forefront of precision medicine brings new challenges, particularly in matters relating to speed to market for patient benefit. These challenges are not unique to blood cancers, but blood cancers have some unique features that merit cooperation to overcome the challenges.??

Better treatments...
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Concluding Remarks

Blood cancers represent some of the rarest and highest cost conditions to treat, and there are significant barriers to access therapies within New Zealand. Trial recruitment improves health outcomes, has been cost effective in the past and provides New Zealanders with access to new treatments. These benefits were demonstrated by the dramatic improvement in overall survival in AML patients recruited to the UK collaborative AML19 trial, compared to historical controls (poster at the 'Cancer at a Crossroads' conference 2019 *attached*). If patients were not able to access these trials due to logistical or financial barriers, there would be significant impacts on health outcomes in New Zealand in haematological patients. ALLG members welcome the opportunity to discuss or expand on our points further.

Yours sincerely,

Delaine Smith

Delaine Smith
cn=Delaine Smith, o=ALLG, ou=CEO, email=delaine.smith@allg.org.au, c=AU
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Delaine Smith
CEO
ALLG

On behalf of the Co-Chairs of the ALLG Medicines Access New Zealand Committee Members:
Dr Claire Hemmaway
Dr Travis Perera

Australasian Leukaemia & Lymphoma Group
35 Elizabeth Street
Richmond VIC Australia

Why it is valuable from a scientific, disease-outcome and financial point of view for independent, international, clinician-initiated, New Zealand-wide trials to be supported by good, time-sensitive funding systems by the Health Research Council, Pharmac and the DHBs

Dr Ruth Spearing, Haematologist, Christchurch Hospital; Leanne Berkahn, Haematologist, Auckland Hospital and New Zealand Councillor for the Haematology Society of Australia and New Zealand; Rosalie Stephens, Medical Oncologist, Auckland Hospital

Background

Advantages of clinician-initiated international trials are that they

- look at questions that pharmaceutic trials won't

  eg would a shorter period of treatment be as effective
- often give patients access to free or heavily subsidised cutting edge drugs and/or access to expensive state of the art investigations leading to significantly improved survival
- give access to international experts for second opinions
- give kudos to NZ, good for recruitment and retention

The problem of taking part in these trials

Clinician-initiated international trials often don't come with funding and only stay open for a couple of years. May have small numbers in any one DHB

Therefore for NZ to benefit we require

- a nimble, quick turnaround funding systems,
- efficient supportive administrative systems within DHBs who see these trials as being beneficial to patient care
- cross DHB contracts to reduce the administrative burden on smaller DHBs
- ability for Pharmac to consider funding a drug for use within a specific international clinician initiated trial for a limited time, if the overall benefits of the trial make this worthwhile
- leadership at the highest level to make these things happen

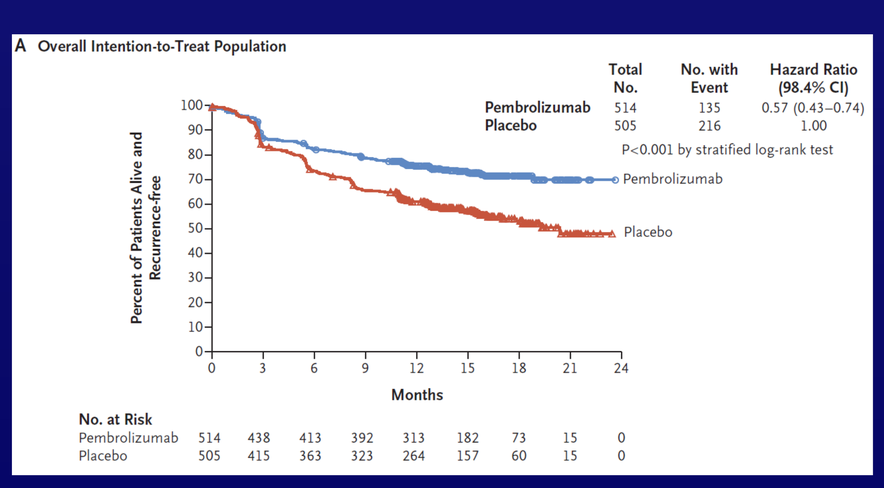
EORTC-1325: a successful melanoma trial

EORTC-ANZMTG designed trial examined adjuvant pembrolizuamb in patients with resected stage 3 melanoma.

Approximately 30 patients were enrolled across four NZ sites.
The unique design addresses the important question of whether immediate (adjuvant) or delayed pembrolizumab changes survival.

Undertaken at a time when no funded treatment options existed for advanced melanoma patients, and offered patients state of the art treatment.

The primary endpoint analysis is compelling and adjuvant pembrolizumab is likely to become the standard of care.
However – it was only possible for NZ to participate in this study because funding was provided by the pharmaceutical company.

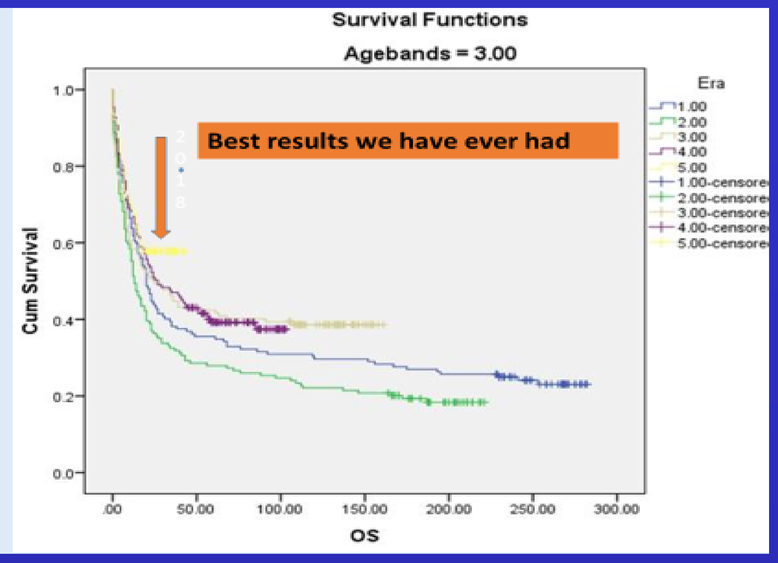


AML19 –an example of where the system has worked

NZ data for OS for 41-60 year olds

Era 1= 1995-1999,
2=2000-2004,
3=2005-2009,
4=2010-2014,
5=2015-2018 ie AML19
(Overall survival in months)

Over the last 30 years that we have been involved in the UK AML trials no new AML chemotherapy agents approved by Pharmac. AML19 has given us access to new drugs but also looks at ways drugs are combined/scheduled



Pharmac approved the DHBs to buy subsidised mylotarg

As a result, NZ got $4.5 million of now FDA approved drugs, $76K of free molecular tests which have reduced the number of allogeneic transplants (each average 350-730K), and detected early relapse, plus support to set up flow MRD lab in NZ AND the best ever NZ outcomes in the 41-60 year old age group.

An Example of where the system has failed: the STOP-GAP study in melanoma

STOP-GAP is a randomised discontinuation study of pembrolizumab in patients with advanced melanoma, designed and co-ordinated by the Canadian Cancer Trials Group and ANZMTG.

Addresses the critical question of duration of therapy; this issue is particularly relevant in NZ where pharmaceutical spending is constrained and where there is geographical isolation and financial hardship for patients.

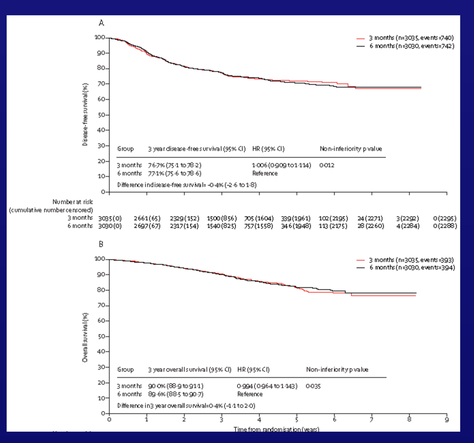
Study design is pragmatic - NZ would be expected to recruit well. Analysis will include quality of life and economic endpoints with potential benefits for patients, DHBs and health funders including Pharmac.

A small amount of funding for the study is provided by ANZMTG; the budget shortfall is $50-100K per site.

Numerous grant applications in different NZ localities declined - set-up in NZ has been paused.

Another example of where the system has failed

SCOT TRIAL looked at 12 v standard 24 weeks of oxaliplatin and 5-fluorouracil chemotherapy for bowel cancer,
ie of real potential benefit to funders as well as patients $2500 /patient for investigations and trials staff.
Had planned for 9500 patients, reduced to 6088 because of poor international recruitment.
Excessive time trying to source funding.
By time funding obtained, trial almost closed and NZ only contributed 12 patients.



Working together, Pharmac, DHBs and Health Research Council could make these trials happen…