

ATTACHMENT 1

Medicines Australia Response to Questions on Notice Following June 2017 hearings of the Senate Select Committee Inquiry into the funding of research and development in brain cancer and low survival cancers

Introduction

We welcome the opportunity to respond to the four (4) Questions on Notice to Medicines Australia during its appearance before the Committee's hearings in Canberra hearing on 8 June 2017. We have also provided some further information for the Committee on a different Question answered at the hearings.

The ultimate aim of this Inquiry is to identify what might be done in Australia to help improve survival rates in low survival cancers. Increasing clinical trial activity, of and by itself, is not sufficient. We believe improved access to medicines via the PBS is the best way forward. Medicines Australia stands ready to participate in, and contribute to, the PBS system improvement recently called for by Minister Hunt, and as outlined in the Strategic Agreement between Medicines Australia and the Australian Government (available at <https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2017/05/09-May-2017-Strategic-Agreement-with-Commonwealth-Signed.pdf>).

Medicines Australia's would ask that the Committee recommendations encourage Australian governments to support the formation of a Co-ordinating Clinical Trials body, lead federally and in strong collaboration with the States and Territories, to ensure Australia continues to compete well in the global clinical trials sector.

We trust the Committee will find the following responses helpful, and we look forward to the final Inquiry report.

Responses to Questions on Notice to Medicines Australia

1. Low survival cancer research in China

ACTING CHAIR (Senator Bushby): *I am interested in your mentioning China. What sort of scale of investment is occurring at the moment in medical research, particularly in low-survival cancer, in China?*

Dr Grady: *I would have to take on notice and get specific figures on the rare cancers.*

This question ultimately relates to how Australia's clinical trial competitiveness, and our ability to attract clinical trial research investment in an increasingly competitive environment, might be maintained, fostered and enhanced.

To this end, Medicines Australia's key recommendation as presented in our original submission, is that the Australian Government needs to work both with industry and the states and territories, to ensure there is a dedicated co-ordinating body for clinical trials in Australia. A body like this would be able to identify best practice(s) across the jurisdictions, help optimise the delivery of consistent and better quality standards and regulation across all jurisdictions, and also help drive accountability for adherence to these standards. Having such a body would also enable the states and territories to deliver consistent multicentre best practice clinical trials in Australia.

Whilst some national and state-based initiatives have been progressed, they have not gone far enough, and we think this is due to the absence of a dedicated body willing to work with the jurisdictions and industry. Such a body would not only help drive more harmonisation and co-ordination of clinical trials in Australia but increase Australia's attraction as a clinical trial investment destination of choice, because it could help optimise improvements and timing of their delivery. This is particularly pertinent in the face of the rapidly improving clinical trial environment in the region.

In reference to China itself as per the Question on Notice, while the magnitude of investment in terms of a common currency is not readily available, a line-by-line examination of oncology trials registered with the FDA (ClinicalTrials.gov) searching on the terms "rare cancers" located ten (10) trials conducted in Australia and 29 conducted in China.

To provide further context, an analysis (**Figure 1**) of the number of oncology trials (all oncology) which started over time (2007 to 2016), across a number of countries (Australia, South Korea, UK, Canada, China and the United States of America), illustrates the extent of clinical trial activity in China compared to other countries. Trial activity has tripled in China in less than a decade. This trend is set to accelerate, because of two developments at the Chinese Food and Drug Administration (CFDA).

- Firstly, the CFDA is actively encouraging the conduct of China clinical studies (including phase I, II and III studies) at the same time as the global clinical trials program; in the past, China studies were inevitably conducted after global programs were largely complete; and
- Secondly, CFDA is actively accelerating the review of Clinical Trial Applications (CTA) and in the last 24 months the number of approvals has increased from 687 (in 2014) to 3666 (in 2016). This is a five-fold increase in just two (2) years across all therapeutic areas; we estimate about half of these approvals are in oncology.

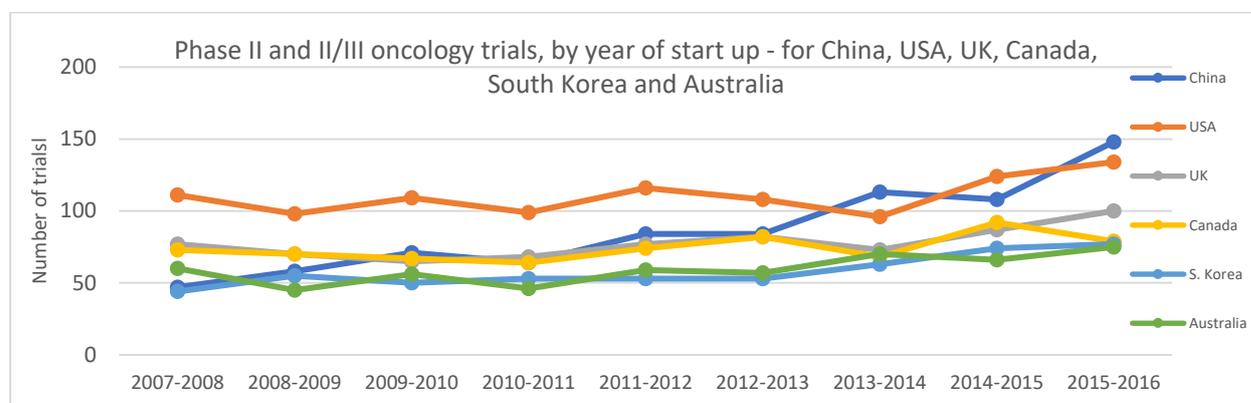
The implication of these developments is that China will start to run more clinical trials as part of global trial programs and that it will recruit quickly. For innovator medicines companies, which must make decisions about where to place trials in the global setting, this means that trials will most likely begin to move from slower and/or more costly markets, to China.

Further, the situation in which Australia finds itself is clearly illustrated in **Figure 1**, with South Korea and Canada each commencing almost the same number of oncology trials in recent years.

The impact of clinical trials reforms, if steered collaboratively, can help a country's ability to attract clinical trials, as demonstrated in the acceleration of the number of clinical trials started in the UK in recent years. As Medicines Australia noted in its earlier submission, the establishment of a research network has helped increased trial participation, more than three-fold, in the UK.

Australia must prepare and reform for the future now; standing still means we are likely to be left behind.

Figure 1 Phase II/III and III oncology trials, by year of start-up - for China, USA, UK, Canada, South Korea and Australia



Reference: Citeline Trialtrove

2. NHMRC Good Practice Process

Senator GRIFF: Which states are doing it well?

Mrs Aunedi: We have seen some improvement in New South Wales, and Victoria as well.

Senator GRIFF: How can that be enabled so every state does act on it?

Mrs Aunedi: I think the national office for clinical trials. It might be as simple as mandating some of these really good initiatives that have happened across the states and that various groups like the NHMRC have put forward. This is precisely where we think the national office could step in to help streamline this process.

Senator GRIFF: How many sites would you imagine are now running it?

Mrs Aunedi: It depends. I do not have that figure for the total industry. We can go back to find feedback to give you on that.

Ms de Somer: I think there is a wide range of variation not only across institutions but also across significant specialist centres or researchers and investigators. I think it is going to be quite a difficult question to answer. But we may be able to give you some top-line responses.

The Medicines Australia/Medical Technology Association of Australia (MTAA) Research and Development Task Force (R&D TF¹) advises that it is important to look at several Human Research Ethics Committees (HRECs) including the 16 sites which were part of the NHMRC's Good Practice Pilot.

One recommendation, which is generally adopted, relates to timeline tracking. The R&D TF notes that most HRECs and Research Governance Offices (RGO) are now tracking their timelines. Consequently, it is known that variances in timelines remain for the same HREC, regardless if they were part of the pilot or not.

This variability and lack of transparency on complete national performance in HREC and RGO timelines further supports the need to implement some oversight in this sector to set benchmarks and improve performance.

Further, the improvements that were achieved while the project was ongoing demonstrate that when there is oversight, and when participants are accountable, performance will improve. Unfortunately, funding for the Good Practice initiative has ceased with the Federal Budget 2017-18, and sites are now adopting recommendations, if at all, on an ad hoc basis at best.

Meanwhile, a June 2017 report by MTPConnect via LEK Consulting (see https://www.mtpconnect.org.au/Attachment?Action=Download&Attachment_id=54) predicts that the investment in Clinical Trials in Australia could more than double by 2025 (\$1 billion reported this year, \$2.5 billion estimated by 2025). This potential growth cannot be reached, however, without continued reform efforts that will accelerate access to treatments via clinical trials to patients with rare cancers.

It is for these reasons and more, that Medicines Australia's earlier submission to the Committee proposed the establishment of a whole-of-Australia coordinating office for clinical trials. Accelerating sector performance is key, and we believe that more impetus needs to be given to this important objective.

Having an independent body or network that can work with the States and Territories to optimise efficiencies and promote consistent processes, will help the Australian clinical trials sector to be as globally competitive as possible.

¹ The R&D TF is a unique cross-sector collaboration of clinical trial specialists drawn not only from MA member companies but also the devices sector, Clinical Research Organisations (CROs) and ARCS (the peak professional education and training association in Australia for people employed in medicines and medical technology). The R&D TF aims to be the pre-eminent industry voice focused on improving the local clinical trial sector.

3. Per capita clinical trial activity

Senator KETTER: Ms de Somer, in your opening statement you talked about the number of clinical trials for brain cancer in Australia in comparison with some other comparable countries. Am I right in assuming that on a per capita basis Australia is doing quite well in terms of the number of clinical trials generally for our population base?

Ms de Somer: I can certainly say that Australia is still considered a very attractive destination for clinical trials, because we still do have extraordinarily talented researchers and fabulous infrastructure, but we could be better. We are seeing that we will not stay doing really well if we do not address these fundamental issues.

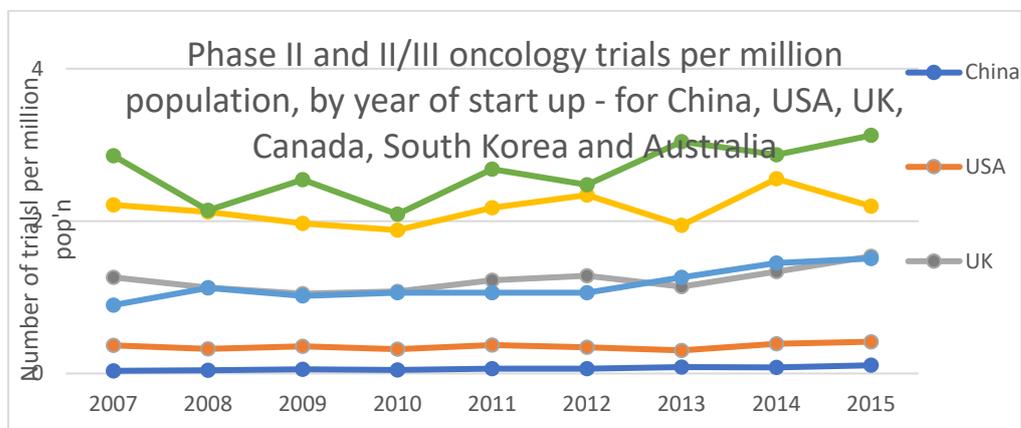
Senator KETTER: I fully accept that, but are there any statistics out there that measure the number of clinical trials versus population base?

Ms de Somer: I am not sure, and I can take that on notice and have a look, and we might have some individual experiences from companies.

Medicines Australia's earlier submission noted that the important role of public reimbursement on the PBS. Listing is dependent on a reimbursement system which is fit for purpose and can account for issues characteristic of studies in rare and low survival conditions, such as: low patient numbers, treatment switch, surrogate outcomes.

In relation to per capita trial activity, we note that countries like China and the USA have much larger populations than Australia, and that all countries are competing for finite numbers of trials in oncology. Countries with relatively smaller populations will have a relatively larger number of trials per capita. Accordingly, we note that statistics based on 'number of trials per capita' can be somewhat misleading. **Figure 2** below helps illustrate this point when comparing the number of trials per million population.

Figure 2 - Phase II, II/III and II trials, per million population, by year of start-up - for China, USA, UK, Canada, South Korea and Australia



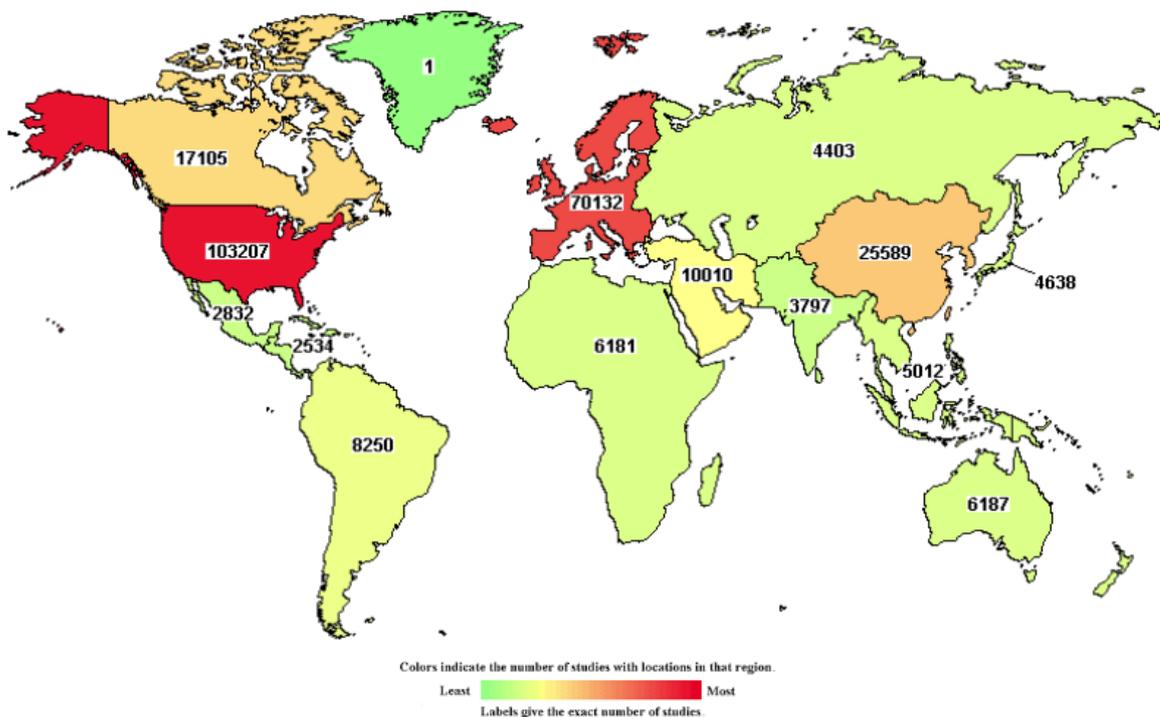
Reference: Citeline Trialtrove

A further representation of overall clinical trial activity (i.e. not only oncology) is presented in **Figure 3**, with data from the US FDA's ClinicalTrials.gov registry.

Figure 3 - All Clinical Trial Activity in Australia, and globally

Map of All Studies on ClinicalTrials.gov

On the map below, click on a region to show a more detailed map (when available) or see a list of studies with locations in that region (when a detailed map is not available).



Source: <https://ClinicalTrials.gov>

Source: <https://clinicaltrials.gov/ct2/search/map/>. Accessed 11 July 2017

4. Approvals in other countries

Ms de Somer: I am not sure of the approval time frames or processes in China, but what I can tell you is that China has been very active in looking at Australia's and other countries' methods of assessing, evaluating and funding medicines. Whilst I do not know their particular processes today, I do know that different provinces and jurisdictions in China have brought deputations over to Australia to look at our system for evaluating and funding medicines, and they are incorporating some of those assessment processes.

CHAIR: Dr Grady or Mrs Aunedi, have you got any—

Dr Grady: Sorry, I could not comment on that. I would not know.

CHAIR: That is fine.

Ms de Somer: I can take on notice whether there are differences in the approval time frames.

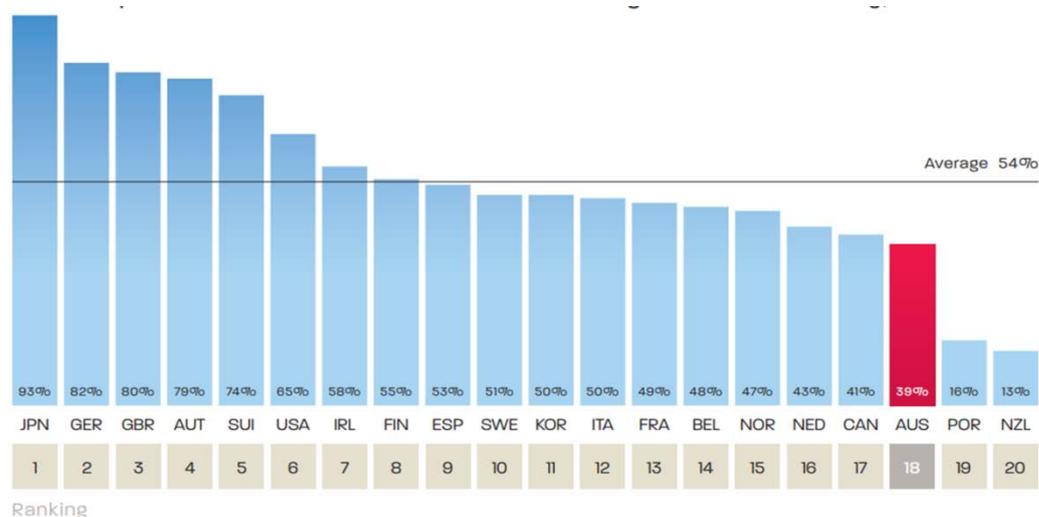
CHAIR: Okay; the time lines and the processes. It would be interesting to see what happens in other countries with the globalisation of medicines and treatments if you have got that information, thank you. Thank you for your time today.

Medicines Australia acknowledges the regulatory reforms being undertaken at the national level, and welcomes reimbursement process reforms that are envisaged as result of the Strategic Agreement between MA and the Australian Government. The Minister for Health's announcement at the 2017 Rare Cancer Forum in Canberra is also welcome. An effective response to the Minister's call for action truly has the potential to achieve a key aim of this Inquiry, being the improvement of outcomes for people with rare and low survival cancers.

The need for reforms to our reimbursement system can be seen when looking across several OECD countries (and NZ) at the proportion of registered new medicines that were ultimately reimbursed. **Figure 4** below (from Medicines Australia's COMPARE 2 report 2015 – available on request) indicates that Australia ranked 18th of 20 countries, just ahead of Portugal and NZ. Another way to look at it is - of all the new medicines registered by the TGA between 2009 and 2014, only 39 per cent of them were reimbursed in Australia.

Unfortunately, we have not been able to clearly establish reliable timeframes from the Chinese regulatory and access systems either centrally or within provinces. Nevertheless, one member company anecdotally has told MA that it has had recent experience of a new medicine being registered and launched into the Chinese market in less than eight (8) months. This is significantly faster than Australia where the standard registration process takes at least 12-15 months and reimbursement assessments take much longer (see below).

Figure 4 -Proportion of registered medicine which eventually secured reimbursement – by country - 2009 to 20014



We hope that the information provided below, on the approval processes in South Korea, the Netherlands, Canada and the UK, is useful to the Committee.

South Korea

The process of reimbursement of medicines incorporates a “Health Economics Exemption” option for medicines for cancer and rare diseases. For a medicine to be eligible for this process, it should have been approved by the regulatory authority after consideration of a single arm trial, or a phase II trial without a condition to provide a Phase III trial, or it should be for a condition affecting less than 200 patients per year. This acknowledges and accounts for the fact that, for such diseases, there will be very limited data for health economic analysis.

In cases where a Phase III study is available, the reimbursement authority uses a higher cost-effectiveness threshold, which is based on the national gross domestic product (up to 2 x GDP versus 1 x GDP for less rare conditions).

The Netherlands

The regulatory process in Europe allows for expedited registration for medicines for high need conditions. This is like what has been discussed in Australia.

The reimbursement/funding system in the Netherlands incorporates different cost effectiveness thresholds based on severity of disease. For example, the threshold is EUR20.000/QALY for less severe conditions, EUR50.000/QALY for more severe and EUR 80.000/QALY for the most severe. This recognises clinical need and means that medicines for more severe diseases, such as low survival cancers (or conditions like Pompe disease or cystic fibrosis) are more likely to be accessible. In addition, the Netherlands has a budget impact threshold of EUR2.5 million/year, below which a medicine is not required to undergo a comprehensive health technology assessment to determine its cost-

effectiveness. That is, there is immediate reimbursement in the Netherlands for hospital drugs costing <2.5 million EUR/year or 10,000 EUR/patient per year.

Canada

The regulatory process in Canada allows for approval of some medicines with certain conditions attached (for example: special monitoring, or delivery of a Phase III study). The time for registration can also be shorter (9 months) than the standard 12-month timeline.

The reimbursement system requires Phase III data. However, where medicines are under consideration for conditions where there are no current options, and where no further trials are planned, reimbursement submissions will be accepted in the absence of Phase III data.

In Canada, there is an oncology-specific assessment group called pod (the Pan-Canadian Oncology Drug Review) which does consider oncology medicines somewhat differently from other types of medicines. In general, this neither hastens or slows down reimbursement.

Regarding rare cancers, while there is no specific formal framework, the reimbursement process for all medicines explicitly involves input from patients and patient organisations. This input is sought throughout the reimbursement submission process from the time the application is first lodged.

United Kingdom (UK)

In the United Kingdom, the National Institute for Clinical Excellence (NICE) incorporates a lower cost-effectiveness threshold for end-of-life medicines, and incorporates a fast-track process for medicines at lower cost effectiveness thresholds. Furthermore, drugs for the treatment of rare diseases will be measured against much more lenient cost-effectiveness thresholds (up to 30 times higher compared to medicines for non-rare conditions). However, in the UK, the NICE requests appraisals from sponsors (rather than sponsors proactively submitting them). In practice, drugs for the treatment of rare diseases or low budget impact may not be selected for appraisal at all.

5. Why are clinical trials conducted in late lines of disease, and why are participant eligibility criteria so stringent?

<p>Senator BURSTON: Some submitters were suggesting that, because they had grade 1 or grade 2 cancer, they were not far enough advanced and they would only trial on somebody who had grade 4, which was, obviously, terminal.</p>

Further to our response to this question at the hearing, Medicines Australia would like to reiterate some key points:

- the availability of a clinical trial may provide access to new medicines but this is only for some patients who are in the right geographical area, who are also diagnosed at the 'right time' in relation to study enrolment, and whose clinician is aware of the clinical trial as a possible option;

- in the long term, the most important way to enable sustainable access to new medicines and improve health outcomes for people with low survival cancer, is access to relevant treatments via the PBS;
- in relation to the PBS, it is critical for our evaluation system to be fit for purpose so that it can take account of and accept the data limitations which characterise rare/low survival cancers (low patient numbers, single arm trials, treatment switch etc.).

Regarding the stringent level of entry criteria for clinical trials, these criteria are determined by medical experts and are put in place to ensure that clinical trials answer specific questions without risk of confounding factors. It would be unfortunate to the extreme if a clinical trial is a wasted effort, and so could not be used to support TGA approval and PBS listing, because of some confounding factor which could have been avoided through application of a proper level of control at entry.

This balance between access for some within a clinical trial and long term access (equitable access for all appropriate patients via the PBS) is why eligibility criteria are stringent.

It is noteworthy that the 2015 Senate Report into the Availability of New, Innovative and Specialist Cancer Drugs in Australia, references research undertaken by Deloitte Access Economics into pre-PBS access. This research found that in 2011-2012 in Australia, a sample of only 9 pharmaceutical companies provided almost 5000 patients with medicines on a compassionate basis. In most cases, the medicines - representing approximately \$10 million - were provided free of charge and prior to PBS listing, or experimentally prior to TGA approval, through specialist cancer centres.

[Deloitte Access Economics Research into cancer medicines access](#)

Finally, Medicines Australia notes a recently published 2017 Deloitte Access Economics analysis: “A Collaborative Assessment of Access to Cancer Medicines in Australia”. The report, available at <https://www2.deloitte.com/content/dam/Deloitte/au/Documents/Economics/deloitte-au-economics-access-cancer-medicines-australia-2017-150617.pdf> makes recommendations to:

- i) Make real world evidence a reality in Australia
- ii) Agree on the evidence requirement for cancer medicines
- iii) Implement provisional PBS listings
- iv) Make patient care, clinician and community engagement meaningful.

These are consistent with the collective recommendations of the 281 submissions to the Inquiry, and the evidence provided by many of the witnesses.