Australian Clinical Trials Alliance

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Office of the Clerk Assistant (Committees)
House of Representatives
PO Box 6021
Parliament House
CANBERRA ACT 2600

Dear Committee Secretariat

Parliamentary Inquiry into approval processes for new drugs and novel medical technologies in Australia

The Australian Clinical Trials Alliance (ACTA) welcomes the opportunity to respond to the Parliamentary Inquiry into approval processes for new drugs and novel medical technologies in Australia.

ACTA is the national peak body supporting and representing Clinical Trial Networks (CTNs) conducting investigator-initiated clinical trials, Clinical Quality Registries (CQRs), and the Coordinating Centres (CCs) supporting CQRs and CTNs. Our vision is for *better health through best evidence*.

Our Members are among Australia's most productive and high impact clinical researchers, and incorporate thousands of senior doctors, nurses, allied health professionals and career researchers around Australia. They are responsible for establishing the effectiveness, and in some cases, the harm, associated with numerous new and commonly used medical therapies through investigator-initiated clinical trials, or identifying unwarranted variation in practice and outcomes through clinical quality registries.

Please find attached ACTA's responses to Terms of Reference 2-4. We would be very pleased to speak to the Committee to help clarify any of the issues raised in this submission if that would be helpful.

Yours sincerely,

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TERMS OF REFERENCE 2

Incentives to research, develop and commercialise new drugs and novel medical technologies for conditions where there is an unmet need, in particular orphan, personalised drugs and off-patent that could be repurposed and used to treat new conditions

TERMS OF REFERENCE 3

Measures that could make Australia a more attractive location for clinical trials for new drugs and novel medical technologies

Recommendations

Our key recommendations support the overarching objective of making Australia a more attractive location for clinical trials for new drugs and novel medical technologies. They include:

1. Further increase funding to Clinical Trial Networks (CTNs) to ensure core infrastructure support so that CTNs can operate optimally to address not only the investigator-initiated questions but also develop mechanisms to liaise with industry.
2. Enable pathways for the optimal utilisation of CTNs by promoting that new drugs and novel medical technologies are provided to CTNs.
3. Increase the amount of funding available to investigator-led clinical trials, which will allow the sector to address conditions where there is an unmet need, in particular orphan, personalised drugs and off-patent that could be repurposed and used to treat new conditions.

Context

Clinical trials are commonly led by commercial entities with a financial interest in the intervention being tested. These might include pharmaceutical, biotechnical and medical device organisations, for example. Clinical trials are also established and managed by independent clinical investigators and researchers working in health institutions, such as those working within public institutions, including universities, and the healthcare system (including acute, sub-acute and primary care settings). These trials are conducted to improve the safety and quality of health care by testing interventions and generating clinical evidence that informs health-related decisions. These trials are frequently referred to as investigator-initiated trials (IITs).

Clinical Trial Networks (CTNs) represent aggregated groups of clinicians and researchers, generally national, spanning a wide range of disease areas and disciplines. These networks incorporate upwards of 10,000 clinical researchers across the country – the majority of whom are practicing clinicians. There are currently over 50 established and emerging CTNs in Australia, but there are many areas of high importance to community health that are not currently supported by a CTN.

A recent gap analysis undertaken by ACTA found that there were still areas of high disease-burden that did not have a nationally coordinated CTN, such as primary care and indigenous health. ACTA believes that organising trial activity within a network increases the number, efficiency of conduct, and impact of clinical trials. While it is for each discipline- or disease-area to determine if the interests of their patients are best served through a formalised CTN, funding opportunities must be considered by funding organisations and the Government to increase the number and sustainability of CTNs. Additional funding would also enable existing CTNs to expand and have greater reach and translational impact. CTNs play a significant role in increasing clinical trial recruitment to address unanswered clinical questions. CTNs help to ensure that national, consumer and community priorities are met. Clinical trials require specialised skill sets. CTNs, and the coordinating centres that support them, strengthen the collaborative development of research

proposals through extensive consultation processes involving internal peer review of study proposals to ensure scientific merit and rigour.

Considerable efficiencies are created through the recruitment of specialists in trial design that build and share intellectual and virtual infrastructure across a longitudinal series of trials conducted within a network, making trial initiation easier, quicker and more cost-effective. Peer input and experienced coordinators generate a higher-quality trial design with a greater impact on patient outcomes and gross value generation. CTNs also make participation in trials accessible and equitable. The only requirement for clinicians to be involved is that they treat or see patients who are suitable for inclusion in the trial in question, leading to greater and more diverse recruitment, increasing the external validity of the evidence generated.

Established CTNs possess critical trial infrastructure including access to a greater sample size through the collaboration of more sites, CTNs are ideally placed to conduct trials for orphan, personalised and off-patent drugs that could be repurposed and used to treat new conditions.

Additionally, network-driven trials contribute to the faster translation of results into clinical practice. Anecdotal evidence from the international literature suggests that CTNs are well placed to enable such translation.[1,2] Moreover, clinicians who contribute to trial design or participate in a trial (that is addressing a clinically important question) are more likely to implement the results of that trial in their practice and help to translate new knowledge to their clinical colleagues.

ACTA continues to work with the Commonwealth Department of Health to increase the effectiveness and efficiency of CTNs in Australia. However, ongoing funding and resources have been identified as critical to CTN sustainability. Many CTNs have only limited or short- to mid-term funding, and very few have certain long-term funding.[3] While there are some strong and well-resourced CTNs, many are struggling to achieve sustainable funding. New CTNs require assistance and seed funding to ensure that they survive and thrive, and sustainable funding is a major limiting factor. Greater funding is needed for CTNs to support large-scale, investigator-led clinical research in Australia to generate evidence of comparative effectiveness and test innovative approaches. Networks need core infrastructure support. Infrastructure support will enable networks to be more efficient and sustainable in order to liaise with industry and facilitate further trials.

The National Health and Medical Research Council (NHMRC) is the largest single provider of medical research funding to the academic clinical trials sector in Australia. Investigator-initiated trials undertaken by CTNs deliver benefits exceeding their costs, at a return on investment of 5.8:1, with 25 trials conducted by three selected CTNs generating $2b in gross value annually. Further, where these trials were NHMRC supported, the return increased to 51:1.[4]

It is conservatively estimated that studies undertaken by CTNs account for approximately one-third of all NHMRC funding awarded for clinical trial-related activities since 2000[5]. As new therapies and technologies enter clinical practice across the entire spectrum of health states, there is an urgent role for more trials to

[1] Kaukonen KM et al. (2013). Glycaemic control in Australia and New Zealand before and after the NICE-SUGAR trial: a translational study. Critical Care 17(5):R215.
[2] Australian Clinical Trials Alliance. Economic evaluation of investigator-initiated clinical trials conducted by networks. Sydney: ACSQHC; 2017. https://www.safetyandquality.gov.au/sites/default/files/migrated/Economic-evaluation-of-investigator-initiated-clinical-trials-conducted-by-networks.pdf
[3] Australian Clinical Trials Alliance. Activities critical to success and growth of Clinical Trials Networks: Sector consultation. ACTA; May 2019 https://clinicaltrialsalliance.org.au/wp-content/uploads/2019/11/Activities-critical-to-success-of-CTNs-Sector-Consultation.pdf
[4] Gross benefit of $2 billion is in 2014 Dollars. Australian Clinical Trials Alliance. Economic evaluation of investigator-initiated clinical trials conducted by networks. Sydney: ACSQHC; 2017
[5] Prepared by Australian Clinical Trials Alliance for the National Health and Medical Research Council. Report on the Activities & Achievement of Clinical Trials Networks in Australia 2004-2014. Nov 2015.

consider the most effective clinical approaches for patients and to enhance the evidence-base on which new strategies can be based. However, in 2019, the number of grants awarded under the NHMRC Clinical Trials and Cohort Studies scheme fell to just 31, with an overall success rate by category of 5.4%.

In conclusion, CTNs are an underutilised vehicle for enabling effective and efficient research and translation, particularly for conditions where there is an unmet need, specifically orphan, personalised and off-patent drugs. CTNs are in an excellent position to facilitate further development of the investigator-led research sector, ultimately making Australia a more attractive location for clinical trials for new drugs and novel medical technologies

TERMS OF REFERENCE 4

Without compromising the assessment of safety, quality, efficacy or cost-effectiveness, whether the approval process for new drugs and novel medical technologies, could be made more efficient, including through greater use of international approval processes, greater alignment of registration and reimbursement processes or post market assessment.

Recommendations

Our key recommendations relate to supporting the overarching objective that Australia continues to be well-positioned to access new drugs and novel medical technologies in a timely manner and respond to emerging global trends.

1. Establish a rigorous pathway for treatments, services and technologies that are unproven in the real world to enter practice as quickly as possible through a conditional scheme. This scheme would require participation in either a trial conducted by a Clinical Trial Networks (CTNs) and/or Clinical Quality Registries (CQRs) capable of generating important real-world data about the clinical effectiveness and value of the intervention in the real-world context. We believe that this would enable the Government to acquire more data, enhance patient access and enable doctors to gain invaluable experience with new drugs and medical technologies. Such an arrangement would enable Australian healthcare to be evidence-based as well as self-learning.
2. Conduct a review of potential reforms to the Medicare Benefits Schedule (MBS), aimed at facilitating the better generation of real-world evidence to improve outcomes and deliver value gains. The review should consider ways to use savings generated through investigator-initiated trials (IITs) and CQRs as a means of funding these activities.
3. Expand the current Parliamentary Inquiry to include all medical interventions, including tests, procedures, devices and new drugs.

ACTA believes that this review offers a critical opportunity to take a bold and visionary step toward enhancing the efficiency of the drug approval processes in Australia, as well as embedding research into clinical practice. We believe that such a scheme is long overdue and would not only lead to greater generation of real-world data and evidence by boosting participation in important IITs and CQRs, but ultimately also save money and directly improve quality of care.

Context

Access to new drugs and novel medical technologies must be a balance between the speed of availability and the need for high-quality evidence on effectiveness and cost-effectiveness. The approval of new drugs and novel medical technologies is an increasingly complicated process, and clinical trial designs and procedures have also become progressively more complex. The assessment of a new drug or novel medical technology traditionally involves a sequence of clinical trials (phase I–III). The accumulated evidence of dose justification (where relevant), efficacy and safety in specified treatment indications and target populations then enables the drug's sponsor to apply for registration of the drug or medical technology.[6]

New drugs and novel medical technologies are regularly brought to Australia, but often the evidence showing that they are cost-effective is limited because of the nature of the trials or because they may be indicated for the treatment of a rare condition.

[6] Kubler P. (2018). Fast-tracking of new drugs: getting the balance right. Aust Prescr. 2018;41(4):98-99.

In such a scenario, releasing new drugs or devices to CQRs or Medical Device Registries respectively can enable the generation of critical data about the clinical effectiveness and/or value of the intervention in the real-world context. We believe that this will enable the Government to acquire greater certainty though more data, enhance patient access and enable doctors to gain invaluable experience with respect to new drugs and medical technologies.

The primary purpose of a CQR is to monitor outcomes and report on the quality of care. Quality indicators collected by CQRs assess whether care is safe and effective and delivered in a timely and appropriate manner and report this back to institutions and clinicians.

A further advantage of doing this is that it in cases of diseases that have significant mortality or morbidity, a drug associated with some uncertainty about the evidence (usually because the duration and magnitude of the benefit relative to the cost of the drug is uncertain rather than there being any uncertainty around the efficacy of the drug), can be accessed early by the patients. This also serves as an opportunity to address significant patient needs particularly for rare conditions because it is usually the rare diseases for which there are limited randomised trials, and there is likely to be insufficient evidence.

By way of illustrating this approach (as per the Australian Government Federal Register of Legislation, the *National Health (Highly specialised drugs program) Special Arrangement 2010),* patients receiving PBS-subsidised ivacaftor (a CFTR modulator used for the treatment of patients with Cystic Fibrosis) must be registered in the Australian Cystic Fibrosis Database Registry. Such mandatory participation required at a minimum that the clinician register each patient receiving the drug be registered with the registry, thus enabling further data collection. As a result of the *Highly specialised drugs program*, the Pharmaceutical Benefits Advisory Committee (PBAC) was satisfied that tezacaftor/ivacaftor provided, for some patients, a significant improvement in efficacy over best supportive care.[7]

Similar to clinical quality registries, drug and medical device registries are critical for the identification and study of intervention outcomes. Drug registries are composed of patients exposed to a drug and allow the study of drug utilisation patterns, including, for example, off-label use. Device registries are used for many purposes, including short- and long-term surveillance, the fulfilment of post-market observational study commitments for regulatory bodies, and comparative safety and effectiveness assessments, including those in under-studied subpopulations. However, it should be noted that when linked to disease-based registries (as opposed to drug-only registries) there is as much valuable information learned from those not treated with the new drug as there is from people who are treated with the new agent.

An excellent example of a medical device registry is the Australian Breast Device Register (ABDR) to track the long-term safety and performance of breast implants as well as identify best surgical practice to help safeguard health outcomes for patients. Given that the safety profile for breast implants was unclear, safety alerts were set up and subsequently, the ABDR was set up to collect evidence. The ABDR aims to record and track all breast devices implanted in Australia, as well as any adverse events associated with those devices, to help medical practitioners improve their patient outcomes. A medical device register is focused on long term safety and post-market surveillance of medical devices.

ACTA believes that the approval pathway for certain new services/technologies that are likely to be significant to patients and represent a high-cost to the MBS should be expanded to incorporate the

[7] Public Summary Document. (2019). TEZACAFTOR with IVACAFTOR, Pack containing tezacaftor 100 mg with ivacaftor 150 mg tablets and ivacaftor 150 mg tablets, Symdeko®, Vertex Pharmaceuticals. https://webcache.googleusercontent.com/search?q=cache:hT-qwyh22EwJ:https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2019-03/files/tezacaftor-with-ivacaftor-RFmutation-psd-march-2019.docx+&cd=2&hl=en&ct=clnk&gl=au

conditional listing of the new item subject to the collection and analysis of robust clinical and patient-centred outcome data through either a randomised clinical trial or a clinical quality registry.

Models that used elements of this mechanism are available in the United Kingdom (UK) and United States (USA). As their health systems are so different from Australia, neither are an ideal model for Australia to follow. Nonetheless, they present Australia with an excellent opportunity to utilise learnings from these countries to develop a novel process.

One such model is the *Coverage with Evidence Development* (CED) scheme in place in the USA. Under this scheme, Medicare covers items and services on the condition that they are provided in the context of approved clinical studies or with the collection of additional clinical data to assess the utility of an item or service for use with a particular patient group. A recent review of the CED scheme revealed that the program has the potential to improve access for Medicare beneficiaries and understanding of novel therapies.[8]

A parallel to this can also be found in the recently revamped UK Cancer Drug Fund, which provides patients with access to promising new treatments, via managed access arrangements, while further evidence is collected to address clinical uncertainty. Additionally, interim funding is provided for all newly recommended cancer drugs, giving patients access to these treatments many months earlier than before.

In addition, releasing drugs and devices to investigator-initiated trials (IITs) and clinical quality registries represents a unique opportunity to develop innovative funding models for IITs and CQRs. IITs are established and managed by non-pharmaceutical researchers, such as clinicians and researchers working in a health institution. One of the consequential outcomes of making an item available only within the context of a randomised controlled trial (in which the control arm of the study receive the current standard of care) is that the MBS will only be billed for half of the patients that would have otherwise received the new service or technology. This provides a unique opportunity to reinvest a proportion of the direct cost savings associated with this approach to support the cost of the trial.

Another consequence of providing reimbursements within a clinical trial for an unproven new intervention or an existing item of potentially low-value is the potential for costs savings associated with the rigour of trial protocols. ACTA suggests that this is another mechanism through which the Government could seek to identify savings to offset the cost of conducting large IITs and establishing as well as maintaining CQRs.

Using the MBS as a much stronger driver for the development of large IITs and registries is likely to encourage more partnership between governments, clinical communities, industry and the not-for-profit sector to fund these activities. One example of this is the consortium of public/private partners that formed to establish the Bariatric Surgery Registry.

Additionally, ACTA believes that such a system could be readily implemented in Australia where we have a number of well-established and highly successful CTNs upon which to model the successful conduct of large IITs as well as world-class expertise in the development and operation of CQRs.

In conclusion, ACTA strongly recommends the approval processes for new drugs and novel medical technologies could be made significantly more efficient by releasing these first to CTNs or CQRs. This would not only enable the generation of real-world data, but also ensure earlier patient access to potentially life-saving drugs and medical technologies in the safest possible manner.

[8] Zeitler et al. (2019). COVERAGE WITH EVIDENCE DEVELOPMENT: WHERE ARE WE NOW? Journal of the American College of Cardiology 73: No 9.