Received: 15 March 2021 | Accepted: 27 April 2021 | Published on: 24 June 2021

DOI: 10.1111/ajco.13606

ORIGINAL ARTICLE

WILEY

Barriers and potential solutions to international collaboration in neuro-oncology clinical trials: Challenges from the Australian perspective

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Abstract

Aim: The neuro-oncology community in Australia is well positioned to collaborate internationally, with a motivated trials group, strong regulatory bodies and an attractive fiscal environment. We sought to identify gaps in the Australian neuro-oncology clinical trials landscape and describe strategies to increase international trial access in Australia.

Methods: We searched clinical trial registries to identify active adult primary brain cancer trials. We compared the participation rate and phase of these trials between tumour types and countries. A survey was distributed to the Cooperative Trials Group for Neuro-Oncology membership to identify barriers and solutions to effective international collaboration.

Results: Globally, 307 trials for adult primary brain cancers were identified. These included 50% pharmaceutical agents, 18% cellular therapies and 9% radiation therapy. Twelve adult primary brain cancer trials were actively recruiting in Australia at the time the survey was sent out. There were more early phase brain cancer trials (34%) compared with colorectal and breast cancer (21% and 24%, respectively). In Australia, 92% of brain cancer trials were involving pharmaceutical agents. The most commonly cited barrier was lack of funding for international trials (86%) and insufficient research time (75%). High ranking solutions included increasing the availability of funding for international trials and creating opportunities to develop personal relationships with collaborators. Accreditation of clinical research key performance indicators into practice (88%) and hospital accreditation (73%) also ranked highly.

Conclusions: Participation in international research in Australia could be improved by embedding clinical research targets into institutional funding, provision of funding for early phase studies and streamlining mutual ethics schemes.

KEYWORDS
clinical trials, ethics, funding, international cooperation, neuro-oncology

1 | INTRODUCTION

In 2016, 1771 brain cancers were diagnosed, and 1460 brain cancer deaths occurred in Australia.[1] The 5-year survival rate for all adult brain cancers combined is 22%, which is unchanged compared to 1986–1990. In contrast, the 5-year relative survival rates for prostate cancer, kidney cancer, colon and rectal cancer, breast cancer and myeloma and non-Hodgkin lymphoma have shown improvement. Breast, prostate, colon and rectal cancer have received the highest levels of direct funding.[2] Research investment for specific tumour types has led to advances in early detection and treatment, improvements in patient survival and reduced burden of disease.[1]

Conducting brain cancer clinical trials is challenging. The low incidence of primary brain cancer necessitates international collaboration to achieve statistically significant results.[3] The median overall survival of over 10 years[4] observed in lower grade glioma leads to lengthy studies to measure endpoints such as overall survival. In addition, the rapidly evolving molecular characterisation of gliomas[5] can lead to refinement of molecular diagnosis during clinical trials, introducing genetic markers of unknown predictive or prognostic significance.[6,7] This creates ever-shrinking patient populations defined by molecular characteristics for which demonstrating efficacy of treatment is difficult. In this context, survival rates remain dismal, and there is an urgent need for patients to gain access to new treatments.

Here, we focus on the landscape of adult primary brain cancer clinical trials in the Australian context. A systematic initiative was performed to critically appraise barriers and solutions to Australian participation in international brain cancer research. We sought to identify gaps in the Australian neuro-oncology clinical trials landscape by comparing the Australian trial landscape to the perceived trial landscape in other countries and to describe strategies to increase international trial access in Australia by surveying Australian neuro-oncology clinicians and researchers.

2 | MATERIALS AND METHODS

We conducted this project in two stages: 1. A cross-sectional analysis of the current landscape of neuro-oncology clinical trials in Australia, and 2. A survey of the Australian neuro-oncology community to identify perceived barriers and solutions to international trial access and collaboration.

2.1 | Cross-sectional analysis of neuro-oncology trials available in Australia

We searched for all current neuro-oncology trials registered on clinicaltrials.gov in Feb 2019. The following search criteria were applied: Recruiting, Not yet recruiting Studies | Interventional Studies | glioma OR brain cancer OR brain tumour OR brain tumour OR glioblastoma | Adult, Older Adult | and Phase 1, 2, or 3. Results were filtered by

country to obtain a list of neuro-oncology trials that were single country or multi-national. Trials involving adolescents and young adults, primary pituitary tumours, CNS lymphoma, and brain metastases were excluded from analysis. Selected trials were further analysed based on the main intervention, subcategorising them into drug therapy, cellular therapy, radiation, imaging, dietary, medical device, surgical, or other trials. A search of colorectal and breast cancer trials was conducted simultaneously on clinicaltrials.gov to compare the participation rates in clinical trials. The search criteria used were Recruiting; Not yet recruiting Studies; Interventional Studies; Breast Cancer, Colorectal Cancer; Adult; Older Adult; and Phase 1, 2, or 3.

2.2 | Survey to identify barriers and solutions to international collaboration

A survey was developed to identify perceived barriers and facilitators to accessing and conducting international brain cancer trials within Australia.

To design the survey, a PubMed search was conducted to identify studies of barriers to international collaboration in clinical trials with a cross-sectional survey component using the search terms 'survey' OR 'questionnaire' AND 'collaboration' AND 'international' limited to 'English language' and after 2011. Five studies were identified, and the abstracts were reviewed. Two studies were excluded because the research question was limited to collaboration between defined countries. One study was excluded because of limited scope. Another was excluded as it was not focused on international collaboration. One relevant publication was identified entitled *Facilitators and Barriers to International Collaboration in Spinal Cord Injury*.[8] Using the key themes informed by the spinal cord injury survey and literature review, we developed an Australian-specific, neuro-oncology survey (Appendix 2).

The survey consisted of six parts: 1. Demographics and role of the participant. 2. Participant perception of clinical trial access in Australia. 3. Advantages of conducting trials in Australia. 4. Facilitators of international collaboration. 5. Barriers to international collaboration. 6. Views on proposed initiatives to facilitate future international collaboration. No personally identifying information was collected. Questions 4–8 included questions with five response options on a Likert scale that ranged from "strongly agree" to "strongly disagree." Free text responses were sought after each question to allow participants to express views not encompassed by the questions. The survey was tested for face validity by 15 expert members of the Cooperative Trials Group for Neuro-Oncology (COGNO) International Collaborative Research Subcommittee. Following pilot testing, a number of items were added including a question on participant profession as well as a question on social media as a facilitator of international clinical trials was added. The wording was updated to make questions more relevant to respondents who are not directly involved with setting up international clinical trials.

The electronic survey link was distributed via email on 13 June 2019 to all full members of the COGNO, which includes Australian and New Zealand researchers and health professionals with an interest in brain tumor clinical trials. Additionally, paper surveys were distributed to attendees at the COGNO Annual Scientific meeting in on October 27, 2019 for completion by those who had not responded to the electronic survey. Data from both survey formats were collated prior to analysis. COGNO members are nominated by two current members and approved by the COGNO management committee as having interest and expertise in brain cancer clinical care or research. For each question, the data were analysed qualitatively by reporting the most frequent response (mode).

3 | RESULTS

3.1 | Gaps in neuro-oncology trials in Australia

Our search identified 523 trials, 307 of which included primary brain cancers in adults. Of these 307 trials, the location of trial activity/patient recruitment was specified for 285 trials. Of these, 259 were conducted in a single country, and 26 were international. Australia was a location in 12 (4.2%) of the 285 trials, including being the only recruiting country for two trials, and one of multiple countries in 10 trials (Table 1). On a per capita basis, the number of neuro-oncology trials in the USA is well above similar sized countries. Despite being the second largest country by population, 197 neuro-oncology trials were identified in the USA, compared with China and Japan with 19 and eight trials, respectively.

Comparison of neuro-oncology trials with trials for other tumour types resulted in the following: among 690 colorectal cancer studies, 636 listed a location, 538 were single country, and 98 were multi-national trials. Of the 636 trials, Australia was listed as a location for 36 (5.6%), three as a single country and 29 as one of multiple countries. Among 1025 breast cancer trials, 963 listed a location, 836 were single country, and 127 were multi-national trials. Of the 936 trials, Australia was listed as a location for 53 (5.7%), 10 as a single country and 43 as one of multiple countries.

To further characterise the trials and differences in trial participation across tumour streams, we compared the phases of currently recruiting trials in neuro-oncology, colorectal cancer and breast cancer. Of the 307 trials in primary adult brain cancer, 53.5% were Phase I, and only 10.1% were later phase trials (Phase III) (Appendix 2). There was no statistical difference between tumour types. However, a trend towards difference was noted (χ^2 8.72, 4df, P = 0.07). In comparison, 22.7% of colorectal trials and 18.3% of breast cancer trials were phase III. Of the 12 trials in which Australia was active, four were phase I, three were phase I/II, one was phase II, and four were phase III.

The 307 trials in primary adult brain cancer were classified by trial type based on the main study treatment/question (Figure 1). Of the 12 trials in Australia, eight used targeted therapy, three trials involved checkpoint inhibitors, and one trial was addressing management of treatment side effects. No trials involving vaccines, viruses, or immune cell therapies/immune modulators included Australia. While the regulatory and technical capabilities available in Australia make access to these therapies difficult, identifying this gap highlights a potential opportunity for future neuro-oncology trials.

TABLE 1 Multi-national neuro-oncology trial participation by country and population

Country	Population (July 2017)[9]	Number single country trials (of 259 total)	Number multi-national trials (of 26 total)	Total neuro-oncology trials
China	1,409,517,397	18	1	19
USA	324,459,463	174	23	197
Japan	127,484,450	2	6	8
Germany	82,114,224	6	9	15
UK	66,181,585	3	8	11
France	64,979,548	11	12	23
Italy	59,359,900	0	6	6
South Korea	50,982,212	3	5	8
Spain	46,354,321	6	9	15
Canada	36,624,199	6	15	21
Australia	24,450,561	2	10	12
Taiwan	23,626,456	4	4	8
Netherlands	17,035,938	6	11	17
Belgium	11,429,336	3	6	9
Sweden	9,910,701	1	3	4
Austria	8,735,453	0	5	5
Switzerland	8,476,005	4	8	12
Denmark	5,733,551	2	4	6
Singapore	5,708,844	0	4	4
Norway	5,305,383	3	4	7
Other countries		5		5

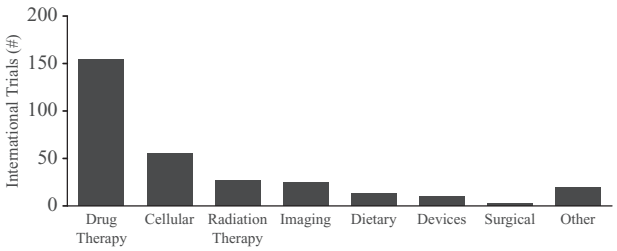

FIGURE 1 Number of and type of neuro-oncology trials internationally: Internationally, drug therapy trials are the most common, while surgical interventions are the least common trials. Drug therapy treatments include checkpoint inhibitors, targeted therapy, chemotherapy, radio-protectants and chemo-sensitisers. Cell-based trials include cell-based immune therapy, CAR-T cells, vaccines and viral-based therapy. Dietary trials include cannabinoids, supportive care, metabolic and side-effect studies. Device trials include TTF/Optune and laser interstitial thermal therapy

3.2 | Barriers and facilitators to international trial participation in Australia

The target population was Australian neuro-oncologists actively engaged as investigators in clinical trials or in leadership positions, which was estimated to be 60–80 members. The survey was completed by 64 respondents which yields broad coverage of the target group. The largest group of respondents were medical oncologists (48%) followed by radiation oncologists (16%).

The survey found that 22% of respondents strongly disagreed with the statement that 'neuro-oncology patients in Australia have sufficient opportunities to participate in clinical trials'. When respondents were asked if they perceived Australian patients to have good access compared to patients from the USA, 68% of respondents disagreed. This contrasts with the respondents' perceptions of clinical trial access in Europe, Singapore and Canada, where the majority selected 'neutral' (33%, 65% and 44%, respectively) (Figure 2).

Respondents provided their perception of the advantages to conducting trials in Australia. The quality of clinical data generated received the most positive response, with 44% of respondents strongly agreeing and 35% agreeing that this was an advantage of conducting local trials. Other advantages where respondents agreed centred around government regulation including the National Mutual Acceptance Scheme (mutual ethics approval) (46%), the Clinical Trials Notification scheme (federal regulatory notification) (35%) and standardised site agreements with Medicines Australia (42%) (the pharmaceutical industry body).

The survey indicated that lack of specific funding for international trials was perceived as the strongest barrier to international

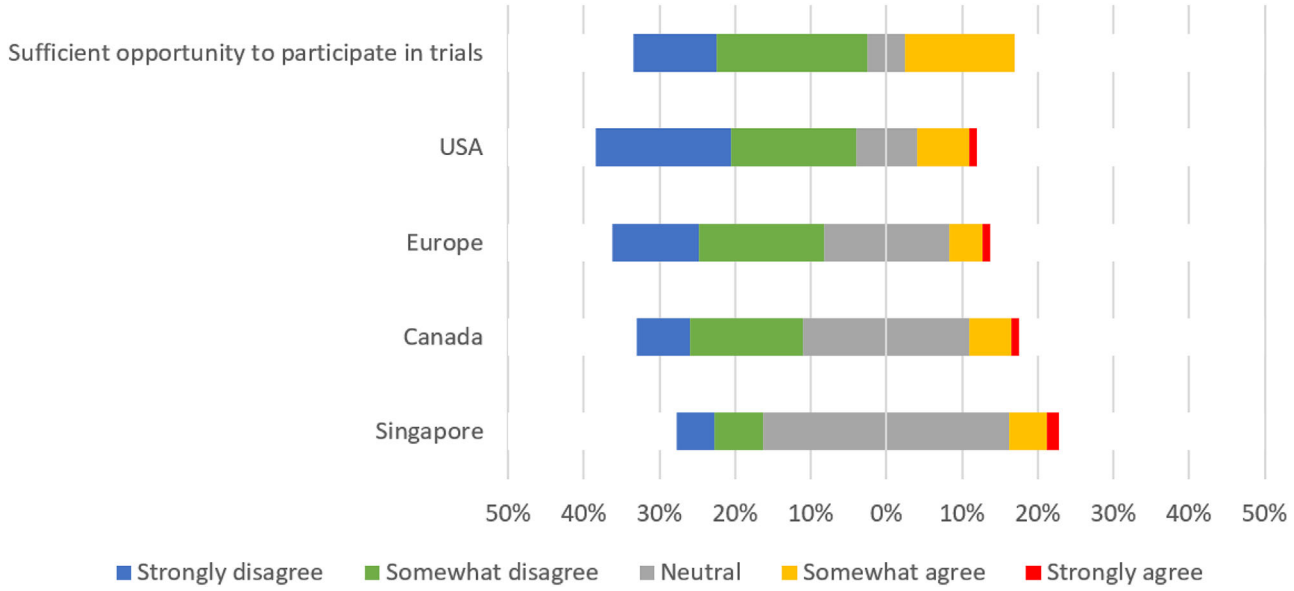

FIGURE 2 Perceived access to neuro-oncology clinical trials in Australia

collaboration, with 54% of respondents identifying this as a strong area of need (Figure 3A). Insufficient protected research time also scored highly as a barrier, with 48% of respondents agreeing that they had inadequate time to dedicate to research. Interestingly, the majority of respondents did not find that language barriers, cultural diversity, ethics requirements, privacy requirements, knowledge and experience or the ability to recruit were strong barriers. These results highlight further strengths of the clinical trial landscape in Australia indicating that Australia has struck a positive balance in privacy and ethics regulation without significantly impeding clinical trial activity. Furthermore, the respondents are confident in the level of available clinical trial expertise, and despite the rich cultural diversity of the country, language or culture does not seem to be a barrier (Figure 3B). The ability to recruit is both a negative, due to Australia having one of the highest cancer rates in the world and a positive indicating inclusivity and accessibility of the health care system.

Several proposed initiatives relating to embedding clinical research into routine clinical care received strong support. The two aspects that respondents rated highest as facilitators were the availability of trial funding that could be used internationally (44%) and personal relationships with international mentors or networks (54%) (Figure 3A), thus supporting the need for Australian investigators to actively participate in international conferences and exchanges. Initiatives directed at improving opportunities for personal relationships in international collaboration were highly rated, with 53% of respondents strongly agreeing that this was a desirable initiative. Embedding clinical research into clinical practice, hospital accreditation and hospital performance indicators also received strong agreement from 56%, 49% and 52% of respondents, respectively, which is consistent with other survey questions (Figure 4).

4 | DISCUSSION

Neuro-oncology trials in Australia are skewed towards early phase trials. This is particularly evident in high-grade glioma, where a paucity of effective therapeutics means that few recent phase III trials have led to practice change.[9] Compared with other countries of similar size, (e.g., the Netherlands, Taiwan), a similar number of local and multi-national trials were being run in Australia. However, compared with countries where there is perceived better access to international trials (e.g., USA), Australia has a more limited portfolio of treatment modalities. Australia lacks a portfolio of cellular, vaccine and oncolytic viral therapies in favour of pharmaceutical agents. In spite of these challenges, international trial participation by Australian patients has contributed to practice changing research at the same time as benefitting Australian patients. An example is the Phase III CATNON study of anaplastic astrocytoma, in which Australian patients made up 11% of the total trial accrual.[7,10]

The lack of promising agents in phase III trials in neuro-oncology mandates that early phase trials are essential to promote drug development and increase patient access. In keeping with the literature search, national aggregate statistics for clinical trials across all indications in Australian public hospitals indicate that the majority of clinical trials in public hospitals are phase II or III.[11] An example of the barriers to implementing new technology in Australia is the lack of uptake of Tumour Treating Fields (TTF) (Optune). The factors that have limited the availability of TTF include the lack of government reimbursement and also the need for technicians with specialty skills to administer the treatment. The relatively small patient population and large geographical distances between major population hubs impacts the enthusiasm for companies to make an investment in facilitating access to new technologies in Australia. Overall, clinical trial funding is one

FIGURE 3 Perceived facilitators (A) and barriers (B) to conducting trials in Australia

contributing factor. Australia, Canada and Japan have similar per capita spending on clinical trials at €7.93, €8.27 and, €7.88, respectively.[12] In comparison, Europe as a whole only spends €5.79 per capita. However, spending in the original EU 15 Member States is higher at €8.20 per capita. At €17.98 per capita, USA funding is one of the highest in the world along with the UK, which spends approximately €18.5 per capita (€13.18 comes directly from funding organisations, and the remainder flows through infrastructure funding to the university and healthcare systems).[12]

Funding for international neuro-oncology collaborations was identified as a significant concern among survey respondents. For early phase trials, infrastructure and expert personnel are critical for supportive functions such as Institutional Biosafety Committees. The lack of dedicated institutional funding for scientific staff in many institutions has skewed Australian trials towards easily monitored 'off the shelf' treatments.[11] However, international participation has been strengthened by involvement of clinical trials co-operative trials groups, which have enabled the scale required to participate in global trials.[10,13] Further, directed funding is required to cover the recurring infrastructure and personnel costs to enable participation in international studies.

Australian participation in international trials does not generate additional funding from lead groups for Australian sites or funding tied to patient recruitment. This represents a funding 'gap' for participation in international trials that must be filled by competitive funding rounds, for example, via the National Health and Medical Research Council (NHMRC) or other similar funding bodies. There is an inherent delay in such funding applications as the clinical trial scheme is only open annually. Factoring in the time taken between submission and approval

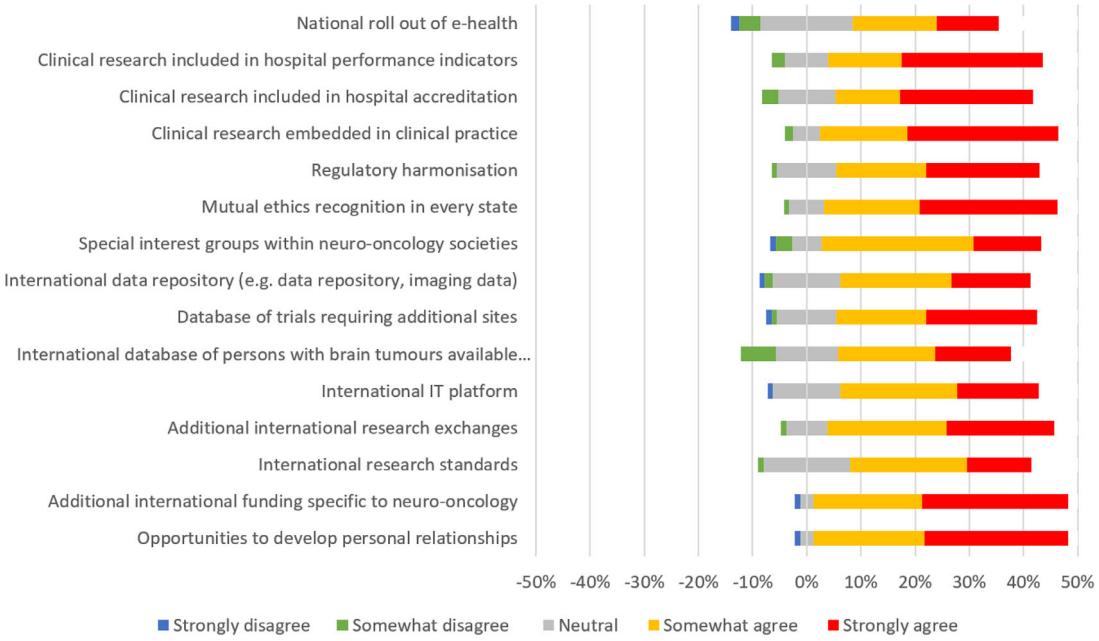

FIGURE 4 Proposed Initiatives to Increase Neuro-Oncology Trials in Australia

(often >6 months) and the possibility of needing multiple submissions prior to granting success means that Australian participation in international trials is often delayed beyond the trial recruitment period.

The lack of sufficient dedicated research time and decline of clinical academics is an issue that has been raised elsewhere.[14–17] The availability of trained academic clinicians to act as principal investigators in clinical trials is a barrier to investigator-initiated clinical trials.[18] In Australia, funding for research positions comes from federal sources, generally through the NHMRC, while funding for clinical care is state-based, leading to competing demands on clinicians engaged in research. Funding early phase research (i.e., translational research of novel treatments into the clinic), requires a highly coordinated approach. The conduct of clinical trials is inherently more time-intensive than treating patients with standard-of-care regimens due to the time required to discuss the range of therapeutic options, consent patients and complete paperwork. Indeed, enrolling patients specifically in commercial clinical trials is a stated key performance indicator within some Australian jurisdictions.[19] The increased time necessary to participate in clinical trials along with competing prioritisation of commercial clinical trials over investigator-initiated trials creates a conflict in funding outcome measures for individual practitioners. Along with fragmented funding models for clinician salaries, this is a disincentive to clinicians devoting time to participation in academic clinical trials at the expense of routine clinical care. Embedding a 'research culture' within hospitals that is linked to funding-backed, key-performance indicators is a potential solution to harmonising the disparate goals of funding bodies that is currently split between service delivery oriented goals and research output oriented goals.[20]

The National Aggregate Statistics (NAS) database for measuring clinical trials metrics in Australia shows that the aspirational target of 60 days for initiation of the regulatory process to site specific approval is met by just 46% of Australian trials.[20] Industry surveys continue to cite the lengthening research governance approval timelines as one of the main barriers to starting trials in Australia.[11,21] Previous studies have shown research governance reviews add 49 calendar days to approval times in Australia.[22] These data indicate that ethics governance approvals need to be streamlined across jurisdictions for Australia to remain internationally competitive in clinical trials.

The current governance approval system in Australia is a burden for investigators. For example, to start up a national clinical trial, an investigator needs to complete research governance applications to individual hospitals or health organisations. This decentralised governance approval process leads to variation in the time for site activation and study start up.

The majority of respondents were supportive of all of the proposed initiatives to increase clinical trial activity in Australia making prioritisation difficult. However, the initiatives can be categorised into themes that can be addressed by individual collaborative groups, hospitals or policy makers as appropriate. Policy makers could focus on building technological infrastructure and developing streamlined regulatory policies. Hospitals could work to increase incentives for clinical trial research, and collaborative groups could continue to provide targeted support by specialty and advocacy for clinical researchers.

Clinical trials require close cooperation between patients, their treating clinicians and the pharmaceutical industry. International neuro-oncology trial participation in Australia would benefit from a predictable and efficient clinical trial environment. The barriers we have identified in this study could be overcome with increased funding for international trials and harmonisation of clinician-researcher funding models together with ethics and governance processes. The barriers identified in this study are likely to apply to other jurisdictions within the Asia-Pacific region that face similarly geographical and logistical challenges as those in Australia, despite regional differences in health care delivery. Significantly, the barriers and solutions we have

outlined are generalisable beyond the neuro-oncology setting and are pertinent to all areas of medicine in which international collaboration is important.

ACKNOWLEDGEMENTS

Yi Feng assisted with production of figures and collation of collected data. Jenny Chow assisted with distribution of surveys and data collection.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

This study was exempted from ethical review as only non-identifiable data were collected, and the study falls into the 'negligible risk' category as defined by the Australian NHMRC National Statement on Ethical Conduct in Human Research.

DATA STATEMENT

All authors had access to the data used to generate figures for this article.

FUNDING INFORMATION

The survey on the barriers and potential solutions to international collaboration in neuro-oncology clinical trials from the Australian perspective is part of a project funded by the Australian Government through Cancer Australia, the Australian Brain Cancer Mission and the Medical Research Future Fund. The contents of this paper are solely the responsibility of the authors and do not reflect the views of the Australian Government.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kong BY, Carter C, Nowak AK, et al. Barriers and potential solutions to international collaboration in neuro-oncology clinical trials: Challenges from the Australian perspective. *Asia-Pac J Clin Oncol*. 2022;18:259–266. https://doi.org/10.1111/ajco.13606