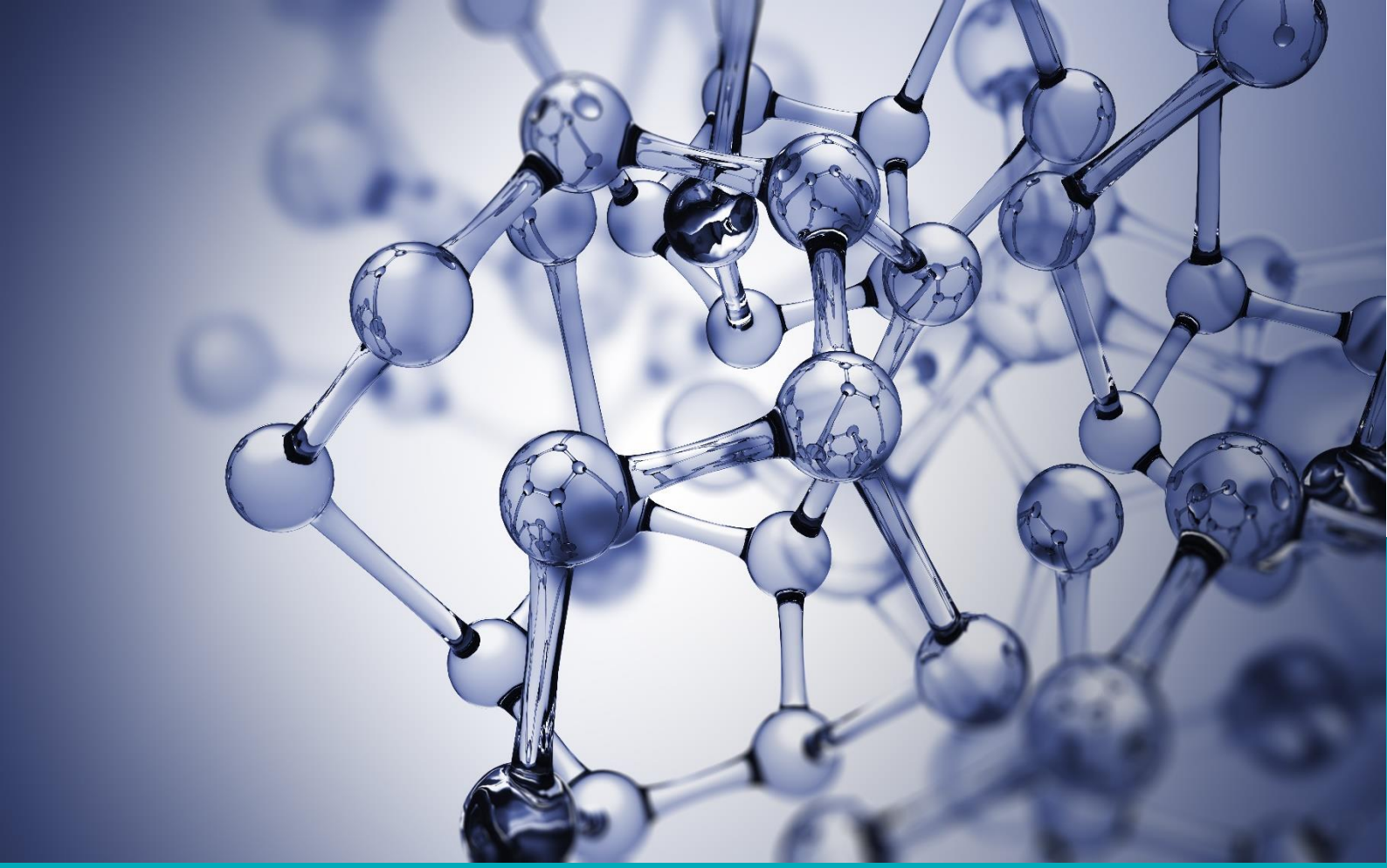

Navigating (Compassionate) Access to Medicines For Trials

Medicines Australia

August 2020

TABLE OF CONTENTS

Navigating (Compassionate) Access to Medicines For Trials

Learnings from Industry to aid the Zero Childhood Cancer Trial and Recommendations arising from Industry / PRISM[1] engagement

EXECUTIVE SUMMARY

Compassionate access to medicines is a route of supply that some pharmaceutical companies (the sponsor[2]) offer in extraordinary cases to patients in need of treatment where no licensed and/or reimbursed option is suitable. Irrespective of the cost of the medicine or the resource involved in administering the programs to satisfy the needs of both the regulator and company, it is normally offered to these patients free of charge. Clinicians regularly seek compassionate access to medicines for less common conditions, or populations, such as paediatric cancer where there are few approved therapies, and brain cancer where almost no therapies are specifically approved.

Compassionate access, particularly for unapproved medicines, can be challenging to achieve in a timeframe consistent with optimal patient care; this may be due to an inability to grant access on the part of the sponsor company or because there is insufficient time to navigate the supply processes. Clinicians leading the Zero Childhood Cancer (ZCC) Program have experienced these challenges in seeking and securing access to medicines for patients enrolled in their program.

The ZCC trial is a multicentre study aimed at identifying optimal treatment for paediatric patients through tumour assessment and mutational screening. Trials like the ZCC rely on rapid availability of single use access (i.e., access for a single patient) or compassionate access. A major issue for such trials is that the appropriate medicine is only determined following the mutational assessment, with resultant limited time to request and secure access. Optimising medicine choices through trials like the ZCC program may improve patient outcomes if the recommended medicine choice can be accessed and administered in as short a period as is reasonably possible.

Requested medicines range from early stage to commercialised. Drugs that are unapproved for the indication for which they are requested are more challenging to acquire and contribute a significant proportion of likely requests for the ZCC. In view of these past experiences and future requests, a project aimed at improving the chances of overcoming these challenges was conducted. Industry sponsors willingly engaged in sharing their insights and, along with ZCC trial leaders, sought to develop suggested improvements – with a focus on preparatory effort which may be "at risk" of never being needed if patients with tumours exhibiting the relevant mutation were never identified.

---

[1] PRecISion Medicine for Children With Cancer (PRISM). The PRISM clinical trial aims to discover whether individual personalised tumour profiling can provide a compelling new approach to the treatment of young patients who face the most aggressive cancers. The clinical trial study will analyse and evaluate information generated from Zero Childhood Cancer, which is focussed on finding new tumour treatment and approaches for children and young people with cancers, where they have a less than 30% chance of survival.

[2] Sponsor in this context refers to the TGA definition of a pharmaceutical company who manufactures a medicine being requested for compassionate supply (https://www.tga.gov.au/sites/default/files/special-access-scheme-guidance-for-health-practitioners-and-sponsors.pdf). It does not refer to the use of the term in the clinical trial context or indicate any clinical trial sponsor responsibilities

This report therefore shares the learnings and the recommendations arising from a combined, collaborative effort to improve access to medicines in trials such as ZCC.

The key learning, perhaps unsurprisingly, was the extent of variability in approaches, decision-making and outcomes. Nonetheless, it was agreed that small, proactive changes to the process of requesting supply could have meaningful impact on medicines access, and therefore on patient outcomes. The goal of improving access was too important not to try to impact seemingly intractable processes; a small improvement is relevant.

Discussions broadly resulted in three goals: a) increasing the knowledge and transparency about sponsor definitions, b) pathways to deliver access, and c) the processes of, and factors influencing, decision-making. Definitions of compassionate access, with a variety of definitions uncovered are not always aligned. The pathways that might be employed in delivering medicines access and how sponsors make such determinations is described, ranging from rollover to existing trials, developing customised arrangements and the more common single use access pathways. Communication and clarity about the factors affecting decision-making, whilst variably applied based on many factors, are intended to aid understanding about the rationale for decisions, the predictability of the same, and accordingly where points of leverage do and do not exist.

Taking a solution-oriented approach to the process, both industry and the trial leaders made commitments to actions each could take to improve the chances for successful delivery of compassionate access in the ZCC trial. These recommendations are structured based on the point of time in the trial progress. They include:

- Increasing prospective awareness within industry of the trial, its hypotheses, processes, design and likelihood of downstream medicines access requests
- Navigating proactive engagement between the sponsor and the trial leaders, with appropriate regard for compliance factors, networks and ensuring clarity and mutual understanding of factors affecting decisions for each medicine and manufacturer
- Investigating and implementing steps to progress commitment, prior to trial start or patient identification – to reduce downstream uncertainty during the decision-making phase and time to access
- Focus on execution post decision, and adopt continuous learning through the trial to address arising issues

At the conclusion of this project, the trial leaders and industry agreed that this report will be collated and its findings will be communicated to advocates of the trial.

It has been suggested there may be broader implications of capturing this dialogue and feedback; these recommendations may be applied to other requests for compassionate access. This underscores the importance of ensuring the report is accessible to others beyond those initially engaged in the discussions.

Finally, there appears to be an opportunity to further build upon these findings, by understanding if the recommendations were successfully implemented and whether they improved the likelihood and timing in which single use /compassionate use access was delivered:

- Where implemented, were the recommendations herein impactful, and are we measuring?
- What future and more impactful role does data collection within “single use” trials have?
- How is “single use” trial evidence used today, how could it be used to inform future clinical decision-making?
- Are we collecting the required information about what is meaningful to patients and how are we ensuring participation in addition to communication?
- For paediatric patients, what steps will accelerate access to trials in Australia, including leverage of overseas initiatives and programs?

INTRODUCTION

The Zero Childhood Cancer national clinical trial

The Zero Childhood Cancer (ZCC) trial involves patients from Australian paediatric centres expert in the treatment of children with cancer. Patients with the most aggressive types of cancer were enrolled, with brain cancer patients making up the majority. This trial is of interest to, and aligned with, the Australian Brain Cancer Mission, through which some funding of the ZCC trial is directed. The trial is expected to run until at least 2020, enrolling up to 400 children.

Upon diagnosis, a tumour sample and a blood sample are taken and tested for mutations. Where possible, the extracted cancer cells may also be tested against a range of drugs (via an established panel) to inform the medicine choice. A Multidisciplinary Tumour Board makes recommendations to the patient's physician on appropriate treatment options. The treating clinical team may then make a medicine request to the relevant industry sponsor.

While the ZCC trial is expected to draw to a close in the near future, studies like it, and the challenges involved, will continue to occur as industry and clinicians pursue precision medicine based approaches in order to improve outcomes for patients.

Defining the problem

The ZCC trial leaders advised that progress on the trial is impeded by the lack of timely access to medicines that have been identified as suitable candidates for patient treatment. The ZCC team is aware that the treatment of patients with such medicines has been impossible, delayed or not available.

There is a strong clinical need in paediatric cancer to identify the industry barriers that prevent timely access to these medicines. Therefore, it is necessary to develop and adopt mitigation strategies that address these barriers.

These difficulties are not unique to the ZCC trial, and the causes of these difficulties are likely to be multifactorial and complex. Addressing the barriers to drug access for the ZCC trial may aid future trials that are similar in design (including those involving mutational screening, for other conditions, or for trials seeking compassionate / single use access of medicines).

It is also suggested that where such mitigation strategies are adopted, the processes, systems and approaches should be considered for other similarly designed studies, notably, those requiring mutational screening or genomic / phenomic assessment.

At the time of dialogue, the ZCC trial group have had issues with a) building relationships with some sponsor companies, b) establishing access to the standard or inclusion to the drug panel, and c) access to the therapy identified for paediatric use.

Why is this important?

It is intended that through sharing of the industry insights and processes of drug access, we gain a better understanding of the key issues influencing the provision of single use drug for individual patients enrolled to the ZCC trial, and where possible, aim to mitigate or eliminate barriers to drug access. This indirectly supports the goal of the ZCC trial to improve patient outcomes; if drug access is improved, more patients can receive the identified treatment and potentially benefit from the targeted nature of the treatment strategy.

Approach

Initial discussions with clinicians from the Sydney Children's Cancer Institute confirmed the issues raised regarding access to the therapies identified for potential utility through the ZCC program. They provided further context and

insight regarding the issues as viewed from the clinical institutional perspective and provided a list of identified potential drug targets that either had, or could have, utility against the mutations identified. It was noted that some experience of direct engagement with sponsor companies had occurred and that specific product discussions were currently at various stages. It was not, and is not, the intention to replace direct discussions between sponsors and the appropriate clinical leaders.

Independently of the ZCC leaders, prospective dialogue also occurred with sponsor companies regarding their perspective on barriers, inter-relationships of the issues, and proposed mitigation steps. While the focus was on sponsors of therapies likely to be used in ZCC, it was recognised that other oncology sponsors may also offer relevant viewpoints. It was also recognised that such issues are not unique to the ZCC trial, but that this study provided a focal point for the discussions.

This process was supported by Medicines Australia's Oncology Industry Taskforce (OIT). The OIT represents most sponsors involved in oncology; through that group, discussions with the medical/clinical leaders were sought. The sponsor company input in this report is de-identified, collated and reported.

Following individual discussions, a roundtable event was convened to bring together the ZCC trial leaders and sponsor representatives. Draft recommendations were shared and discussed, which in turn led to the development of this report.

Issues identified by clinical leads

In the ZCC trial, the Multidisciplinary Tumour Board (MTB) makes recommendations of the appropriate therapies based on the mutational profile identified and informs the treating physician of this recommendation. These recommendations are mostly based on preclinical or clinical data in adult cancer or data in the same paediatric cancer type. The treating clinician then decides on the treatment and makes the request for access of the responsible sponsor.

ZCC trial leaders and clinicians emphasised that industry barriers were problematic and not well understood. They raised several key issues related to their efforts in accessing therapies for use in the ZCC trial, which are common across a variety of the cancers likely to be treated under this program. The reasons for uncertainties or challenges in access relate mainly to the fact that few therapies recommended by the MTB are approved for use in childhood cancer. Issues raised included inadequacy of data to enable a confident decision (with issues of dosing information), uncertainties in the timeline for drug access requests, cost of access, high extent of variability across industry responses, and complexities associated with drug combinations.

RECOMMENDATIONS

The following recommendations are based on discussions with both industry leaders, clinicians and trial leaders for the ZCC trial, including at a roundtable discussion in late 2019. These recommendations are unlikely to resolve all challenges associated with medicines access for individual patients, however, they are intended to ease the process of making a request for access, remove inefficiencies, and reduce time between patient readiness for treatment, access request and subsequent receipt of the medicine.

This section outlines the recommendations focused on prospective action steps, taken well before the patient diagnosis and consequent request for access. Some of these recommendations may not be feasibly executed for all situations or may occur at different timepoints. An emphasis is placed on doing as much as possible ahead of time, so that at the time of patient readiness for treatment, the process is as straight-forward as possible.

The action steps or recommendations are, broadly, to:

1) **Increase awareness** of the trial or initiative being undertaken
2) Seek early **engagement** between the sponsor and the trial leaders / clinicians seeking access
3) Navigate prospective **commitment** and share expectations
4) Collaborate to move through **decision-making** processes
5) Focus on patient **access**, follow through and follow up

Increased Awareness

Clarity on definitions – similarities and differences

Variable definitions exist for different terms used in single use access requests, particularly for the terms "single-use" and "compassionate access"; this creates confusion between trial leaders, clinicians, and sponsors. It is important to clarify these definitions early, as this may impact how and when the access decision is made, and the sponsor pathways used by the sponsor.

RECOMMENDATION 1

increased clarity and alignment on definitions in communications about the likely requests:

- Recognise the aponsors and trial leaders may have varying terms and different definitions for describing the drug access, therefore requiring early clarification and alignment on the nature of drug access request, including what is meant by "single-use" and " compassionate access" requests
- Specify whether the single-use access being sought is for treatment within trial-based settings

Industry awareness of likely access requests

Awareness of the ZCC trial was found to be low amongst companies. Relevant sponsor companies were also generally unaware of a potential future request or of their drug's inclusion on the ZCC potential molecular targets list. Furthermore, there was some confusion about whether the ZCC trial leaders or the lead clinicians were likely to request the specific drug for access. This possibly reflects the difference between a trial-based approach to securing access arrangements (often from the trial leads) and "compassionate access" (generally from the treating clinician). In the ZCC trial, awareness would be generated by the trial leaders, but the individual medicine requests would be made by the treating clinician.

Trial planning may benefit from early awareness and proactive engagement with relevant sponsors. Industry considered it would be helpful to know which multicentre trials were in play, and which sites and investigators may seek access.

RECOMMENDATION 2

Increased proactive awareness within industry of the trials likely to result in single use access requests:

- Trial leaders to develop and implement an awareness plan of the trial / program using industry association mechanisms to disseminate, at the point of trial proposal / funding confirmation
- Trial leaders to construct a simple summary (or link to same) about the study, including:
    - theoretical (druggable) targets for which drug access may be sought; and
    - the sites and treating clinicians involved in multicentre studies, to increase awareness of potential future access requestors
- Industry to determine and advise an appropriate method for disseminating this information to industry, thereby increasing awareness of the study within the industry

Efficiently disseminating information to create awareness via existing initiatives

In considering the development of appropriate materials to create trial awareness and facilitate information sharing between industry and clinicians about medicines access, it is also important to consider existing/ongoing initiatives without generating new channels. Such initiatives might be explored to house information about ZCC (or similar trials), contact details, and medicines access.

Medicines Australia, Medical Oncology Group Australia (MOGA) and Haematology Society Of Australia And New Zealand (HSANZ) are collectively working on an initiative, the Medicine access portal, that will allow clinicians to view a list of access programs available in Australia. The portal will launch with haematology/oncology products and will only be accessible by oncologists and haematologists, with the view of expanding to other disease areas in the future.[3]

It may also provide a pathway to identifying access for therapies that are approved, but not for the indication of interest. A link to the trial information, trial leaders, and contact persons for both industry and the trial(s) is worthy of exploration.

Other initiatives which facilitate a single point of information about trials might also be leveraged and similarly, other initiatives looking into compassionate access methods are also relevant.

[3] Products that can be entered onto the Medicine access portal include:
• For a medicine included on the Register (ARTG), only the indications which have been registered may be listed on the portal; if the registered product may be used for unapproved indications, the portal will direct the oncologist/haematologist to contact the sponsor in relation to compassionate access schemes; and
• For unregistered products (not included on the Register for any indication), the portal will allow a statement for indications for which a compassionate access program is available and direct the oncologist/haematologist to contact the sponsor.
Medicines Australia has accepted the legal advice provided by the Therapeutic Good Administration (TGA) that the Medicine access portal model as described is compliant with all relevant legislation, particularly the Therapeutic Goods Act (the Act). In addition, the medicine access portal meets the necessary compliance requirements for Medicines Australia Code of Conduct.
The Oncology Industry Taskforce has generously provided funding to build the website structure and portal. The Medicine access portal committee has selected a vendor after a competitive tendering process and are currently drafting a contract with the aim to start the build of the portal early next year.

RECOMMENDATION 3

Leverage existing initiatives for disseminating trial / program information and key contact points, that can be regularly updated:

- Consider role of recently approved Medicines Australia sponsored website highlighting access programs, including whether this is appropriate for listing a call for support.
- Leverage and apply the learnings and mechanisms already in train from the Medicines Australia initiative in identifying access programs in place and/or in identifying contact person(s).
- Consider role of other mechanisms and processes for creating greater awareness of studies - such as Clintrial.refer and "one-stop-shop" or clinical trial "front door" proposals in progress
- Industry to share insights based on other programs to facilitate appropriate means of providing trial information and key contact points

Regularly updating to progress

Sponsors indicated that it was challenging to independently locate up-to-date information about the trial, necessitating a request of the trial leaders. This approach creates inefficiencies for the trial leaders and risks a disparity in knowledge about the trial based on when the request was made and answered. Sponsors may also have reporting requirements about the status of the study (and future progress) and therefore require the most update to trial progress.

RECOMMENDATION 4

Trial leaders to establish a plan for regular briefing to industry about the trial, and construct appropriate trial summaries, including:

- the trial project plan, protocol changes, timing of updates and approach
- trial progress, including key milestones
- where possible, the retrospective examination of therapeutic recommendations (for example, which mutations were identified in which indication
- Industry to guide useful content, accessibility of information and appropriate mechanisms for distribution, and leverage of industry mechanisms to distribute updates

Increasing awareness of existing programs and trials

Trial leaders indicated that they did not always know about the types of existing programs or trials for a particular medicine. The rationale for sponsors to leverage existing trials stems mainly from the potential for learning and sharing patient outcomes (which currently, cannot easily be served through compassionate supply). This is not always possible since it is relatively rare that an appropriate existing trial is available at the time of patient need, or the existing trial may have features that preclude the required alignment for patient transfer. There is a need to ensure a common understanding and awareness of parallel (or competing) trials.

This has been raised previously in the context of patient access programs and is being addressed by MOGA and HSANZ in conjunction with Medicines Australia with an intended website to publish the existence of relevant programs (see earlier 2.1.3). As before, it is hoped that this existing initiative might be leveraged to publish programs of relevance to trials like the ZCC program. Similarly, there are existing mechanisms available that publish the existence of planned, ongoing and completed trials, and these too might be leveraged to increase knowledge about existing trials.

Sponsors may also have website portals for a medicine, through which all drug requests are to be channelled into the company, that were then followed up by the relevant person within the local affiliate. However, where portals do exist, definitions and eligibility if occurring within a trial (like ZCC) are unclear.

RECOMMENDATION 5

For each medicine likely to be sought, trial leaders must stay aware of other trials and sponsor programs that may enable a more acceptable path to single use access:

- Engage with sponsors on existing programs or plans for programs for systemic patient access requests, including whether the eligibility will (or could) match the likely requests
- Leverage of existing programs where possible, while also enabling links to sponsors where further information or clarity can be sought.
- Sponsors to check if their portals allow for identification of the ZCC trial as a trial (or similarly designed studies), while enabling request for single use access.
- Sponsors identifying appropriate trials that could "sit alongside" the (ZCC) trial or become the sole preferred means of providing single use access to drug identified for treatment.
- Trial leaders to proactively discuss, identify and potentially contract to transfer patients to trials agreed as optimal or preferred path to drug access
- Trial leaders to proactively communicate with all investigating clinicians if parallel trials are identified as the preferred path to drug access.
- Local leaders to leverage the international initiatives that encourage paediatric trials being done, by engaging with local sponsor affiliates to seek involvement in same.
- Establish where a register of access programs (such as those developed by Medicines Australia / MOGA/HSANZ) exist and whether patient access for a trial might be delivered through that existing mechanism, based on its eligibility criteria, and
- Determine if an access program could be modified to enable access through this path

Engagement

Earlier engagement between industry and trial leaders

At times, sponsor engagement begins just prior to access requests. Sponsors noted the opportunities associated with earlier engagement (before patient access requests arise). Therefore, there is a need to proactively communicate an industry-wide message about the trial, its goals, and the expectation that medicine requests will be forthcoming.

Sponsor suggestions referred to the need for an identified "kick-off point" where it was clear that the trial leaders were ready to engage with sponsors regarding medicines access. This could take the form of the trial leaders issuing a "call for support". This would work for trial-based medicines access requests, but there is a need to consider how non-trial based requests for access would also be called upon.

Existing compliance rules may prevent sponsors from initiating discussions with trial leaders following publication of the trial protocol; therefore, sponsors are reliant on the trial leaders to make the first contact. If a call for support is issued, this might be a sufficient trigger for the sponsor to reach out, having received the request to do so.

Furthermore, sponsors require detailed information regarding which of their medicines might be included for potential requests and which mutations may be identified in the study. There is a need for communication about the molecular targets, the identified target classes of agents (if possible) based either on biological rationale or insights gleaned from prior study and a summary of available evidence relating to that target, indication and molecule. Sponsors indicated that this needed to be identified and communicated by the time of protocol finalisation.

RECOMMENDATION 6

Increase earlier engagement steps between industry and trial leaders:

- Trial leaders publishing a call for industry support, or expression of interest, with reliable mechanisms to communicate with all (potential) industry sponsors.
- Leverage existing on-line mechanisms for communication between clinicians and sponsors, including potentially housing a link to the relevant protocol and relevant, updated information about the trial timelines.
- Industry to use this "call for support" to kick-off due diligence required, and to convey any intent to agree/not agree to participate in the study.
- Consider compliance with rules of engagement, identify acceptable mechanism that allows sponsors to engage in discussions on future possibilities for access should the molecular target be identified.
- Provide earlier and greater clarity on the potential medicines that may be sought for single use approval, by at least at the time of protocol finalisation, with trial leaders publishing and prospectively engaging with sponsors on the individual medicines likely to be sought, based on insights and evidence available. Trial leaders need to provide summaries of relevant evidence to the utilisation of the potential medicine for a given target/indication
- Trial leaders to consider mapping out the different molecular subtypes expected from testing (or summarise based on what is learned) to estimate the incidence of each, thereby helping companies plan appropriate access pathways.

Awareness of who to engage with to request access to drug

It is not always clear with whom the trial leaders should initially engage in each company, what the role of the local company is, and how to maintain connections. Having a local champion within the sponsor company can aid the timeliness of internal processes. The role of the local champion was highlighted by several sponsors, as being the local point of contact who would navigate the various "behind the scenes" processes required to deliver both a decision and the drug access.

RECOMMENDATION 7

Sponsors to provide a single point of contact for all requests for medicines access:

- prospective identification and publication of a single contact person or portal that enables the requestor to easily identify the local champion for single use or compassionate requests, and if different, the champion for particular trials
- Medicines Australia (and possibly AusBiotech) to consider including a provision to publish contact points on its latest website update or links to appropriate websites that identify the contact points for compassionate use requests, and be accountable for keeping it up to date

Identifying the range of potential pathways for medicine access

It is crucial to have an early understanding of the pathway most suited to securing access to the relevant medicine. Early engagement with the sponsors of relevant agents will save time and enable understanding of the range of options that need to be considered in the timelines and design of the study.

Different sponsors may seek different pathways, depending on the drug's stage and status. The types of pathways generally fall into one of the following pathways, noting that for the ZCC trial patients at least, the access requested is generally for single use (i.e., access for a single patient):

a) Existing trials (including awareness of such trials, and potential roll-over of patients into these)

b) ISRs [4](with contracted arrangements customised for the trial)

c) Compassionate access for single use provision of medicine – generally unapproved medicines

d) Patient access programs (often for approved, non-reimbursed uses where sponsor has existing access program to cover a number of patients)

RECOMMENDATION 8

Engage with relevant sponsors to build awareness of the relationship between the protocol design and what this means for feasibility of pathways:

- Agree circumstances under which compassionate access pathways can be used (or not used)
- Ensure that the trial design considers (and potentially incorporates) aspects needed to ensure patient access pathways
- Note range of pathways likely to be needed and include these in trial preparations (including timelines).

Identify and progress Investigator sponsored research (ISRs) agreements

ISRs generally require a contractual agreement between the sponsor and the lead investigator(s) institution(s) and can take time to initiate the request, gain approval (generally involving global viewpoints and decision-makers), and implement. While ISRs may be an appropriate pathway to achieve medicines access, and for some sponsors may be the only legitimate pathway, the time taken may be extensive unless a customised ISR is agreed with every sponsor. Sponsors also noted that for a trial like the ZCC trial, this had implications for processing time at the start and potentially throughout, since adjustments may be required to budget, ethics, consents, and other site-specific content per site.

RECOMMENDATION 9

Trial leaders to proactively identify and progress ISR agreements where needed as a path to access, by:

- Proactive identification of the likely drug access pathway through ISR, and seeking early resolution to contractual and other processes before the trial begins

Sponsors to proactively give guidance to trial leaders if the ISR is the only identified means to drug access.

Awareness of factors impacting decision-making

Factors impacting decision-making for drug requests were relatively consistent, but varied depending on the status of the medicine, acceptable level of evidence, and role and consistency with pathways already determined. Before making recommendations on how to best navigate the decision-making process, sponsors suggested that overall clarity on the types of aspects to affect decision-making would enhance overall understanding.

Sponsors were all very clear on who is responsible for the internal processes of communicating with global teams, and what role the local company plays. The driver of the process is primarily the pathway deemed most appropriate, followed by other key decision factors. Thereafter, the sponsors were very clearly able to describe the processes and systems in place to handle individual requests. The variability between companies in handling the requests varied significantly, in terms of pathway definitions and other factors. Nonetheless, once established, sponsors indicated

[4] Investigator Sponsored Research. The acronym used by sponsors can vary. Generally used for studies proposed by trial leaders where there is a request for support for the study, and usually sponsors are not involved in the trial conduct. Support may be provision of drug, financial support, and/or medical information support.

that only a change in status of the drug (like regulatory approval being achieved) would change the processes per drug, engendering a level of reliability and predictability per company about the approach needed for that drug.

RECOMMENDATION 10

Increase knowledge about factors affecting decisions to grant medicine access:

- Ensure sponsor knowledge and awareness of decision-making influences is shared, and
- Communicate and acknowledge the role of the medicine's development status, and understand any impact in decision-making over the same term of the trial or period in which access will be sought

Commitment

Aligning on expectations

Sponsors indicated that many current requests for medicines access are made upon patient diagnosis. Sponsor feedback suggested that under certain situations, steps might be taken in anticipation of future patient access requests. Sponsors noted the risk to be high in a trial like the ZCC trial, where only one or two patients might be expected per medicine. This risk in taking proactive steps was considered worthwhile, if the pathway was subsequently quicker and easier upon patient identification. Alignment on expectations was considered essential, to balance risk and benefits of early efforts.

RECOMMENDATION 11

Align expectations on what steps can be achieved ahead of individual patient access requests:

- Clinicians and sponsors to engage and agree which steps of the pathway might be enacted ahead of time, and
- Align on expectations regarding actions to be taken to balance the risk of effort not realised versus benefits of readiness

Enacting agreed proactive steps and making commitments

ISRs and trial contracts take time to enact as they are generally bespoke for the relevant trial use, vary across companies, and involve third parties and processes such as ethics reviews, legal reviews and compliance reviews. Moreover, ISRs often require global inputs and decisions, which can also take time. Although significant effort is required to make ISR commitments ahead of time, patient access is significantly enhanced if these arrangements are in place. For some sponsors, ISRs are the only legitimate pathway for access for certain medicines; having these in place generates confidence that if that medicine were later determined to have potential utility, access would be feasible.

Sponsors can also proactively secure the medicine supply. For many products still in development, supply is fully allocated to sponsored studies, leaving limited supply for compassionate or single use. Seeking allocations, even for a few patients, is a significant task in this context.

Ensuring clarity about the decision making process is critical and can be undertaken ahead of patient identification. Many sponsors will do this in any respect, in anticipation of patient access requests; nonetheless clarity and communication about the decision-making will aid subsequent processes.

RECOMMENDATION 12

Enact steps to secure the likely pathway before patients enter the trial:

- Discuss and agree ISRs or other contractual arrangements
- Sponsors to seek allocation of product and clarity regarding supply chain needs
- Sponsors assure of the decision-making criteria and influencing factors
- Ensure clarity of same with clinicians and trial leaders

Establishing the evidence base for medicine use

For the ZCC trial, and others like it, sponsor companies frequently hold the most evidence supporting their medicine, which may be additional to that published in the scientific literature. This evidence may include the molecular target identified, therefore providing a biological rationale for the choice. Dosing information for unapproved paediatric therapies, however, is frequently scant or non-existent.

It was suggested that a prospective request for evidence could be made by the trial leaders of each sponsor to potentially save time, noting appropriate confidentiality provisions are in place. The sponsor and investigator could prospectively collate the evidence of the potential drugs beforehand and make the drug requests accordingly. Sponsors would then have the time to seek globally-held evidence and have information readily available for the potential request. While noting that this effort may be incurred without any request ever being made (wasted effort), it may be time-saving for any identified patients.

Providing information proactively to a clinician for unapproved therapies is not compliant to internal and external rules. The concern is that to do so would be akin to promoting an unapproved therapy. This means that the request for information that might support the drug request must be made by the clinician and, only then, may the sponsor respond; however, this approach is time consuming.

RECOMMENDATION 13

Ensure early establishment of the evidence base for prescribing of and seeking access to medicines likely to be sought:

- trial leaders to make specific request for relevant evidence in support of the medicine's use in the likely population, including molecular targets and postulated drugs having potential utility and/or subject to future potential requests.
- trial leaders and sponsors to discuss the form of the request that would enable sponsor companies to compliantly respond to that request, and would outline a request not only for the evidence to date, but evidence that would support that drugs' use in the trial.
- sponsors to support prospective collation of the evidence to support single use access under the trial conditions, including "at risk" collection of information.
- Trial leaders and sponsors to identify gaps in knowledge and where possible, sponsors to seek early provision of that information to the trial leaders.

Consistency in communication about the trial

Currently, sponsors indicate that there is significant variability of information provided to the company about the purpose of the request or more specifically, the information about the trial. Sponsors indicated that it was critical that each access request for the same study was accompanied by the same materials. This is particularly important when there are multiple clinicians involved in making the requests of companies. Consistency in information about the trial or intended use would aim to reduce the duplicative work in reviewing disparate information, or that prior agreements or precedents made to supply within the trial would be overlooked, notwithstanding that access was being sought under the same or similar conditions.

Suggestions were made for inclusions to an "information package" that would routinely be supplied by the clinician in accompanying a medicine access request. This is in addition to any evidence that would support the use of that particular drug.

- If under a trial, provide the primary hypothesis of the study, and the drug's use in addressing that primary hypothesis
- Who are the relevant primary treating oncologists
- Information about what happens if the request is granted, in such areas as:
  - Adverse event management, PV and reporting – confirmation of these practices
  - Any expectations about funding and responsible party to procurement processes
  - Whether and what would be communicated about individual patient outcomes (and when)
  - What would be communicated about the ZCC trial progress
  - Who would own the data with respect to accessing it for purposes of future indications or publications
  - Where to seek future updates and progress reports

RECOMMENDATION 14

Ensure consistency of information about the trial is provided to all sponsors from which access is to be sought:

- Trial leaders to consider development of a "information package" that will accompany every access request, regardless of medicine or sponsor
- Information package may include timing, handling of data, management of adverse effects, and likely number patients
- Information package could be shared with sponsors prior to trial start to use with internal discussions to pre-empt future access requests

Sponsor expectations of requestor's obligations at the time of making the request

Sponsors and trial leaders indicate that clarity on expectations for timing of the supply at the point of access request, and throughout the trial or program, is critical. The clinician should anticipate being asked to provide the timeline of the treatment initiation and expected completion. Sponsors were highly concerned to ensure that realistic expectations were both given to and received from trial leaders before committing to proceed with the initial processes. There is an emphasis on ongoing communication, as this also aids prompt and accurate communications with the patient.

Sponsors expect that clinicians also commit to quality use of medicines, including reporting of adverse effects, ethics approvals, and adherence to stated protocols for treatment. This was a stated condition of supply for some, but not always articulated at the point of request. For trials, the expectations are clearly laid out in the protocol, including provision of supply in the event of continued response following trial closure. For systemic access programs (e.g. PAP / EAPs), the expectations are outlined during the process of registration, including the relevant timing to provision of access.

It is important to ensure that expectations for ongoing supply are communicated, including what occurs if the patient ceases treatment and if the patient requires longer than envisaged supply. At the time of access request, it is also important to reiterate where there is an intersection with other trials or programs, and what happens in those circumstances – including rollover, ethics, collection of data and sharing of de-identified patient outcomes.

RECOMMENDATION 15

Ensure clarity about the commitments made at the point of access request and ensure ongoing alignment of expectations:

- Consider usual commitments to quality use of medicines, including adverse event reporting
- Communicate if treatment will be in context of a clinical trial
- Communicate relevance of adjacent trials and programs
- Ensure that any intended collection, collation, reporting and accessibility of patient outcome data is transparent and aligned
- Clinicians and relevant sponsor liaison to establish seamless communication channel to allow efficient updates
- Clinicians and sponsor liaison ensure clarity about expectations, including timelines and factors affecting decisions, and make adjustments as necessary to improve quick resolution
- After the request is made, sponsor and clinician to provide timely updates per patient request, and agree appropriate changes to process to inform future requests.

Seek pre-approval of medicine access

Given the various factors in the decision-making process, and the variability across different drugs, sponsors and pathways, it may be worthwhile attempting an "approval in principle", which could save up to one month in time according to one sponsor. This may not always be possible, but some sponsors indicated that under certain conditions, such pre-approvals might be considered.

The sponsor might reasonably be able to navigate many of the supply and logistics constraints ahead of time, based on the expected number of patients, timing of the study and likely quantity per patient. Such "approvals-in-principle" would need to be time-bound (not open ended). This would alleviate some of the uncertainty in both the timing and ability to achieve medicine access, and importantly is resolved before the patient has entered the study or is otherwise determined to potentially benefit from the medicine. Further, a confidence in this ability to secure access provides confidence in the ability of the trial to deliver an answer to its hypothesis.

RECOMMENDATION 16

Sponsors to consider whether an "approval-in-principle" could be established based on trial leaders expert advice regarding number of patients, timing of the study and likely drug quantity:
Explore the concept of pre-approval commitment to access:

- Sponsors to provide insights to what would be required to enable pre-approvals
- Sponsors to advise the benefits regarding time and predictability if pre-approvals could be secured
- Sponsors and trial leaders to continue discussions for optimising pre-approval options.

Access Provision

Communicating the decision and relevant context

Sponsors do not routinely convey the detailed rationale for an access decision back to the trial leads or the treating oncologists, which limits the learnings that can be applied for subsequent requests. In the case of negative decisions (or those that take too long), this may inappropriately discourage future requests from being made on an assumption of the process being too hard, or unlikely to be positive.

RECOMMENDATION 17

Facilitate continuous improvements and greater awareness of decision-making processes, by sponsor communication of the rationale for decision

Securing supply

Supply is generally handled behind the scenes and can be opaque to both trial leaders and requesting clinicians. A positive decision to grant single use access does not confer automatic receipt of the medicine requested; supply will not be available within the country for many unapproved medicines and the supply chain may not be established for some medicines. Furthermore, there is often competition between markets for unapproved medicines, with company trials dominating allocations. Sponsors may be able to initiate some steps ahead of the individual patient request, such as securing an allocation or validating the quality assurance processes. Even where this is feasible, sponsors indicated that the physical supply would often await positive decision to grant access before it was released.

RECOMMENDATION 18

Gain earliest insights to supply requirements:

- Sponsors to seek allocations for supply of Australian patients if possible, and communicate likelihood of, and timelines for, securing allocations and physical supply

Costs of supply

Costs associated with supply of single use medicines are highly dependent on the status of its approval. On-forwarding of costs of supply is unusual for unapproved medicines. Supply for approved medicines is unlikely to be distinct from other (non-trial) uses, and the sponsor will not usually be aware of such use for single patient access. Institutions sometimes cover the costs of medicine supply. Some sponsor programs do include an administrative charge. For some ISRs and trials, the sponsor may be asked as part of the contractual obligations to supply the medicine as a contribution to the conduct of the study.

RECOMMENDATION 19

Supply costs should be clearly articulated and agreed:

- Include costs of supply in initial discussions and agreements with the sponsor, for example in ISR contracts
- Otherwise, where costs will be applied on an individual patient basis, the funding source should be pre-determined and agreed, and if relevant, included in study budgets.

Maintaining relationships to facilitate learning

To date, very few sponsors expect that any data on patient outcomes would be collected, conveyed and reported following single use access (except for adverse events), or information around the timeframes of supply. This limits learning by the clinical community and the sponsor about the safety and efficacy of the therapy in individuals, or the compassionate supply process, and also limits opportunities for improvements in process or to inform future single use requests. There is significant community discussion about how real world evidence is or can be used in facilitating a path to (full) access, and the role of single use or compassionate access in contributing to this data.

In the case of adverse event reporting, sponsors expressed concerns about duplications or omissions in reporting. Since reporting to the TGA can result in duplicative reports (both clinicians and sponsors have obligations to report),

sponsors commented that it would be helpful to link any adverse events to a particular trial or described circumstances, to understand the context for the event and identify duplications or omissions.

RECOMMENDATION 20

Facilitate and maximise opportunities to learn:

- Maintain the relationships between trial leaders and sponsors and consider best practices for sharing individual case studies and/or improvements in processes
- Ensure clarity in adverse event reporting to avoid duplications and omissions

Process for optimising outcomes

Next steps include ensuring there is a process in place to discuss and agree which of the included recommendations to take forward, and for those, to develop a collaborative implementation plan to optimise the outcomes.

Enabling progression of the project and its outcomes

Discussions between the trial leaders, clinicians and industry sponsors suggested follow up and follow through of the recommendations were important to maximise the potential to improve single use access. Accountability, ownership, regular follow ups, and a willingness to share with others and gain additional insights were all raised in discussions. Without dedicated follow up and follow through, the recommendations risk languishing and the opportunity for improving patient access is diminished.

RECOMMENDATION 21

Establish future collaborative discussions and accountable leaders to continue dialogue and implement recommendations:

- Convene an industry sub-group with responsibilities for single use access approval processes within companies, to discuss and align on feasible recommendations
- Convene regular discussions with trial leaders
- Trial leaders, clinicians and sponsors consider means of communication and dissemination of the agreed recommendations (and report)
- Celebrate the collaborative effort to date, designed to facilitate medicines access where possible and therefore improve patient access
- Continue advocating implementation of agreed recommendations with others beyond those originally involved in the ZCC discussions.

Securing appropriate fora for ongoing dialogue

As with all reports recommending change, improvements will rely upon support, agreement, and execution of recommendations. Medicines Australia and the ZCC trial group have established an appropriate channel for ongoing dialogue, which may also enable dedicated effort towards incremental changes leading to overall improvement.

Equally important will be the measurement of success, and if overall improvements are lacking, further dialogue and re-challenging recommendations will be required.

RECOMMENDATION 22

Ensure ongoing dialogue aimed at continuous improvement in the process:

- Industry to consider mechanisms for ongoing dialogue with other clinical groups, trial leaders
- Industry and clinical groups expand the discussion insights to ensure patient and consumer views are incorporated into future improvements

Clarifying and improving the role of single use in evidentiary profiles of unapproved uses

In programs or trials involving multiple agents conducted with multiple sponsors, it is not always clear if sponsors or other clinicians can access the case study data specific to a particular medicine, as opposed to overall results. It is currently unknown if sponsors can access the data that has been collected and how they might legitimately use that data to inform future trials.

The capacity to learn and inform future requests is limited when there are few patients; however, this may form the start of an evidence base or supplement other international efforts for real world evidence.

RECOMMENDATION 23

Explore ways for any collection of patient outcomes through single use:

- Understand the barriers to collation of patient outcomes when use occurs through compassionate access
- Consider means to ensure progress towards (or contribution to) long term patient access based on evidence (real world evidence)
- Ensure research efforts and patient outcomes collected are meaningful to patients and outcomes of interest are captured to then inform future patient decisions

Improving access to and number of paediatric studies

Given the aligned goal of increasing the number of paediatric trials in Australia, there is reason to be optimistic that this is achievable, through alignment with global programs and initiatives.

Global initiatives may have positive impacts on sponsor likelihood of conducting clinical trials in certain populations. There has been an incentive in the United States and Europe to encourage paediatric research (potential for extended intellectual property), and, more recently, the Research to Accelerate Cures and Equity (RACE) for Children Act may also have positive impacts. This underscores the importance of global initiatives as they impact sponsor decisions on development plans.

Given the international effort, it is expected and hoped that paediatric study numbers will increase. Local affiliates of sponsors conveyed their engagement in the above initiatives at the global level and considered it more likely that with the close network of paediatric centres in Australia, the trials being encouraged overseas might also be requested for Australian participation.

RECOMMENDATION 24

Explore ways to increase the number of paediatric trials in Australia:

- Leverage the paediatric clinical networks in Australia with international counterparts to remain at the forefront of research by seeking collaborations and participation in international studies,
- Use local champions within the local industry to advocate for paediatric trials to be brought to Australia.

Outstanding questions

This discussion with trial leaders and sponsors was predicated on the perception that improvements to single use drug access could be made through a better understanding of the industry challenges and decision-making processes. Few of the recommendations within require significant shifts in the processes currently being applied, but subject to sponsor and clinical views, may ease the pathways for drug access in some way.

A seminar to air these perspectives is planned, during which these recommendations can be discussed and, ideally, embraced and expanded for greater impact. Some of the outstanding questions to input to that seminar might include the following:

- Are clinicians confident to try to access an unapproved medicine? What is needed to aid this?
- What can be done to support the relevant request and navigate decision-making, both in a proactive manner, and at the time of patient identification?
- What recommendations for change are acceptable and can be made?
- Do we expect we can improve patient outcomes with this effort?
- For the future, what will change, as these sorts of studies or approaches become more common, including sponsors' own development plans related to a "mutational signal" rather than a specific tumour type.
- For the future, what needs to be done to increase patient access to non-sponsor (paediatric) trials?
- Can we measure the patient outcomes in a meaningful way, that can be collated or merged with other data sources to provide a more solid evidence base – or even evidence suitable for a path to access?

Implications for broader applications of single use patient access

During sponsor discussions, the issues raised were centred on the ZCC trial. However, many sponsors raised or acknowledged the value of developing and improving the interaction between trial leaders, clinicians and sponsors as this would have broader implications for single use patient access. Implications and learning was also acknowledged for:

- Genomic-based / mutational testing trials
- Future brain cancer trials
- Paediatric trials
- Compassionate or single use access more generally

ATTACHMENT 1: BRIEFING DOCUMENT PREFACING INDUSTRY DISCUSSIONS

Australian Brain Cancer Mission:

Barriers to drug access in clinical trials

A focus on the Zero Childhood Cancer (ZCC) national trial:

Seeking industry perspectives

Objective: To understand, communicate and propose mitigation strategies to address or overcome industry barriers to facilitating *identified*[5] drug access in the ZCC clinical trial.

Rationale: Cancer Australia and the Strategic Advisory Group have been advised that progress on one of its key supporting trials (ZCC) is (or may be) hampered by access to the therapies identified as being suitable candidates for patient treatment. In follow up with clinical researchers, it is recognised that this is not a unique situation to this trial; indeed addressing the barriers to drug access may aid future trials in brain cancer (or other conditions). It is also recognised that the issues regarding drug access are likely to multi-factorial, and that industry barriers were problematic but not well understood. Given the strong clinical need in brain cancer, there is likely to be strong motivation to overcome such barriers. To do so, there is a need for a better understanding of the industry barriers in drug access for trials, and to re-open collaborative dialogue to addressing the barriers at least for the ZCC trial.

Approach: to prospectively seek dialogue with individual companies in the pharmaceutical industry in Australia regarding their perspective on barriers, inter-relationships of the issues, and to uncover any proposed mitigation steps. The ZCC researchers will identify the most likely therapies being sought through the ZCC trial, as a starting point for discussions, although it is recognised that other (oncology) companies may also offer relevant viewpoints. As the industry representative on the Mission Strategic Advisory Group, Michelle Burke will seek individual discussions with key medical and/or clinical leads. The input will be de-identified, collated and reported, initially to a collaborative discussion group between the ZCC researchers and industry representatives (using their existing Oncology Industry Taskforce) and Cancer Australia, with the goal of correctly framing the issues, proposed agreed resolutions and plan of action.

Attached background information on the ZCC trial, potential areas for discussion.

[5] Identified and recommended by the ZCC trial Multidisciplinary Tumour Board

Background – why is the focus on the ZCC trial?

As a supporter of the Zero Childhood Cancer (ZCC) national clinical trial, the Australian Brain Cancer Mission's Strategic Advisory Board (ABCM SAG) is interested in the progress and outcomes of this trial. From time to time, Research Leaders and Trial clinicians provide updates to Cancer Australia (responsible for administering the Brain Cancer Mission) and ABCM SAG.

The Zero Childhood Cancer national clinical trial

In brief, the ZCC trial involves patients from across Australia, from paediatric centres expert in the treatment of children with cancer. Typically enrolling patients with the most aggressive types of cancer, the majority of patients enrolled were predicted to be, and have so far been found to be, brain cancer patients. The trial is expected to run until at least 2020, enrolling up to 400 children.

Upon diagnosis (and other suitable treatment including surgery), a tumour sample and a blood sample is taken and tested for mutations. Where possible, the extracted cancer cells may also be tested against a range of drugs (established panel) to inform the medicine choice. A Multidisciplinary Tumour Board makes recommendations to the patient's physician on appropriate treatment options.

At this point, a request may be made of the industry sponsor of the medicine. It is the processes from this request point that will be discussed.

Defining the problem

The ABCM SAG has been informed that, at times, the treatment of patients with medicines identified as being suitable for use has been impossible, delayed or not available. This issue is not unique to the ZCC trial, nor are the reasons for this likely to be unifactorial or simple. Nonetheless there is an enthusiastic response to the suggestion that the barriers to medicines access for the ZCC trial be investigated and that, where possible, mitigation strategies be identified and adopted.

(It is also suggested that where such mitigation strategies are embraced, that such processes, systems and approaches be considered for other similarly designed studies – notably those requiring mutational screening or genomic / phenomic assessment to refine the medicine choice – and accordingly that findings be transparent to researchers. For these reasons, industry participants might reasonably use other study learnings to inform the Mission: any knowledge or information aimed at improving or facilitating access is useful input).

It is noted that for some sponsor companies, discussions with the trial group have occurred and at least for some therapies, no access issues remain. In this case, successful strategies can be learned, shared and implemented. For others, the discussions have resulted in inclusion to the panel of targets tested, but the access to the therapies has been untested. For others still, there have been issues in building any relationship or establishing any access to either the standard for testing or to the therapy for paediatric use.

Potential discussion areas

Progress to date suggests that for a majority of patients, a potential "druggable target" has been able to be identified through the mechanisms described and a proportion of those targets have a developed medicine either approved or near approval (albeit usually only for other indications and/or for adult cancers). This project seeks to understand the barriers to access of these medicines, including (but not limited to) gaining clarity on the following issues:

- Improvements in communications between the research and clinical teams and the relevant company – extent to which access is impacted by inadequate information about key appropriate contact points and ability to reach them

- The processes by which the industry sponsor would handle the request may be complex, variable, and lengthy resulting in delays or an inability of the sponsor to accommodate the request
- There may be an issue of ability of either researchers or the industry sponsor to provide the necessary information (or commitments to information) which is either unknown or variable (for example, information about dosing, how adverse effects will be reported in the context of the study and communicated to regulatory authorities).

Given the ZCC trial has been underway for several months, and there are still reports of existing barriers to medicines access, it is appropriate that some effort be given to understanding these issues, developing suggestions for improvements and piloting or implementing these.

Understanding the issues as they relate to the ZCC trial is proposed to begin with understanding the industry experiences through recent case studies. The ZCC investigators have provided a list of potential therapies that either have or may be sought.

Discussions may have regard to the issues under different scenarios, namely:

- Where the therapy is not registered in Australia, nor is likely to be registered for this indication
- Where the therapy is not registered in Australia, but development plans for associated research (i.e. in adult patients) are planned or in progress
- Where the therapy is registered, but for a different indication and where reimbursement is absent
- Where the therapy is registered, but for a different indication in which it is reimbursed
- Where the therapy is registered and where the reimbursement would cover its use

By having discussions with individual relevant sponsors, the goal is to:

- Remove immediate barriers to access if they still exist
- Learn why the barrier arose, what preparations could have avoided the issue, what could be done differently
- Prospectively define and design what the ideal yet realistic processes might be to alleviate any real or perceived barriers to access the identified drugs
- In a de-identified way, make suggestions to the research team and industry sponsors regarding potential improvements, potentially at a joint discussion across industry and the ZCC team

It is reasonable to believe that any barriers and/or issues identified are not unique to the ZCC trial, and so an additional goal may be to:

- Make available any recommendations or findings to the broader researcher community about engagement with industry on trials of similar nature

ATTACHMENT 2: COMMONLY RECOMMENDED CLASSES OF TARGETED AGENTS

Supplied by Dr Peter Wejbora, Director, Research Development & Partnerships, Children's Cancer Institute

The Sydney Children's Cancer Institute, based on their experiences of the ZCC trial thus far, plus existing research and data, advised that there are four most commonly recommended classes of targeted agents. In line with their due diligence and investigation, they provide the classes of agents, the therapies within those classes and the relevant sponsors.

1. PI3K/mTOR inhibitors
    - Restricted to using mTORC1 inhibitors (access generally not a problem)
    - Newer inhibitors in this class, e.g. PIK3CA inhibitor, dual PI3K/MTOR inhibitors and dual MTORC1/2 inhibitors, are not accessible as they are experimental agents with no paediatric dose
        - Alpelisib (PIK3CA inhibitor; Novartis)
        - Dual PI3K/mTOR – GDC-0084 (Kazia Therapeutics; Aussie company), PQR620 (PIQUR Therapeutics)
        - Dual mTORC1/2 – sapanisertib (TAK228; Takeda Oncology), vistusertib (AZD2014, AstraZeneca)
2. MEK inhibitors
    - Trametinib (Novartis; paediatric dose available)
3. CDK4/6 inhibitors
    - Palbociclib (Pfizer; paediatric dose available)
    - Ribociclib (Novartis; paediatric dose available)
4. PARP inhibitors
    - Olaparib (AstraZeneca; no paediatric dose)
    - Talazoparib (Pfizer; paediatric dose available)
    - Velaparib (Abbvie; paediatric dose available)