Member Experiences in an Australian Translational Cancer Research Centre, Sydney Catalyst, and Their Understanding of Translational Research

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Abstract

Background: The experience of membership of multidisciplinary translational research collaborations (TRCs) is largely unreported. Sydney Catalyst Translational Cancer Research Centre is a multidisciplinary consortium of researchers and clinicians from institutions in metropolitan Sydney and regional New South Wales, Australia. This study aimed to qualitatively explore the experience of being a member of Sydney Catalyst and to identify members’ understanding of translational research and perceptions of the benefits of membership of a TRC.

Methods: Sydney Catalyst members were purposively sampled for heterogeneity over discipline and seniority and completed individual semi-structured interviews either face-to-face or by telephone. Interviews were audio-recorded, transcribed verbatim and analysed using thematic text analysis with an inductive, data-driven approach. Trochim’s program logic model was used as a comparator for emergent themes.

Results: Twenty-two members from across T1-3 translational research participated, including healthcare professionals, academic researchers and postgraduate students drawn from multiple biomedical, behavioural and clinical disciplines. Five superordinate themes were identified: 1) Exposure to and understanding of the nature of translational research; 2) Benefits of membership; 3) Participating as a member of a TRC; 4) The role and identity of a TRC; and, 5) Education as a vehicle for collaboration. Feedback about potential improvements to Sydney Catalyst was also received.

Conclusions: Membership in a cancer TRC was viewed as a highly positive experience that facilitates the acquisition of new knowledge beyond the boundaries of a member’s discipline, increases their visibility in the research community, broadens opportunities to network, collaborate, and access translational research funding. The findings suggest that further work is needed to better align clinicians’ and researchers’ understanding of the translational research continuum and the benefits of engaging in a translational research network that foster team science.

ABBREVIATIONS

TRC: Translational Research Collaborative; CINSW: Cancer Institute New South Wales; NSW: New South Wales; CTSA: Clinical and Translational Science Awards

INTRODUCTION

Translational research collaborations (TRCs) have emerged over the past three decades in areas such as science and technology, engineering, art and humanities, social sciences, medicine and healthcare [1-3]. In healthcare settings, such collaborations engage clinicians and researchers from diverse disciplines to address the gaps that exist between research knowledge and clinical practice. TRCs are reported to stimulate new insights into complex problems [4], increase research productivity [5], allow more rapid and broader dissemination of findings across multiple disciplines and produce outcomes with practical applications [6].

‘Team science’ is an emerging field of enquiry that is inclusive of TRCs, as it seeks to study the research efforts, processes and outcomes of large, complex initiatives [4,7]. These initiatives may comprise of many investigators working together on multiple projects that are closely related, but can be dispersed across

different locations (departments, institutions and geographic) [4,8]. As the barriers and facilitators to collaboration within TRCs have begun to be captured within team science research [4,9-12], so too has the development and adaptation of theoretical approaches to enable TCR evaluation [13]. Trochim and colleagues have proposed a comprehensive program logic model to evaluate large scientific research initiatives that incorporates constructs across the temporal groupings of short-term and intermediate markers, and long term outcomes (see Figure 1).

Barriers to collaboration within TRCs have been identified in primary health care, cancer, kidney disease, diabetes, cardio-vascular disease and mental health settings [14-19]. These barriers include conceptual and scientific differences, and differences in discipline-based values, theories, methods, terminologies and work styles that may inhibit integration of various disciplines. Practical barriers include limited published guidance about how to engage parties in collaborative efforts, cross-disciplinary project management challenges [6], as well as designing and conducting research across multiple geographical sites[14]. The enablers and benefits of collaborative research are also forthcoming and include active bridge-building across common divides in the professions and across researchers of different career stages or areas of interest. These enablers can potentially help to create larger, more resilient TRCs [20]. However, there is relatively little documented about the experiences of TRC members and what they identify as the factors that facilitate successful collaboration.

The experiences of TRC members and institutions have been evaluated using social network theory, visual mapping and through qualitative interviews and surveys [6,12, 21-24]. We identified four main studies about TRCs in the cancer setting [6,21,22,25]. Vogel and colleagues have highlighted the challenges, facilitators and broad impacts of participating in a team science initiative in cancer entitled TREC I (Transdisciplinary Research on Energetics and Cancer I) [6]. Their findings emphasize the beneficial attitudes and beliefs about team science, engaging in team processes and bridge-building activities, as well as funding initiatives that support team science. In a case study from Arizona, USA, member organizations reported an increased opportunity for knowledge sharing as a key benefit [21]. However, tangible outcomes, such as funding, and new tools or methods for solving common research problems were not being realized. Geography was the main barrier to collaboration and knowledge sharing efforts. Similarly, Long et al., found that individual researchers experienced barriers including that traditional funding schemes and reward systems do not recognize or reward collaborative research efforts in a manner similar to discipline-specific scientific initiatives. Individuals’ past professional relationships play a significant role in their participation in networks; they can also be disadvantaged by geographical remoteness relative to other research centres [22]. An analysis of secondary data sources from TREC I reported similar findings [25], about established professional relationships.

However, no qualitative studies have been conducted in the Australian setting, where research mechanisms and structures differ from the USA. Therefore, this qualitative study aimed to explore the experiences of individual members of one TRC, Sydney Catalyst, to understand their perceptions of translational research and the benefits of membership. The specific research question for the study was: ‘how do members (researchers, clinicians and postgraduate students) assess their experience of being part of a TRC in cancer?’ We used the program logic model developed by Trochim et al. [8], to evaluate the short-term and intermediate markers of success during the first three and half years of operation (see Figure 1).

![Figure 1: Trochim’s program logic model – a comprehensive conceptual model [8] The five key constructs are: Scientific Integration, Collaboration, Professional Validation, Communication and Health Impacts.](image-url)
METHODS
Context of the current study

In 2011, the Cancer Institute New South Wales (CINSW) called for expressions of interest to establish cancer TRCs in NSW, Australia’s most populated state of 7.5 million people. CINSW set four key objectives, which can be summarised as: 1) facilitate research to improve patient outcomes; 2) facilitate evidence into practice research; 3) develop formal governance structures to enable collaboration; and, 4) build capacity and leverage additional funding [26]. The CINSW adopted the Westfall model for translational research [27] (Figure 2).

Seven cancer TRCs were established, covering the state’s major teaching hospitals, research centres and universities. Sydney Catalyst commenced in July 2011 as a multidisciplinary and multi-institutional virtual consortium of researchers and clinicians from more than 20 member organisations spread across metropolitan Sydney and regional NSW [28]. Membership is open to cancer researchers, clinicians and interested postgraduate students.

Sydney Catalyst’s goals are to: 1) develop and implement a comprehensive ‘bench to bedside’ research program of integrating basic sciences, clinical trials and including individualized care in clinical research (T1/T2); 2) develop and implement a comprehensive ‘evidence to practice’ implementation science program (T2/T3); 3) build capacity and facilitate improved communication and collaboration across the consortium; and, 4) facilitate professional development, education and training [28].

Sydney Catalyst provides professional education activities, funding opportunities through post-graduate scholarships and pilot and seed funding, and research support such as assistance with finding collaborators. Regular member contact is supported via face-to-face events (e.g. seminars, scientific symposia) and electronic communication (e.g. newsletter and email bulletins about upcoming events, funding opportunities and highlighting members’ achievements).

Participants and procedure

Participants were a purposive sample of Sydney Catalyst members. Two researchers (NR and SY) identified members from all participating institutions and ensured that all career development stages were represented. Members were sent a personal email invitation seeking their participation; those who agreed to participate were emailed an information sheet and consent form to complete. Consenting participants’ home institution, career stage and research discipline were monitored by AW throughout the study duration to ensure a balanced sample.

Participants completed a demographic questionnaire and semi-structured interview, administered either face-to-face or by telephone, according to the participant’s preference. The interview questions addressed: 1) the impact of TRC membership on research collaborations, access to expertise, equipment and resources, 2) benefits of TRC membership, 3) the impact of TRC membership on knowledge and research practice, 4) views on the website and use of social media, and 5) the education program offered by the TRC. A copy of the interview schedule is included.

Figure 2 Westfall NIH Roadmap translational model [27].
in Appendix 1. Recruitment and interviews continued until data saturation was reached (no new themes). Interviews took an average of 36 minutes to complete (range 19-64 minutes). All interviews were audiotaped and professionally transcribed for analysis. Ethics approval was granted by The University of Sydney Human Research Ethics Committee (Project number 2014/566).

Analysis

The research team reviewed and interpreted the data using thematic text analysis with an inductive, data-driven approach managed with NVivo10 [29]. Transcripts were explored with respect to the five key areas covered in the interviews. Six transcripts were initially analysed by two researchers (AW, NR) to form a preliminary coding framework, which was applied to the remaining transcripts with additional discussion undertaken as necessary to refine codes and establish agreement. Through iterative reading, recurrent themes and illustrative examples were identified. Successive rounds of discussion and resolution of code names/definitions and emergent themes and review of coding procedures by investigators (PB, SY, DM) not directly involved in developing the coding framework ensured methodological rigor [30]. Themes were subsequently mapped to the program logic model [8].

RESULTS

Sydney Catalyst had 412 members when this study was conducted; these members reported their broad research areas as: basic science (44%); clinical medicine & science (31%); public health and health services research (18%); or, not reported (7%). Approximately one third (n=152, 37%) of Sydney Catalyst members (across broad research areas and across member organisations/groups) were approached to participate. Twenty-two members consented and were interviewed, representing approximately 14% of members approached and 5% of the total membership of Sydney Catalyst. Participant demographics are described in Table (1) and comparison data for members is presented where available. Participants’ mean age was 42 years (range 24-66 years) and the majorities were clinician-researchers (41%) who had been working in cancer research for less than ten years (50%). Participants were more likely to be from T2/3 areas than T1/2 (about half were from T2/3) when compared with the whole membership (two thirds nominate T1/2); however, the sample was broadly spread across the T1-2-3 translational areas and across career stage. About two thirds (63%) were members of other cancer TRCs or research centres in addition to being Sydney Catalyst members.

Five superordinate themes were identified: 1) Exposure to and understanding of the nature of translational research; 2) Benefits of membership; 3) Participating as a TRC member; 4) The role and identity of a TRC; and, 5) Education as a vehicle for collaboration. We describe the themes and map these to the constructs of the program logic [8].

Exposure to and understanding of the nature of translational research

Participants highlighted having exposure to, and gaining a greater understanding of, translational research as a primary outcome of their TRC membership. Some participants spoke of this as a transformative experience (see Table 2 for selected quotations). This theme maps to the scientific integration construct of the program logic, which incorporates elements of transdisciplinary integration, methods, and science and models [8].

When asked about their understanding of translational research processes, most members described a unidirectional approach in a continuum towards implementation; that is, findings from ‘lab’ settings are implemented into clinical practice. Few participants described a cyclical research process where problems identified in the clinical setting facilitate the discovery of further research questions, where interventions/studies addressing these problems are subsequently developed, and are then implemented in clinical practice.

There were considerable variations in members’ understanding of T1-T2-T3 definitions of translational research that were not consistent with the Westfall model (Figure 2). Most participants perceived divisions along traditional disciplinary lines rather than a continuum of translation. The most common conceptualisation was that T1 equated with basic science/ biomedical laboratory work, while T2 was clinical trials and T3 was inclusive of public health, psychosocial and nursing research.

Being engaged in a TRC elevated the prominence of translational research in some participants’ thought processes about how to conduct research. Some participants reported their changed perceptions of translational research having directly impacted on preparing research proposals and funding applications. Some members found it challenging to conceptualise how a focus on ‘translation to practice’ could be incorporated into their research activities, specifically in preparing funding applications. This appeared to be more common amongst basic biomedical focused researchers.

Membership benefits

Participants discussed the benefits of membership, particularly with regards to funding opportunities and establishing new collaborations (see Table 2 for quotes). This theme mapped to program logic constructs of collaboration and professional validation [8].

The main perceived benefits of membership related to collaboration; gaining exposure to other researchers, new ideas, new content, and different approaches to conducting research. Support and encouragement from other members was seen as beneficial. Some participants described this professional validation as an unexpected benefit of allowing individuals to build a research identity, a reputation and collaborative network that may otherwise be more challenging to attain independently.

Facilitating collaboration across the membership and research disciplines was perceived as a core TRC function. Some participants described successfully initiating new collaborations or strengthening existing ones. Some participants with less experience in conducting research described challenges with establishing collaborations; many lacked confidence in contacting potential collaborators and knowing how to negotiate roles and responsibilities across organisations. It was suggested that Sydney Catalyst act as a ‘match maker’ to help initiate researcher-
clincian collaborations. Participants with existing cross-disciplinary collaborations (surgical, nursing or psychosocial disciplines) placed less emphasis on this.

Funding opportunities were highlighted as unique and very helpful. This included a pilot and seed funding program and participants spoke about these opportunities being rare or non-existent in other research settings. This funding was seen as crucial for enabling preliminary work to be undertaken that could leverage larger grants in the future. It also aided professional validation for researchers without an established track record. Some described Sydney Catalyst funding as enabling participation in conferences or enabling access to essential study materials. Funding appeared to be of most benefit to junior researchers and those from traditionally unidisciplinary areas, including the basic sciences.

Junior researchers described networking experiences, such as presenting their work at regular symposia or meetings as a source of professional validation. This included an ‘unanticipated benefit’ of meeting members from other disciplines and directly interacting with cancer patients and carers. In particular, the latter resulted in thinking about the real-world impact that research outcomes can have on the lives of people diagnosed with cancer (Table 2).

**Participation and engagement in a TRC**

This theme captured participants’ views about what it means to participate and engage in a TRC (Table 3). Researchers who actively engaged and participated in Sydney Catalyst led activities reported greater benefit from their membership. This theme mapped to both communication and collaboration constructs in the logic model [8]. Sydney Catalyst’s communication strategy includes regular email bulletins and this was nominated by participants as an effective strategy for facilitating member participation. Members preferred this active outreach style over more passive strategies. Participants suggested that Sydney Catalyst proactively pursue new members within member organisations to enhance collaboration and communication. For some participants, new collaborations could not be directly attributed to their involvement in the TCR; this was emphasised by some mid-career and senior researchers. Such research leaders already had access to existing collaborations and had existing recognition as a scientist. They invariably nominated themselves as too busy to make use of the collaborative opportunities on offer.

**The role and identity of a TRC**

The theme about role and identity of a TRC reflects participants’ views that the focus on translation was the most unique element of Sydney Catalyst. This theme mapped to the scientific integration construct, but also demonstrated that participants were thinking about the intermediate to long-term health impacts of a TRC. Participants expressed the view that research translation should remain the central consideration in all TRC activities. Some cautioned against the TCR ‘trying to be all things to all people,’ as it risks wasting resources or replicating existing services, and potentially diluting the organisation’s core goals.

Several participants suggested that Sydney Catalyst could take a more active and visible role in advocating for the health impacts of research translation, promoting successes amongst members through greater activity in the press and social media. It was perceived that members’ research results would be of greater public discussion about road-blocks to implementing new interventions. There was some indication that participants perceived the organisation to be predominantly focussed on basic-biomedical research. However, they reported that there was a visible shift towards greater cross-disciplinary engagement with other disciplines (psycho-oncology, epidemiology, radiation physics and surgery) as time passed.

**Education as a vehicle for collaboration**

The final theme focused on education activities, with
Table 2: Selected quotes from Themes 1 and 2.

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<th>Theme 1: Exposure to and understanding of the nature of translational research</th>
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Table 3: Selected quotes from Themes 3 and 4 and 5.

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Quotes Theme 3: Participating as a member of a TRC

| **Quote (Qt)1** | “I’d say that really I joined because I wanted to do that in terms of to be able to link in to (Sydney) Catalyst and also it enabled me, in terms of applying for grants and things like that. You want to be part of a TRC...” (Participant) P020 |
| **Qt2** | I think the communication I find useful, that’s one of the big benefits. You see what’s going around... the newsletter’s probably the thing that prompts me... they’re informative.” P003 |
| **Qt3** | “Perhaps having a key contact person who you could email or telephone and say look I’m interested in a getting a proposal together, have you any ideas of who might be interested in it as well?” P011 |

Quotes for Theme 4: The Role and Identity of a TRC

| **Qt4** | “…I don’t think it has to do everything, I don’t really see the point in just reproducing something that you can already get on another website, like I would personally caution against just trying to [be all things to all people]” P008 |
| **Qt5** | “… it needs to advocate for translational science – I see it having a role not only in fostering relationships but advocating and lobbying... it needs stand up and strong for translational research.” P013 |
| **Qt6** | “The reason I probably haven’t engaged in the past as much is because I felt that it was rather biology-focused... they do have a very strong and prominent voice, but I’d like to see that change. So the positive is that openness to change. There’s also a very strong psych (psycho-oncology) side to Catalyst... I think it’s excellent, I think that’s the sort of thing we should raise our awareness of... I really recognise the importance of it.” P015 |

Quotes for Theme 5: Education as a vehicle for collaboration

| **Qt7** | “The [education] dinner meetings I found very useful... One of them was immunology in cancer. (It was) pitched at the right level. It’s very hard when there’s multidisciplinary people (presenting) but I think that makes people think hard about how they’re going to present. It was a good opportunity for questions, very non-threatening environment.” P003 |
| **Qt8** | “And I must say the [implementation] master class was very, very useful [for] spending the time focused on that and I found that very valuable.” P012 |
| **Qt9** | “I do think that concept of mentoring is a good one and there might be people who would want to be mentored and... that sort of senior/junior sort of link could be another way of trying to get people involved.” P006 |
members emphasizing a need for continued training about how to conduct translational research (see Table 3). This theme maps to the ‘training’ element within the collaboration construct of the program logic [8]. All participants reported valuing training opportunities in research translation. Regular education dinner series events were highlighted as a vehicle for learning about translational research. Several participants strongly identified the need for more training in T3 implementation research, particularly scientific methods and models, and case studies that demonstrate how to conceptualise the ‘real-world’ aspects of research for grant applications. Four participants suggested that TRCs could foster mentorship programs to pair junior and senior researchers. Opportunities for members to visit labs and clinical settings to improve exposure to novel research and clinical practice methods in different settings were also suggested.

**DISCUSSION**

This study aimed to explore how Sydney Catalyst TRC members (researchers, clinicians and postgraduate students) assessed their experience of being part of a TRC in cancer, focused on the first 3.5 years of operation. Five themes were identified from conducting qualitative interviews with 22 members. We used Trochim’s program logic model to interpret findings across constructs for the short and intermediate term [8]. We found that our themes mapped closely to the constructs in the program logic, with scientific integration, collaboration, communication, and professional validation being identified as part of the thematic analysis.

The logic model situates professional validation as an intermediate-term marker for TRCs. Our findings suggest that, in fact, professional validation was a short-term marker, as observed in our theme of ‘membership benefits’. Participants reported that exposure to clinicians and researchers from other disciplines was highly beneficial. Members placed significant value on the cross-discipline recognition that resulted from presenting at Sydney Catalyst symposia or other events. In particular, junior researchers reported the benefits of professional engagement in Sydney Catalyst in the following ways: making unexpected connections with other researchers outside their discipline; receiving feedback on their research presentations; and, gaining greater visibility in the research community through presenting their work.

The program logic posits publications as a key facilitative mechanism in the intermediate term. Our findings provide new insights into the role that funding plays in the short-term markers of TRC success. The program logic could therefore be adapted to include this construct. Sydney Catalyst provided funding of approximately AUD$0.9M through 14 pilot and seed grants and 16 PhD scholarships in its first three and half years of operation [31]. This role of awarding funds to translational research projects has been at the core of Our TRC success. Such funding may help to overcome the barriers described by individual researchers in previous research about collaborative research efforts [22]. This provision of funds to TRC members has proven to be similarly successful for Harvard Catalyst, whose ‘open innovation process’ sought grant applicants to address all research stages of Type 1 diabetes [32].

Our findings suggest that members identify the unique element of a TRC’s identity as focusing on research translation, which should remain the central consideration in its activities. Some participants cautioned against duplication of efforts and that the TRC should not try to be ‘all things to all members.’ Rather, the construct of scientific integration is core to TRC efforts and facilitated the acquisition of new knowledge outside members’ core discipline. This suggests that continual support from a central mechanism is needed to facilitate establishment of a new TRC. This central mechanism (in the case of Sydney Catalyst) is a core team of research fellows and management who promote opportunities to explore new models of cross-disciplinary research. It is through such a mechanism that communication and collaboration can enable a TRC’s promise to be delivered.

Some participants spoke about membership as being a transformative experience with intangible benefits including collegial encouragement and greater confidence as a researcher. This was particularly the case for more junior clinicians and researchers. Participants who were more senior in their career found it difficult to attribute new collaborations directly to their involvement in Sydney Catalyst due to their pre-existing connections and experience, though this did not appear to diminish their positivity towards the TRC in cancer. This challenge of attributing outcomes to the TRC also perhaps reflects a wider challenge for international evaluators of TCRs [33]. Of note, since 2012 multiple groups have published clinical research process metrics, and applied them to evaluation of translational research including in Australia, in single institutions in the USA [34,35] and at all NIH Clinical and Translational Science Awards (CTSA) program institutions in the UK [36,37].

Participants advocated for Sydney Catalyst to take on an active role in introducing members across disciplines to one another and provide guidance in negotiating roles and responsibilities in resultant collaborations. Sydney Catalyst has facilitated such introductions since inception and recently a ‘matchmaker’ service was promoted at an international conference at which Sydney Catalyst was a sponsor, receiving a positive response.

Members’ understanding of translational research varied considerably. This is not surprising given the multiple definitions and models of translational research in the literature [27,38-42]. We noted the inconsistency in members’ understanding, with many viewing divisions along lines of research disciplines, where T1 is viewed as basic/biomedical lab work, T2 as clinical trials, T3 as psychosocial/nursing research, rather than stages in a translation continuum. Few participants identified a cyclical model of translational research whereby clinical problems are fed back to the discovery setting to develop and evaluate solutions. When prompted, all remarked that this was indeed an important component of translational research. Our findings suggest that bringing researchers and clinicians together to create definitions of how ‘science and models’ and ‘methods’ operate in a collaborative endeavor need constant efforts to engage in dialogue and communication. A broadened understanding of translational research was evident for some members, particularly in basic biomedical research, extending their research thought processes beyond their individual area of expertise to include considerations about patient care.
Some studies suggest that scientific research teams have become more dispersed geographically and across multiple universities [8,43,44]. In the past 20 years, the spread of the internet and other virtual platforms such as video-conferencing, have reduced the negative impact of geography on these collaborations [45]. The importance of developing strong research collaborations to ensure translational research has also been described in other settings [46]. Our findings did not reveal any significant barriers due to geography. However, our sample included only a small number of participants from outside central Sydney. Research with regionally-based researchers about the barriers and facilitators to TRC participation could be pursued in the future.

Limitations

A purposive sampling strategy was used to identify potential participants and views expressed may not be representative of all Sydney Catalyst members. It is possible that those who participated were more engaged in Sydney Catalyst overall than those who did not respond to recruitment emails. Several participants had received some form of funding or scholarship from Sydney Catalyst and may have had stronger motivation to participate or may have felt more positively about the impact on their membership. Every effort was made to ensure the final sample had broad representation across translational research areas, career stages, dedicated researchers and clinician-researchers and inclusion of students. Some participants gave critical feedback and suggestions for improvements, showing that the sample was not exclusively those with positive perceptions of Sydney Catalyst. Interpretation of the themes may be biased as all investigators involved in the design and conduct of this study are members of Sydney Catalyst. However, considerable effort was made to ensure that multiple investigators, both directly involved in and peripheral to the analysis, contributed to verification of the emergent themes.

CONCLUSION

Membership in the cancer TRC, Sydney Catalyst, was viewed as a highly positive experience. Membership could facilitate the acquisition of new knowledge beyond the boundaries of a member’s discipline, increase their visibility in the research community, and broaden opportunities to network and collaborate, and offer opportunities to apply for translational research funding. Our findings suggest that cancer TRCs are indeed worth pursuing for the goals of developing comprehensive translational research programs that span the continuum across T1-2-3 and to build capacity in researchers and clinicians to conduct such research in a cross-disciplinary setting. At a time when scientific problems have become increasingly complex and broad expertise must be harnessed through cross-disciplinary collaborations there is a great need for creating, developing and sustaining teams and networks [9], such as TRCs, to enable research findings to result in better patient outcomes.

AUTHORS’ CONTRIBUTIONS

SY proposed the original concept for this research. AW drafted the protocol in consultation with SY, NR and DM, and prepared all documentation for ethics approval. AW conducted all qualitative interviews. AW and NR developed the thematic content and analysed qualitative transcripts. Coding decisions and emergent themes were reviewed by PB, SY and DM. AW, NR, ML and SY all contributed to the review of literature. NR and SY wrote the manuscript. All authors and participated in revising drafts of the manuscript and approved the final manuscript.

ACKNOWLEDGEMENTS

We would like to thank the Sydney Catalyst members who participated in this project. We acknowledge the Sydney Catalyst Governing Council, particularly Professor John Simes, in supporting this research. Sydney Catalyst is funded by the Cancer Institute NSW. The Cancer Institute NSW did not contribute to the design, collection or analysis of the data and did not contribute in the decision to submit this manuscript for publication.

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