

Fertility Understanding through Registry and Evaluation (FUTuRE Fertility)

Australasian Oncofertility Registry Study

Study Protocol:

Version 1, dated 22 August 2014

**COLLABORATING ORGANISATIONS CANCER CENTRES**

Andrew Love Cancer Centre, VIC

Auckland City Hospital, NZ

Austin Hospital, VIC

Ballarat Health Services Base Hospital, VIC

Bendigo Health, VIC

Box Hill Hospital, VIC

Cabrini Health, VIC

Calvery Mater Hospital, NSW

Children's Hospital Westmead, NSW

Christchurch Public Hospital, NZ

Concord Hospital, NSW

Epworth Freemasons, VIC

Fiona Stanley Hospital, WA

Flinders Medical Centre, SA

Fremantle Hospital, WA

Gold Coast University Hospital, QLD

Hollywood Private Hospital, WA

John Hunter Hospital, NSW

Launceston General Hospital, TAS

Liverpool Hospital, NSW

Lyell McEwin Health Service, SA

Mater Adult Hospital, QLD

Mercy Hospital For Women, VIC

Mercy Private Hospital, VIC

Monash Medical, VIC

Port Augusta Hospital, SA

Prince of Wales Hospital, NSW

Princess Alexandra Hospital, QLD

Princess Alexandria Hospital, QLD

Princess Margaret Hospital, WA

Royal Adelaide Hospital, SA

Royal Brisbane and Women’s Hospital, QLD

Royal Children’s Hospital, Victoria

Royal Children’s Hospital Brisbane, QLD

Royal Darwin Hospital, NT

Royal Hobart Hospital, TAS

Royal Hospital for Women Sydney, NSW

Royal Melbourne Hospital, VIC

Royal North Shore Hospital, NSW

Royal Perth Hospital, WA

Royal Prince Alfred Hospital, NSW

Royal Women's Hospital, VIC

Sir Charles Gairdner Hospital, WA

St George Hospital, NSW

St John of God Murdoch Hospital, WA

St John of God Subiaco Hospital, WA

St Vincent's Hospital, NSW

St Vincents Private Hospital, NSW

St Vincents Private Hospital, Victoria

Starship Hospital Auckland, NZ

Sutherland Hospital, NSW

Sydney Children's Hospital, NSW

The Alfred Hospital, VIC

The Canberra Hospital, ACT

The Townsville Hospital, QLD

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Canberra Fertility Centre, ACT

City Fertility Centre Brisbane, QLD

City Fertility Centre Gold, QLD

City Fertility Centre Southside, QLD

Concept Fertility, WA

Concept Fertility Centre, WA

East Melbourne Andrology Unit, VIC

Eve Health South, QLD

Eve Health Spring, QLD

Fertility Associates Christchurch, NZ

Fertility Associates East Auckland, NZ

Fertility Associates Gisborne, NZ

Fertility Associates Hamilton, NZ

Fertility Associates Hawkes Bay, NZ

Fertility Associates Lower Hutt, NZ

Fertility Associates Nelson, NZ

Fertility Associates New Plymouth, NZ

Fertility Associates North Shore, NZ

Fertility Associates Palmerston North, NZ

Fertility Associates Queenstown Medical Centre, NZ

Fertility Associates Tauranga, NZ

Fertility Associates Wanganui, NZ

Fertility Associates Wellington, NZ

Fertility Associates West Auckland, NZ

Fertility Associates Whangarei, NZ

Fertility PLUS, NSW

Fertility Specialist South, NZ

Genea Canberra, ACT

Genea CBD, NSW

Genea Eastern Suburbs, NSW

Genea Inner West, NSW

Genea Newcastle, NSW

Genea North Shore, NSW

Genea North West, NSW

Genea Northern Beaches, NSW

Genea South West, NSW

Genea South West Liverpool, NSW

Genea Wollongong, NSW

Henderson Medical Centre

Hollywood Fertility Centre

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IVF Australia Inner West Burwood, NSW

IVF Australia North Shore, Greenwich, NSW

IVF Australia South City Hospital, Kogarah, NSW

IVF Australia Southern Sydney Miranda, NSW

IVF Australia Sydney City, NSW

IVF Australia Western City Liverpool, NSW

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Melbourne IVF Mount Waverley, VIC

Melbourne IVF Parkville, VIC

Melbourne IVF Werribee, VIC

Monash IVF Auckenflower, QLD

Monash IVF Clayton, VIC

Monash IVF Frankston, VIC

Monash IVF Geelong, VIC

Monash IVF Gold Coast, QLD

Monash IVF Hawthorn, VIC

Monash IVF Mildura, VIC

Monash IVF Richmond, VIC

Monash IVF Rockhampton, VIC

Monash IVF ST Albans, VIC

Monash IVF Townsville, NT

Next Generation Fertility, NSW

Parkville IVF Fertility Clinic, VIC

Peter MacCallum Cancer Centre, VIC

Queensland Fertility Group Cairns, QLD

Queensland Fertility Group Capalaba, QLD

Queensland Fertility Group Gold Coast, QLD

Queensland Fertility Group North Brisbane, QLD

Queensland Fertility Group South Bank, QLD

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Queensland Fertility Group Sunshine Coast, QLD

Queensland Fertility Group The Wesley, QLD

Repromed Adelaide, SA

Repromed Darwin, NT

Repromed Mawson lakes, SA

Repromed Mildura, VIC

Repromed Mount Barker, SA

Repromed Mount Gambier, SA

Repromed Port Lincoln, SA

Repromed PT Augusta, SA

St George Fertility Centre, NSW

Sydney IVF Canberra, ACT

Sydney IVF Illawarra, NSW

Sydney IVF Lauceston, TAS

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# 2 LIST OF ABBREVIATIONS

AOFR Australasian Oncofertility Registry

AOFC Australasian Oncofertility Consortium

ART Assisted Reproductive Therapies

AYA Adolescent Young Adult

CRA Clinical Research Associate

DOHA Department of Health and Aging

FP Fertility Preservation

GNRH Gonadotropin-releasing hormone agonists

IVF In Vitro Fertilisation

SOP Standard operating procedures

# Background and Overview

***Cancer diagnosis among children, adolescents and young adults in Australia***

Great advancements in oncological and haematological diagnosis and treatment have led to significant improvements in survival rates. The average 5-year survival rate for paediatric cancers (0-15 year olds) is 79% and the average 5-year survival rates for adolescent cancer (15-25 year olds) is 88%.[2-6](#_ENREF_2) As the number of cancer survivor’s increase, clinicians are turning their focus to the quality of survivorship. The loss of reproductive function is one of the most distressing and potentially adverse consequences of successful cancer treatment.[7](#_ENREF_7),[8](#_ENREF_8) There are a number of studies on infertility in adult patients that indicate that infertility is a major concern for patients and that potential and actual infertility affects the future quality of life of cancer survivors of reproductive age, which can lead to psychological distress.[7-9](#_ENREF_7) There is currently no data describing the timing and extent to which a cancer patient experiences fertility related mental health related problems and the benefits of interventions such as FP and counselling. AYA patients have difficulties recalling information about FP.[10](#_ENREF_10),[11](#_ENREF_11) Currently, there is little information available regarding an adolescents’ concern over their future fertility at the time of their cancer diagnosis. However, some studies reveal that adolescents have a strong desire to know how their fertility will be affected in the future.[2](#_ENREF_2),[12](#_ENREF_12) Cancers affecting the reproductive organs or the neuroendocrine axis are more likely to cause infertility, however it is also not uncommon for cancer patients to have reduced fertility potential because of the severity of their illness.[1](#_ENREF_1) The human ovary contains a fixed pool of primordial oocytes which declines with age, culminating in menopause at an average age of 50 years.[13](#_ENREF_13) Chemotherapy may deplete the ovarian reserve and cause premature menopause.[14](#_ENREF_14) In males spermatogenesis is extremely vulnerable to the damaging effects of chemotherapy and oligospermia or azoospermia may result.[1](#_ENREF_1),[15](#_ENREF_15),[16](#_ENREF_16) Alkylator chemotherapy agents such as Cyclophosphamide and Melphalan have side effects, which are known to cause infertility. However, little is known about the gonadotoxic (temporary or permanent damage to ovaries or testes) effects of new novel chemotherapy agents and or combination chemotherapy agents which may also result in an increased risk for infertility.[1](#_ENREF_1),[15-18](#_ENREF_15) Surgery or radiation therapy to the gonadal tissue, abdomen, pelvis, lower spine may also cause gonadal damage.

***Fertility Preservation (FP)*** Fertility preservation is the overarching term used for medical and surgical treatment to minimise the impact of cancer treatment on future fertility.[19](#_ENREF_19)The burden of cancer-related infertility is unknown in Australia and is an emerging potentially preventable clinical, public health and quality of life problem. The increasing number of children and young people surviving cancer may indeed be able to expect to plan for and have a family post cancer treatment. Fertility preservation options greatly depend on the patient’s age, sex, type of cancer treatment, cancer diagnosis, whether the patient has a partner at the time and the potential and involvement of gonadal tissue. Options include embryo and oocyte cryopreservation, ovarian tissue cryopreservation and ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists in females and sperm cryopreservation in males. Ovarian tissue cryopreservation is the only option currently offered to female childhood cancer patients.[20](#_ENREF_20) This tissue can be thawed and implanted after cancer treatment as an auto-graft or to a heterotopic site.[20-22](#_ENREF_20) Recent improvements with stimulation (for oocytes and embryo cryopreservation), grafting (for ovarian tissue) and freezing (gonadal tissue – sperm, eggs, embryos and ovarian tissue) have allowed for improved outcomes for ART following fertility preservation. Successful outcomes associated with ovarian cryopreservation have been reported in cancer patients; with 31 live births in adult cancer survivors and 2 paediatric cancer survivors experiencing pubertal induction (onset of puberty following ovarian tissue implantation).35-37 Clinicians are optimistic about the successful outcomes associated with this technique in adult patients but in children there is still the uncertainty surrounding live births.[23-25](#_ENREF_23) Cryopreservation of sperm and ovarian tissue can be performed successfully in adults provided a semen sample can be produced.[26](#_ENREF_26) Additionally, techniques for FP in pre-pubertal boys are limited to testicular tissue harvesting because the post meiotic sperm required for fertilization have not yet developed. It is hoped that in-vitro maturation techniques will provide an option for paediatric patients who have undergone testicular tissue harvesting, however these only experimental at this stage.[27](#_ENREF_27) Collection of longitudinal data will provide evidence-based outcomes for cryopreservation practices becoming standard practice in paediatric and AYA patients. Currently, there are no open paediatric or AYA research studies examining these successful outcomes.

***Barriers for Fertility Preservation*** Despite promising advances in technology in the past decade and an increasing number of patients seeking FP, patients are confronted with several challenges which include: lack of standardised guidelines and referral pathways; difference in or lack of specialist advice;[2](#_ENREF_2),[28](#_ENREF_28),[29](#_ENREF_29) FP costs and psychosocial distress;[30](#_ENREF_30) health literacy[30](#_ENREF_30)and ethical and legal issues. The research study will focus on children and young adults who have been diagnosed with cancer and may receive gonadotoxic cancer treatment. It will be undertaken under five broad and interlinked themes.

# Purpose of this Protocol

This study will provide evidence based data on risks and impact to short and longer term reproductive function after cancer treatment by cancer type as well as fertility outcomes associated with the use of new novel chemotherapy agents. The Australasian Oncofertility Registry will also offer an indepth

understanding into the use of stored gonadal tissue for conception following successful curative treatment for cancer.

Additionally, it will also highlight successful pregnancy outcomes (live births) and complications following uptake of ART post cancer treatment for cancer survivors Currently, there is inequitable access for uptake and utilisation of fertility preservation strategies mainly due to the barriers associated with inadequate referral pathways, access to fertility specialists and prohibitive costs associated with uptake of fertility preservation and assisted reproductive therapies. Barriers associated with fertility preservation uptake have a great impact on certain cancer patient cohorts; for example those cancer patients residing in lower socioeconomic areas, rural and remote areas and patients from minority immigrant and indigenous communities.

Fertility preservation outcomes generated from the Australasian Oncofertility Registry will benefit socioeconomic disadvantaged communities through improving clinical referral pathways between cancer and fertility specialists.

Additionally, outcomes from the Australasian Oncofertility Registry and Medicare will be used to perform a cost modelling health economics study. Long term outcomes associated with health economic modelling to forecast out-of-pocket fertility preservation costs to cancer survivors, will allow the research steering committee to consult with the Department of Health and Aging to address out-of-pocket procedures outlined in the Medicare Benefit Scheme.

As a direct consequence of this study, local cancer and fertility centres will form new links. An Australasian Oncofertility Consortium will be developed comprising of an interdisciplinary collaboration which will translate integral research findings from the project. The Oncofertility Consortium will provide opportunities to partner with European and American oncofertility consortiums in preclinical, clinical and population based international studies. This will lead to development of nationally consistent standardised practices, opportunities for sharing resources and training of relevant staff involved in fertility preservation. The Australasian Oncofertility Consortium will be committed to interdisciplinary innovation with other key professional groups involved in patient care. By fostering collaboration across our diverse network of clinicians and researchers, we endeavour to improve clinical practice.

# Aims of this Protocol

**THEMES 1&2: Referral and Uptake of FP**

**Aim:**

1.To establish a web based Australasian Oncofertility Registry that will collect information on the characteristics of children, adolescent and young adults and adults of childbearing age (under 45 years of age)who seek fertility preservation;

2.To monitor the rate of uptake of fertility preservation by cancer diagnosis, demographics and cancer type.

**THEME 3: FP potential following cancer treatment**

**Aim:**

1.To investigate and monitor the return of reproductive function (gynaecological and/or endocrine function) following cancer treatment and management;

2.To determine the risk for infertility by diagnosis and cancer treatment type following cancer therapy;

3.To estimate the timing of return to normal fertility function (gynaecological and/or endocrine function) following cancer therapy.

**THEME 4: ART following cancer treatment**

**Aim:**

1.To examine the proportion of cancer patients that have been treated with cancer treatment and have suboptimal or abnormal fertility.

2.To monitor the number of cancer patients treated for cancer that pursue and utilise ART post cancer treatment.

3.To monitor the success rate for ART (live births) in cancer survivors who pursue fertility preservation.

**THEME 4: ART following cancer treatment**

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1.To examine the proportion of cancer patients that have been treated with cancer treatment and have suboptimal or abnormal fertility.

2.To monitor the number of cancer patients treated for cancer that pursue and utilise ART post cancer treatment.

3.To monitor the success rate for ART (live births) in cancer survivors who pursue

fertility preservation.

**THEME 5: Mathematical modelling of Fertility Preservation**

**Aim:**

1.To determine the cost of providing a FP program for cancer patients at diagnosis;

2.To determine the cost of FP/ART in cancer survivors who have not had FP at diagnosis or following treatment.

# Eligibility and Sample Size

**Group 1**

Group name for participants in this group: Children

Expected number of participants in this group: 50-100 per year

Age range: 0-12 years

Only those children diagnosed with cancer who pursued a fertility consultation

**Group 2**

Group name for participants in this group: Adolescent young adult patients

Expected number of participants in this group: 500 per year

Age range: 13-25 years who have been diagnosed with cancer irrespective of whether they have been referred for fertility preservation.

**Group 3**

Group name for participants in this group: Adult

Expected number of participants in this group: 1500 adult patients per year

Age range: 26-45 years who have been diagnosed with cancer irrespective of whether they have been referred for fertility preservation.

# Methodology: Planned techniques and significance

**7.1 Planned techniques, significance and sustainability**

**THEMES 1&2: Referral and Uptake of FP**

***Theme relevance and significance***

Clinical responses to infertility in cancer survivors is multifactorial and includes: an understanding of a patient’s gonadotoxic cancer treatment, the patient’s fertility potential prior to and following cancer treatment and uptake and use of fertility measures. The only way that fertility uptake can be reliably documented and hence investigated in this population is through cohort studies (i.e. patients who have been diagnosed with specific types of cancers and requiring different cancer treatment regimens), which require long time frames to follow the required number of participants. The cohort investigations proposed under this theme will provide increased knowledge regarding the rate of referral and uptake of fertility preservation that will be achieved through the development of an AFPR.

***Planned techniques and methodologies***

Development of the AOFR will require extensive site engagement with oncology and fertility specialists. The process is already underway, with a recent pilot study conducted by our research team where findings indicated that 78% of fertility centres in Australia and New Zealand were interested in participating in the fertility preservation registry and would be agreeable to working collaboratively with the referring oncology specialist in maintaining details, regarding shared patients, on the registry; with 57.7% of fertility services stating that they would complete the web based registry during a consultation. As a direct consequence of this study, 50 cancer centres have agreed to participate, recognising the benefits associated with the establishment of the AOFR. This will generate links with local fertility centres and nationally an ANZ Oncofertility Consortium will develop. Ethics approval is underway and will be obtained from all participating sites. There will be three cohorts that will be followed as part of the registry. Cohort 1: children aged 0-12 years who have been diagnosed with cancer, treated with gonadotoxic therapy and who have been referred to a fertility preservation specialist (consultation or procedures). As FP in children is not standard practice and only small numbers of patient tend to be referred to a fertility specialist, a case control study design will be employed to monitor this group. Cohort 2: all AYA patients aged between 13-25 years who have been diagnosed with cancer irrespective of whether they have been referred for fertility preservation will be followed up prospectively. The13-25 year old cohort will be monitored over a five- year period to determine uptake and utilisation of FP before and after cancer treatment, and to monitor the return of reproductive function following cancer treatment. Cohort 3: all adult patients aged between 16-25 years who have been diagnosed with cancer irrespective of whether they have been referred for fertility preservation will be followed up prospectively. The 26 – 45 year old cohort will be monitored over a five- year period to determine uptake and utilisation of FP before and after cancer treatment, and to monitor the return of reproductive function following cancer treatment.

The Australasian Oncofertility Registry will be available to all registered cancer centres and fertility centres with ethics approval. The Australasian Oncofertility Registry will collect fertility related data from:

* New patients prior to cancer treatment
* Relapsed patients who may or may not have had fertility preservation at the time of initial diagnosis
* Patients that have completed cancer treatment who may or may not have had fertility preservation but would like further consultations about their fertility potential following cancer treatment.

All diagnosed patients at participating centres will be given a unique identifying number at diagnosis. Patients will be given information about the registry and a consent form. The Australasian Oncofertility Registry will allow clinicians to capture accurate data at the time of consultations. It will be available on any computer with internet connection. The web-based registry will be easy and simple for users to navigate. To minimise data entry error and the time burden for busy clinicians (cancer and fertility specialists) drop boxes will be provided for most categories. Each state will have a Clinical Research Associate (CRA) who will be responsible to undertaking file-based audits. Alternatively, the data may be provided on a paper-based form, which will be entered manually at the AOFR. The collection of forms, which will detail a patient’s pertinent and confidential information, will be stored in a safe and locked cabinet until entered manually onto the registry. After the paper-based form has been entered onto the registry, the document will be shredded as part of the hospital’s waste management guidelines for privacy and confidentiality purposes.

Cancer physicians will usually be register patients but this can be done by any registered specialist who sees the patient. A copy of the signed consent will be scanned and stored on the registry and a copy will be given to the patient so that consent is only needed once.

Registered doctors/researchers with password protected log-in’s will only have access to patients treated in their own cancer or fertility centres. If a patient transfers to another centre, all centres that have provided treatment will have full access to the patient’s records.

The following details will be collected on the registry to answer Theme 1 and 2:

* demographic characteristics (age, gender, ethnicity, marital status, insurance status, street/suburb/state usual residence, education, language spoken at home; residential postcode, hospital treating centre postcode and treating fertility postcode);
* cancer diagnosis/treatment (date of diagnosis, type of cancer and stage, date of relapse -1st, 2nd, 3rd, type of treatment - chemotherapy, radiotherapy, surgery and BMT and total dose, discussion about FP, data of referral for FP, reasons for declining FP);
* Obstetric and gynaecological history prior to cancer diagnosis
* fertility preservation strategies (patient uptake of FP strategy, oocytes or embryo freezing with details of stimulation regime/no of cycles/response, ovarian cryopreservation and use of GnRH, sperm collection, testicular tissue freezing, method of collection and number of samples frozen).

Site reports highlighting oncofertility outcomes from the registry will be generated on a annual basis and provided to each participating site as part of a continuous quality improvement initiative to improve referral pathways from oncologist to fertility centres.

***Outcomes***

This study, for the first time bi-nationally, will provide evidence-based data on referral and uptake of fertility preservation by age, cancer type and treatment. The registry will establish local and national links between cancer and fertility centres leading to the development of the Australiasian Oncofertility Consortium (AOFC) . The Consortium will implement research-led improvements in the reproductive care of cancer patients through to survivorship.

***Sustainability***

Outcomes from Theme 1 & 2 will assist with the development of clear NHMRC guidelines surrounding the referral process from oncologist to fertility specialist, which will replace the current ad hoc approach. The guidelines have the potential to improve continuity of reproductive health care as well as provision of service delivery. These guidelines will therefore represent an important resource to improve the quality of fertility care offered to patients with cancer, and their families, throughout Australia and internationally. Surveillance data will determine national rates associated with current FP referral patterns, FP uptake and ART outcomes. The data will also allow participating institutes with a rich source of information regarding emerging oncofertility referral patterns as well as reasons for non-referral; FP uptake or deferral and ART outcomes. This will allow participating centres to pursue further translational research studies looking at communication and implementation of practice.

**THEME 3: FP potential following cancer treatment**

***Theme relevance and significance***

AOFR will be the first to provide detailed understanding of the natural history and prevalence of fertility and/or infertility following cancer treatment in children and adolescents in Australia. Longitudinal follow up of this cohort will allow us to determine new knowledge on the short term fertility risks using different types of gonadotoxic chemotherapy treatments by age and cancer type; the proportion of this cohort who resume normal reproductive function; and the time taken for reproductive function to return who to normal reproductive function. We will continue to follow this cohort after the 5-year end of study period to determine long terms risks associated with the same cohort. Surveillance data will highlight patients at “high-risk” for infertility and outcomes will encourage the development of clear NHMRC guidelines to ensure standardised practice regarding FP for patients diagnosed with cancer.

***Planned techniques and methodologies*** Data from cohorts, detailed in themes 1 and 2, will continue to be monitored as part of the data collection process for this theme. Cancer and fertility specialists will collect data at base line (cancer diagnosis) and then again after cancer treatment on an annual basis until year 5 (i.e. years 1-5) in order to determine changes in reproductive function (gynaecological and/or endocrine function). Following these cohorts over a five year time period will allow the research team to examine and describe notable changes in fertility potential, following cancer therapy. This is particular relevant to the younger cohort, where no data on reproductive function following cancer treatment is available. As cancer protocols, on average, administer treatment over a 12-24 month period, this study will allow the research team the opportunity to monitor these patients for at least three years following a patient’s cancer diagnosis, thus allowing us to measure returning fertility potential in patients from childhood to adolescence through to adulthood.

* Routine bloods (for example: FSH, LH, oestradiol, AMH, Inhibin B) and updated gynaecological/obstetric history will be collected and documented by the treating cancer or fertility specialist team annually. Additionally, male patients over 16 years old will be asked to undergo annual sperm banking analysis to assess return of reproductive function until normal function quality has been established. Female patients over 16 years of age will be asked to have an annual pelvic ultrasound to measure the ovarian follicle count.

***Sustainability***

Surveillance outcomes from the registry will assist the steering committee with the development and provision of NH&MRC guidelines for future patients who receive gonadotoxic therapy on the risks of infertility, by age, diagnosis and treatment. These guidelines will also address time taken to return to normal fertility potential and make recommendations for the best time to offer FP strategies to cancer patients who did not have FP at diagnosis.

**THEME 4:** **ART following cancer treatment**

***Theme relevance and significance***

Currently there is no national data to inform the timing and use of FP tissue by cancer survivors, the timing of ART by cancer survivors and the successes associated with timing and long-term storage of ART (pregnancy and live births). Reliable surveillance data on cancer patients who pursue FP and utilise ART will be captured on the AFPR.

***Planned techniques and methodologies***

Data from cohorts, detailed in themes 1-3, will continue to be monitored over a five year period. Baseline data will be used to estimate the prevalence of FP and ART in cancer patients who have been treated with gonadotoxic cancer treatment.

* Data items collected will include: date of FP tissue collection, date of use of FP tissue, type of ART undertaken, date of ART post cancer treatment, non ART pregnancies, ART associated pregnancies, number of live births (occurring naturally and with the use of ART) and pregnancy complications.

**THEME 5: Mathematical modelling of Fertility Preservation**

***Theme relevance and significance:***

Mathematical modeling techniques will be used to forecast the costs of fertility preservation and the out of pocket costs to cancer survivors who have not explored fertility preservation options at diagnosis (medical and psychological). The model will evaluate clinical and socio-demographic (age, gender, menses, cancer diagnosis, ethnicity, language spoken at home, postcode, hospital postcode, marital status) correlates in relation to cancer patients who peruse FP and those who do not. The mathematical models may be helpful with improving decision making support, in relation to FP and uptake of ART, for cancer survivors who are seeking to future plan for a family. Additionally, outcomes should have wider implications in informing the health care system (Medicare) about where financial resources need to be reallocated in supporting cancer survivors to peruse family planning options after treatment.

***Planned techniques and methodologies*** Health economics modeling techniques will be used to forecast the costs of FP at diagnosis; the out of pocket costs to cancer patients who have explored FP options at diagnosis (medical and psychological); and the out of pocket expenses to cancer survivors who pursue FP after cancer treatment. We will use data collected from the registry and Medicare item numbers to analyze this data. The health economics study will lead to an application to the DOHA for Medicare item numbers to be associated with FP strategies in cancer patients leading to equitable access of FP/ART.

# Registration and referral pathways -

The cancer clinician will enter details on demographics, diagnosis, intended or treatment given directly into the database. A referral letter summarising demographic and treatment information will be created by the database and this can be printed for the patient, for the notes and for the fertility preservation provider. An email alert with the same information will also be sent to the nominated fertility preservation provider allowing them to make an appointment.

The web page register will have the referral pathways already programmed, for example patients at Sydney Children’s Hospital and Prince of Wales Hospital will be automatically referred to The Royal Hospital for Women Fertility Preservation Service although this can be over ridden to allow patients choice in who they see. As part of the project we will work with paediatric and adult cancer centres to get an understanding about referral pathways.

Once the patient is seen by fertility preservation specialist, information on consultation advice, choice and procedures will be entered into the register by the fertility preservation provider using the same unique patient identifying number so that each patient has a complete patient record.

The registry will be divided into three sections:

Part 1- Electronic patient record

This will be an electronic medical record where clinical data collected will be identifiable to the treating clinician involved with the research study. This will allow cancer and fertility clinicians to use this tool to provide one accurate record and fertility data per patient.

Part 2 – Research registry

This will involve the exploration of research study themes based on data collected in this registry (these themes have been previously outlined throughout this document). All personal identifiers (name, date of birth, address, Medicare number, phone number) will be removed when analysing the data. Linkage to the Australasian Oncofertility Registry in this de-identified manner will be possible with the use of a unique identifier number created with each new patient.

Part 3 – Linkage with other databases

The AOFR consent will be required the patient to consent to linkage to approved population and health databases in the future (cancer registries, National Death Index, Australia and New Zealand Assisted Reproductive Database, Perinatal Data Collection, admitted patient data collection). The data may therefore may need to be re-identified for linkage purposes and then de-identified again for analysis.

# Data collection

The research team will contact clinicians who are involved in the study once a year for 5 years to confirm the treatment given, patient outcomes and document any subsequent fertility related referral.

The registry is collecting data about what is actually happening with consultation and procedures currently. The only additional tests that we would want patients over 16 years old to have are an endocrine assessment (male and female patients), pelvic ultrasound (females) and assessment of sperm function one year after the end of treatment. This is standard practice in some centres and will help us document the fertility potential following cancer therapy.

**9.1 Data collection process**

The research team acknowledges the workload needed to undertake research at a local level especially when patients are treated in a number of different centres. In order that we are accurate complete data in a timely manner funding will be provided for a CRA in each state who will be responsible for registration of staff, local training, data collection and the safe running of any trials.

**9.2 Data variables**

1. Demographic characteristics – Medicare number, Healthcare Identifier (HI), age, gender, ethnicity, marital status, insurance status, education, language spoken at home; residential postcode, hospital treating centre postcode and treating fertility postcode. (See appendix 8)
2. Cancer diagnosis and treatment details (date of diagnosis; type of cancer and stage; date of relapse (if relevant); type of treatment (chemotherapy, radiotherapy, surgery, BMT type and total dose); discussion about fertility preservation; date of referral for fertility preservation; reasons for declining fertility preservation. (See Appendix 8)
3. Fertility preservation strategies (type of fertility preservation strategy, number of attempts, amount collected, complications, and quality of gonadal tissue). (See Appendix 8).
4. Routine blood tests at diagnosis and after treatment. (See Appendix 8)
5. Gynaecological and obstetric history before and after cancer treatment (See Appendix 8).
6. For male patients older than 16 years of age (after cancer treatment) yearly sperm banking analysis to assess return of normal reproductive function.
7. Female patients over 16 will be asked to have a trans vaginal or trans abdominal scan (position preference) to document the endometrial thickness and antrum follicle count at diagnosis and then 1,3,5 years following end of treatment.

The cancer and fertility doctors will enter data directly onto the registry or use a paper based

data collection form which will be entered manually by the CRAs. Once a year the CRAs will review patient notes and results to get additional patient information.

**9.3 Data storage, security and access**

The Australasian Oncofertility Registry will be hosted by salesforce. The AOFR data will be stored by Salesfroce.com which is an international IT company. Salesforce.com has privacy and security conscious

policies that apply to all information handling practices. Security of data will be ensured in the following ways:

• The AOFR database will be maintained by Salesforce.com. All data will be made secure and will reside on a professionally maintained and physically secure server hosted by Salesforce.com requiring secure password protection.

• Connection to the Salesforce.com service is via secure socket transport layer security, ensuring connection security to data stored on the Registry. Individual user sessions will be uniquely identified with each transaction.User logins will not be accessible by Salesforce.com personnel.

• Hardware and software configurations of the Salesforce.com system have been designed to provide secure user data that permit each user to view only its related data;

• The Salesforce.com service supports delegated authentication.

• All user data is stored in secure data center and is replicated over secure links to a disaster recovery data center. This design provides the ability to rapidly restore the Salesforce.com service in the case of a catastrophic loss.

• Backups: In addition to Salesforce.com disaster recovery capabilities, user data is also backed up to tape in a separate data center. Tapes are not transported offsite from the data center, reducing the risk of loss and for maintenance of security.

• User Controlled Privacy and Security Settings: Users may determine which of their respective designees can access different categories of data.

Clinicians who access the registry will only be able to save data to the registry pages. The security features will not allow clinicians to save to desktop, USB devise or cloud.

Clinicians will have access to the data (oncological and fertility related) to any patient treated at their own hospital site. Patients will have access to their own registry data but not research study data. Full access to the Australasian Fertility Preservation registry will be restricted to project team with secure log-in facility.

External data requests will be reviewed by the Australasian Oncofertility Registry steering committee following the data request protocol to ensure that all research will be scientifically reviewed, have ethical and data provider approvals and can demonstrate a potential for the public good.

Any reports produced for individual centres or nationally will not be able to identify individual patients.

**9.4 Data Ownership**

It is not contemplated that Australasian Oncofertility Registry custodian will own the data collected as part of the operation of the registry. The Australasian Oncofertility Registry custodian will agree on data ownership consistent with Australian commission on safety and quality in health care (ACSQHC) strategic and operating principles for a national approach to Australian clinical quality registries as endorsed by Australian Health Ministers Conference (November 2010).

**9.5 Data access responsibilities**

Access to information collected by the Australasian Oncofertility Registry will be subject to standard operating procedures (SOPs) to ensure that privacy, confidentiality and ethical principles are maintained at all times.

**9.6 Data Policies**

Australasian Oncofertility Registry team will have standard operating policies on data security, data confidentiality, data request and data publication.

# Statistical Analysis

**10.1 Statistical analysis Themes 1-4 and 6**

Descriptive statistics such as means, standard deviations, medians, inter-quartile ranges (for the continuous variables) and frequency distributions (for the categorical variables) will be used to describe characteristics associated with a cancer patient's diagnosis, acquisition of fertility preservation and ART.

New novel statistical techniques such as semi-parametric regression will be used toassess the trends in uptake of fertility preservation (after a cancer diagnosis) over the years which will be stratified by age and gender. Univariable and multivariable logistic regression models will be used to determine the independent predictors of the prevalence for fertility preservation and over the years in Australia.

Kaplan –Meir survival analysis and Cox proportional regression models will be used to identify the factors associated with time to return to normal reproductive function. Health economic strategies will be evaluated using a Markov decision model to conduct and compare the costs of FP strategies for cancer survivors.

# Study Privacy and Confidentiality

**11.1 Registry Privacy and Confidentiality**

The research team will respect the confidentiality and privacy during consultations, consent process and in relation to the patient stored data in keeping with the National Statement on Ethical Conduct in research. The Consent processes will include information about the storage of data (specifically about identifiability of subjects as an electronic medical record and the de-identifiable data using a unique number for the purposes research and reporting. The registry data will be only be used in the manner described in the consent without an amended by HREC and updating current patients and information sheets.

# Consent

**12.1 Registry Consent**

Age appropriate information will be provided for consent and assent to the Australasian Oncofertility Registry. The registry consent will also ask patients to consent to being contacted about further research studies, consent to collect Medicare data and consent for linkage (cancer registries, National Death Index, Australia and New Zealand Assisted Reproductive Database, Perinatal Data Collection, admitted patient data collection). Each separate research study will require a separate consent form to be filled in by that patient (and parent if minor) after they receive age appropriate research study information.

Patients older than ≥18 are viewed by law to be legally responsible for making and consenting to their medical care and associated treatment options and will be able to provide their own consent.

Patients older than 15 years (but under 18 years) who are eligible will require the consent of a parent or caregiver as well as giving their assent in order to participate. The study team will ensure that the patient has received age appropriate information.

Patients younger than 15 years who are eligible will require the consent of a parent or caregiver. The study team will ensure that the patient has received age appropriate information. If a patient notifies the Australasian Oncofertility Registry of withdrawal of consent, the data of that patient will not be collected in the fertility preservation registry from the date of withdrawal.

At 18 years of age the study team will contact the patient with a summary about the Australasian Oncofertility Registry and reminding them that consent was taken on their behalf by a parent. They will be asked if they are still happy for data to be collected. If patients do not want further data to be collected they can complete the adult revocation form and no further data will be collected from the time of completion of this form.

Patients and parents who do not consent to participate in the registry will be asked for the reasons for not participating to allow us if necessary to improve aspects of the study.

# Patient’s who consent to data being stored on the registry will also be asked to consent to data for the treatment period being collected from Medicare. The Medicare consents will be batched and data will be collected from Medicare in batches of 100 patients.

# Reporting

**13.1 Reports**

An annual report must be published by the Australasian Oncofertility Registry Steering Committee that reports on the experience of fertility preservation in Australasia. A reporting framework will be established that is compliant with the National Operating Principles for Clinical Quality Registries.

We would start national reporting after the first full year of data collection. It is envisaged that as the registry matures more detailed de-identified data reports will be published. The research projects outcomes from research studies will be published in peer reviewed journals and result summary circulated to collaborative research groups and consumers. All data will be de-identified to maintain the confidentiality and privacy of participating individuals.

**13.2 Clinical research studies using the Australasian Oncofertility Registry**

Our research team’s aim is over time to undertake a number of prospective medical (clinical and pre-clinical) and psychological studies recruiting patients whose baseline fertility preservation data is already collected within the registry and meet the research study inclusion criteria.

Patients consenting to take part in the Australasian Oncofertility Registry will be asked on the consent form if they would be willing to hear about future research studies. Only those patients who have consented to hear about clinical research studies will ever be contacted about other research studies and at this time they will be given individual study information sheets summarising the study. A separate consent will be taken for each study. We will apply to the ethics committee for a waiver of consent to release the name and address of patients within the registry for the purpose of contacting cases for clinical research if they have given consent for this to happen.

To ensure that patients and cancer and fertility centres are not overburdened with fertility studies the studies that are proposed will need to get approval from the Australasian Oncofertility Registry Steering committee and the committee will want evidence of support from the proposed cancer and fertility centres that they are willing to participate in each study. For studies involving children and AYA patients the support of the scientific committee of ANZCHOG will be sort before starting the project in paediatric cancer centres

# Study Feasibility

This application addresses key issues in examining outcomes associated with cancer diagnosis and treatment in relation to fertility preservation and uptake of ART, and the proposal has received *in principle* support from cancer centres around Australia, it will undoubtedly face a range of challenges at the implementation phase. The investigators and Fertility Preservation Steering Committee are committed to finding pragmatic solutions to such challenges as they emerge.

# Registry patient inclusion criteria

1. All patients (any cancer diagnosis) diagnosed with cancer
2. Cancer patients aged 13-45 who diagnosed with cancer
3. Cancer patients aged 0-12 years of age who are referred for fertility preservation only. Those paediatric patients who are not referred for FP will not be eligible.

# Registry patient exclusion criteria

1. Non-cancer patients who are treated with gonadotoxic drugs will not be registered in phase 1.
2. Parents/siblings who undergo fertility preservation for a child/sibling.
3. Patients who do not consent to data being collected and reported.
4. Patients whose first language is not English when we cannot get an appropriate interpreter to provide consent for the study.
5. Patients who do not consent or assent to the registry
6. Patients who do not have cancer
7. Patients who are not of child bearing age

# Governance structure of Australasian Oncofertility Registry

The will adhere to the Australian Commission on safety and quality in HealthCare (ACSQHC) strategic and operations principles for a national approach to Australian clinical quality registries as endorsed by Australian Health Ministers conference (November 2010).41 To oversee the successful implementation and operation of the AFPR, we have a custodian and an established Oncofertility Registry Steering Committee.

**17.1 Governance of the Australasian Fertility Preservation Registry**

To oversee the successful implementation and operation of the Australasian Oncofertility Registry, there will be a custodian and a steering committee to govern the registry

**17.2 Responsibility of the Custodian**

The Australasian Oncofertility Registry custodian will establish, operate and manage the registry and will be responsible for:

* Allowing direct data entry into the registry by both cancer physicians and FP specialists
* Allow patients to review fertility preservation data held by using a secure pass word protected log-in.
* Storing the agreed minimum data set required to achieve the objectives of the registry
* Not incorporating identifiable patient data
* Complying with the Australian commission on safety and quality in health care (ACSQHC) strategic, operational and technical Principles.
* Developing collaborative links in order to extend the registry bi-national with the goal of achieving bi-national coverage
* Supporting the Australasian Oncofertility Registry steering committee
* Managing administrative processes necessary to support a centralized national FP data collection, while establishing agreements with participating organizations
* Publishing an Annual Report
* Prepare research data sets and outputs for collaborative research
* Maintain all identifiable data under highly secure conditions and in accordance with applicable data policies, accreditation standards and Human Research Ethics Committees (HREC) requirements.
* Not release identifiable patient data without agreement from the relevant HREC, the individual concerned and endorsement by the Steering Committee.

**17.3 Responsibility of the Australasian Oncofertility Registry steering committee**

The Australasian Oncofertility Registry steering committee will be responsible for:

1. Development of the Australasian Oncofertility Registry- development of database items and exclusions and future updates.
2. Data access responsibilities- Access to information collected by the Australasian Oncofertility Registry will be subject to standard operating procedures (SOPs) to ensure that privacy, confidentiality and ethical principles are maintained at all times.
3. Develop data use policy
4. Clinical quality responsibilities- Interpreting and monitor registry data concerning quality and compliance with ethical requirements. Benchmarking and determining the format of quality reports and dissemination of results.
5. Education - Promotion and education about evidence-based best practice and strategies for FP.
6. International benching – Liaising with international bodies, collecting similar data to enable international comparisons
7. The member of the Australasian Oncofertility Registry steering committee will include all study CIs as well as the representatives from other professional organisations and groups.

# Publications

The research team will publish a number of research studies from this study and the cancer and fertility centre’s involved will be acknowledged. Funding for the study will be acknowledged in any publication or talks provided. Patients and parents who participate in the study, the centre’s involved and the registry custodian and steering group will all receive a copy of any publications from this study.

# Registry Annual Report

An annual report will be published by the Australasian Oncofertility Registry Steering Committee. The report will highlight fertility preservation trends in Australasia. A reporting framework will be established, and this will be compliant with the National Operating Principles for Clinical Quality Registries.

National reporting will begin after the first full year of data collection in October 2015. It is envisaged that as the registry matures more detailed reports will be generated and published. Outcomes from the research projects will be published in peer reviewed journals. Results will also be summarized on the FUTuRE Fertility website, after approval has been sought by our collaborative research groups, partners and consumers.

# Ethics

Ethics approval will be sought for each of the participating cancer and fertility centres participating in this study.

# Expected benefits

21.1 Expected benefits that the research study will have for the wider community

This study will provide evidence based data on risks and impact to short and longer term reproductive function cancer treatment by cancer type as well as fertility outcomes associated with the use of new novel chemotherapy agents. The Australasian Oncofertility Registry will also offer an in-depth understanding into the use of stored gonadal tissue for conception following successful curative treatment for cancer. Additionally, it will also highlight successful pregnancy outcomes (live births) and complications following uptake of ART post cancer treatment for cancer survivors.

Currently, there is inequitable access for uptake and utilisation of fertility preservation strategies mainly due to the barriers associated with inadequate referral pathways, access to fertility specialists and prohibitive costs associated with uptake of fertility preservation and assisted reproductive therapies. Barriers associated with fertility preservation uptake have a great impact on certain cancer patient cohorts; for example those cancer patients residing in lower socioeconomic areas, rural and remote areas and patients from minority immigrant and indigenous communities.

Fertility preservation outcomes generated from the Australasian Oncofertility Registry will benefit socioeconomic disadvantaged communities through improving clinical referral pathways between cancer and fertility specialists. Additionally, outcomes from the Australasian Oncofertility Registry and Medicare will be used to perform a cost modelling health economics study. Long term outcomes associated with health economic modelling to forecast out of pocket fertility preservation costs to cancer survivors, will allow the research steering committee to consult with the Department of Health and Aging to address out of pocket procedures outlined in the Medicare Benefit Scheme.

As a direct consequence of this study, local cancer and fertility centres will form new links. An Australasian Oncofertility Consortium will be developed comprising of an interdisciplinary collaboration which will translate integral research findings from the project. The Oncofertility Consortium will provide opportunities to partner with European and American oncofertility consortiums in preclinical, clinical and population based international studies.

This will lead to development of nationally consistent standardised practices, opportunities for sharing resources and training of relevant staff involved in fertility preservation. The Australasian Oncofertility Consortium will be committed to interdisciplinary innovation with other key professional groups involved in patient care. By fostering collaboration across our diverse network of clinicians and researchers, we endeavor to improve clinical practice.

# Mechanisms implemented to monitor the conduct of the study

Clinical research associates (CRA) will be employed at seven sites around Australia and New Zealand (NSW/ACT,VIC/TAS, SA/NT, QLD, WA, NZ) to monitor data entered into the registry. Both the Project Officer and Dr Antoinette Anazodo (CIA) will be responsible for managing and overseeing the daily progress and conduct of the study adhering to good clinical practice guidelines.

The Australasian Oncofertility Registry Steering Committee will meet biannually to discuss and approve protocols, consultation strategies, the project progress and ensure the project protocols are being followed which will include:

1. Development of the Australasian Oncofertility Registry – the data dictionary has been completed and per reviewed;
2. Data access responsibilities – access to information collected by the Australasian Oncofertility Registry will adhere to standard operating procedures (SOPs) to ensure that privacy, confidentiality, equitable and ethical principles are maintained at all times.
3. Develop data use policies to monitor procedures on how data is collected and how findings will be disseminated equitably representing the needs of all participating institutions, their patients and communities.
4. Clinical quality responsibilities Interpreting and monitoring of registry data concerning quality and compliance with ethical requirements. Benchmarking and determining the format of quality reports and dissemination of results.
5. Education- the FUTuRE Fertility Research group have developed the FUTuRE Fertility website, including all content pages that provide patients and clinicians with information and consent forms associated with the research studies. Additionally, the website will house resources such as patient information tools and Elearning tools for clinicians centered around sexual health, sexual dysfunction and FP. The website is currently being edited and will be launched prior to study commencement.
6. Members of the Australasian Oncofertility Registry Steering Committee will include clinician and consumer representatives. This will include all study CIs and other relevant professional organisations and groups.
7. Governance Structure of Australasian Oncofertility Registry – The registry will adhere to the Australian Commission on Safety and Quality in HealthCare (ACSQHC) strategic and operations principles for a national approach to Australian clinical quality registries as endorsed by Australian Health Ministers Conference (November 2010). In order to oversee the successful implementation and operation of the registry, we have instituted a Data Custodian and an established Fertility Preservation Steering Committee

# Sample population

23.1 Number of participant groups involved in the study

There will be three participant groups involved in this study.

23.2 Expected total number of participant in the study at all sites

We anticipate that there will be approximately 10,000 patients aged between 0-45 years in Australia and New Zealand over a five year period from the three groups as discussed earlier in section 6.

23.3 Processes used to identify potential participants

This study will only be conducted with centres that treat cancer patients or provide fertility preservation services. All new patients that meet the eligibility criteria will be given written and verbal study information by their participating treatment centre

23.4 Initiating contact with potential participants

Participating cancer and/or fertility clinicians will give patients verbal and written study information details and offer participation onto the study. An interpreter will be provided by the hospital/fertility centre to explain the study where English is not the first language for patients who are eligible for participation.

23.5 Ratio of male to female participants

The ratio of males to females will be dependent on the type of cancer the patient has been diagnosed. Some cancers will only be seen in one sex, ie, breast cancer and testicular cancer. We anticipate that all other cancers will be seen in equal proportions in male and female cancer patients, although the distribution of cancer types in the various age cohorts will be different.

23.6 Mechanisms used to determine participant’s capacity to participate

 Consent will be required to collect patient's personal data for inclusion on the Australasian Oncofertility Registry, in order to allow the study researcher to review patient's personal medical notes and to allow the research group to collect Medicare data using patient's personal details associated with their treating hospital and/or fertility centre. Additionally, consent will be required from the patient to link to approved population and health databases in the future (cancer registries, National Death Index, Australia and New Zealand Assisted Reproductive Database, Perinatal Data Collection, admitted patient data collection)

# Importance of children’s participation in this research study

 Collection of longitudinal data will provide evidence-based outcomes for fertility preservation referral, uptake and outcomes that are not currently available regarding cryopreservation practices in cancer patients in Australasia. It is important to conduct research in a cohort of younger cancer patients (as well as adults), as there is limited evidence based research conducted examining the effects of cancer treatment on the success of fertility preservation or complications associated with these treatments by age and cancer diagnosis. Currently, children are being offered fertility treatment without evidence based research data to support potential outcomes associated with the effect of cancer therapy on a patients/survivors fertility potential. Outcomes associated with this research study will provide information to support treatment of children with cancer who may also seek to pursue fertility

preservation strategies and options.

# Appropriation of cultural sensitivities relevant to this research project

Research procedures shall be appropriate to all participants. All specialists and researchers will have a

responsibility to be informed of and take steps necessary to respect the social and cultural sensitivity of all participants. As per the study protocol, it will not be acceptable to expose any researcher, clinician or participant to unacceptable standards of risk or harm whether they be physical, social, psychological or culturally incongruous or discordant. When a consultation to acquire consent, assent or provide information regarding the research study is conducted with persons from another culture or language group, consideration will be given to the preferences of the potential participants.

# How the research will remain lawful in the jurisdiction(s) where it is to be conducted.

We will have an investigator group made up of a paediatric and cancer PI and a fertility PI from each participating state and territory in Australia and New Zealand. This investigator group will feed back to the steering committee about any problems with the study. The committee are confident, based on our research and investigation into the laws for each participating institution under their jurisdiction, that the research we are planning to conduct is lawful across Australia and New Zealand. All associated benefits that arise from the project will be fair and equitable to all institutions in each jurisdiction and country participating in the study.

All participating institutes will receive a copy of the study protocol, consent forms, study information sheets and standard operating policies.

# Timetable

**Timeframe**

|  |  |
| --- | --- |
| Year 1- September 2014 - August 2015 | Consultation and ethics application; design and development of Australasian Oncofertility Registry; development of Standard Operation Practices; registration of onco-fertility clinicians; training of clinical research associates in each jurisdiction. |
| Year 2 – September 2015 – August 2016 | Mathematical modelling. Ongoing analysis of AOFR data and annual reporting and dissemination of findings via journal publication and conferences; regular meetings with the Australasian Oncofertility Registry Steering Committee and consumer groups and conferences. |
| Year 3 –  |  |
| September 2016 – August 2017 | Annual reporting and dissemination of Australasian Oncofertility Registry data via journal publication, and at meetings and conferences. Publish data findings from theme 6. Publication of baseline data from FUTuRE Fertility research study |
| Year 4 –  |  |
| September 2018 – August 2019 | Regular analysis and reporting of AOFR data annually and dissemination of data via journal publication, meetings and conferences. |
| Year 5- September 2019-August 2020 | Regular analysis and reporting of AFPR data annually and dissemination of data via journal publication, meetings and conferences. **FUTuRE Fertility** research study July 2020 finishes. Data for the research study is analysed and findings published and presented at meetings and conferences. Apply to ethics to extend data capture until 2025. |

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