

# The National Endometriosis Clinical and Scientific Trials (NECST) Network

## NECST Registry Study Protocol

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## Contents

<b>Collaborating organisations, institutes and centres</b> .....	<b>2</b>
<b>The project team contact list</b> .....	<b>6</b>
<b>List of abbreviations</b> .....	<b>11</b>
<b>1 Background and overview</b> .....	<b>12</b>
1.1 Economic and social costs .....	12
1.2 Impacts on fertility .....	12
1.3 Importance of timely diagnosis and treatment .....	13
1.4 Adenomyosis.....	13
<b>2 Purpose of the NECST Registry Project</b> .....	<b>13</b>
<b>3 Aims of this protocol</b> .....	<b>14</b>
<b>4 Methods</b> .....	<b>15</b>
4.1 Project setting.....	15
4.2 Participants.....	15
4.3 Participant recruitment .....	16
4.4 Consent .....	16
4.4.1 Consent process .....	17
<b>5 Data collection</b> .....	<b>18</b>
5.1 Data variables .....	18
5.2 Data analysis: baseline statistical reporting and regular Registry statistical report .....	19
5.3 Data storage security .....	19
5.4 Intellectual property .....	20
5.5 Governance structure of the NECST Network and Registry.....	20
<b>6 Study privacy and confidentiality</b> .....	<b>21</b>
6.1 Registry privacy and confidentiality.....	21
<b>7 Reporting</b> .....	<b>22</b>
7.1 Reports.....	22
7.2 Clinical research studies using the NECST Registry .....	22
<b>8 Ethics</b> .....	<b>23</b>
<b>9 Mechanisms implemented to monitor conduct of the study</b> .....	<b>23</b>
<b>10 Timetable</b> .....	<b>23</b>
<b>11 References</b> .....	<b>25</b>

## **Collaborating organisations, institutes and centres**

### **PUBLIC HOSPITALS**

Austin Hospital, VIC

Blacktown Hospital, NSW

Calvary Public Hospital, ACT

Centenary Hospital for Women and Children, ACT

King Edward Memorial Hospital, WA

Lyell McEwin Hospital, SA

Mater Adult Hospital, QLD

Mater Hospital, NSW

Mater Mothers' Hospital, QLD

Mercy Hospital for Women, VIC

Monash Health, Monash Medical Centre, Clayton, VIC

Monash Health, Casey Hospital, Casey, VIC

Monash Health, Dandenong Hospital, Dandenong, VIC

Monash Health, Moorabbin Hospital, Moorabbin, VIC

Nepean Hospital, NSW

Queen Elizabeth II Jubilee Hospital, QLD

Royal Brisbane and Women's Hospital, QLD

Royal Hospital for Women, NSW

Royal North Shore Hospital, NSW

Royal Prince Alfred Hospital, NSW

The Royal Women's Hospital, VIC

St George Hospital, NSW

Sunshine Hospital, VIC

The Canberra Hospital, ACT

Westmead Adult's Hospital, NSW

Women's and Children's Hospital, SA

### **PRIVATE HOSPITALS**

#### **Cabrini Health Australia**

Cabrini Malvern, VIC

#### **Calvary**

Calvary Adelaide Hospital, SA

Calvary Bruce Private Hospital, ACT

Calvary Central Districts, SA

Calvary John James, ACT

Calvary North Adelaide, SA

### **Epworth Healthcare**

Epworth Freemasons Victoria Parade, VIC

Epworth Freemasons Clarendon St, VIC

Epworth Geelong, VIC

Epworth Richmond, VIC

### **Healthscope Hospitals**

Nepean Private Hospital, NSW

Norwest Private Hospital, NSW

Prince of Wales Private Hospital, NSW

St George Private Hospital, NSW

### **Ramsay Health Care Hospitals**

Frances Perry Hospital, VIC

North Shore Private Hospital, NSW

St George Private Hospital, NSW

Waverley Private Hospital, VIC

Westmead Private Hospital, NSW

### **Virtus Health**

Spring Hill Specialist Day Hospital, QLD

### **FERTILITY CENTRES**

Embrace Fertility, SA

Eve Health South, QLD

Eve Health Spring, QLD

### **RADIOLOGY IMAGING CENTRES**

Benson Radiology, SA

Camberwell Imaging Ultrasound for Women, Hawthorn East, VIC

City Imaging Ultrasound for Women, Fitzroy, VIC

Junic Specialist Imaging and Women's Centre, Coombs, ACT

OMNI Ultrasound & Gynaecological Care, Nepean, NSW  
OMNI Ultrasound & Gynaecological Care, Sydney, NSW  
OMNI Ultrasound & Gynaecological Care, St Leonards, NSW  
Peninsula Imaging Ultrasound for Women, Frankston South, VIC  
Specialist Imaging Partners, North Adelaide, SA  
Ultrasound Care, Alexandria, NSW  
Ultrasound Care, Bondi Junction, NSW  
Ultrasound Care, Newtown, NSW  
Ultrasound Care, Sydney, NSW  
Ultrasound for Women, Hawkesbury, NSW  
Ultrasound for Women, Parramatta, NSW  
Ultrasound for Women, Penrith, NSW

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**PREPARED BY**

Dr Cecilia Hoi Man Ng, Clinical Trials Network Manager of the NECST Network  
Jean Hailes for Women's Health  
Level 4, 176 Wellington Parade  
EAST MELBOURNE, VIC 3002  
T: +61 4 1680 7183  
E: [cecilia.ng@jeanhailes.org.au](mailto:cecilia.ng@jeanhailes.org.au)

**CONTACT DETAILS**

Professor Jason Abbott (Professor of Gynaecological Surgery)  
School of Women's and Children's Health  
UNSW MEDICINE  
UNSW SYDNEY NSW 2052  
Level 1, Royal Hospital for Women  
Barker Street  
RANDWICK NSW 2031  
Australia  
E: [j.abbott@unsw.edu.au](mailto:j.abbott@unsw.edu.au)  
T: +61 (2) 9382 6733  
F: +61 (2) 9382 6444

W: [www.swch.med.unsw.edu.au](http://www.swch.med.unsw.edu.au)

## The project team contact list

### Principal researcher/Investigator 1

Professor Jason Abbott  
Professor of Gynaecological Surgery  
School of Women's and Children's Health  
UNSW Medicine  
Level 1, Royal Hospital for Women  
Barker Street  
RANDWICK, NSW 2031  
E: [j.abbott@unsw.edu.au](mailto:j.abbott@unsw.edu.au)  
T: +61 (2) 9382 6733  
F: +61 (2) 9382 6444

### Principal researcher/Investigator 2

Professor Gita Mishra  
Director of Australian Longitudinal Study on Women's Health (ALSWH)  
Professor of Life Course Epidemiology  
School of Public Health  
The University of Queensland  
288 Herston Road  
HERSTON, QLD 4006  
E: [g.mishra@uq.edu.au](mailto:g.mishra@uq.edu.au)  
T: +61 7 3346 5224  
M +61 423 097 485

### Principal researcher/Investigator 3

Professor Grant Montgomery  
Director of Genome Innovation Hub  
Professorial Research Fellow  
Institute for Molecular Bioscience  
The University of Queensland  
288 Herston Road  
HERSTON, QLD 4006  
E: [g.montgomery1@uq.edu.au](mailto:g.montgomery1@uq.edu.au)  
T: +61 7 3346 2612

### Principal researcher/Investigator 4

Professor Peter Rogers  
Professor of Women's Health Research  
University of Melbourne, Department of Obstetrics and Gynaecology  
Director of Research  
Royal Women's Hospital  
Level 7, 20 Flemington Road  
PARKVILLE, VIC 3052  
E: [parogers@unimelb.edu.au](mailto:parogers@unimelb.edu.au)  
T: +61 3 8345 3722  
F: +61 3 8345 3702

### Principal researcher/Investigator 5

Dr Cecilia Hoi Man Ng  
Clinical Trials Network Manager  
Jean Hailes for Women's Health  
Level 4, 176 Wellington Parade  
EAST MELBOURNE, VIC 3002  
E: [cecilia.ng@jeanhailes.org.au](mailto:cecilia.ng@jeanhailes.org.au)  
M: +61 416 807 183

**Principal researcher/Investigator 6**

Professor Luk Rombauts  
Adjunct Clinical Professor, Monash University  
Group Medical Director, Monash IVF Group  
Head of Reproductive Medicine, Monash Health  
Suite 9.3, 89 Bridge Road  
RICHMOND, VIC 3121  
E: [luk.rombauts@bigpond.com](mailto:luk.rombauts@bigpond.com)  
T: +61 3 9516 2897  
F: +61 3 9421 5932

**Principal researcher/Investigator 7**

Dr Mike Armour  
Post-doctoral Research Fellow  
NICM Health Research Institute  
Western Sydney University  
58-160 Hawkesbury Road  
WESTMEAD, NSW 2145  
E: [m.armour@westernsydney.edu.au](mailto:m.armour@westernsydney.edu.au)  
T: +61 2 4620 3345  
F: +61 2 9685 4760

**Principal researcher/Investigator 8**

Associate Professor Mary Louise Hull  
Leader of the Fertility and Research Theme  
Robinson Research Institute, University of Adelaide  
Staff Specialist, Women's and Children's Hospital, Adelaide  
266 Melbourne Street  
NORTH ADELAIDE, SA 5006  
E: [louise.hull@adelaide.edu.au](mailto:louise.hull@adelaide.edu.au)  
T: 1300 848 470

**Principal researcher/Investigator 9**

Professor Anusch Yazdani  
Director, Eve Health  
55 Little Edward Street  
SPRING HILL, QLD 4000  
E: [anusch@evehealth.com.au](mailto:anusch@evehealth.com.au)  
T: +61 7 3332 1999  
F: +61 7 3332 1990

**Principal researcher/Investigator 10**

Dr Sofie Piessens  
Department of Ultrasound Imaging, Monash Health  
Imaging Ultrasound for Women  
The Healy Wing  
Suite 2, Level 3, 41 Victoria Parade  
FITZROY, VIC 3065  
E: [sofiepiessens@hotmail.com](mailto:sofiepiessens@hotmail.com)  
T: +61 3 96508833  
F: + 61 3 96501167

**Principal researcher/Investigator 11**

Dr Rebecca Deans



**Lecturer**

The Royal Hospital for Women  
Level 1, Royal Hospital for Women  
Barker Street  
RANDWICK, NSW 2031  
E: [r.deans@unsw.edu.au](mailto:r.deans@unsw.edu.au)  
T: +61 2 9382 6727  
F: + 61 2 9382 6444

**Associate researcher/Investigator 1**

Associate Professor Alan Lam  
Clinical Associate Professor  
Northern Clinical School,  
Royal North Shore Hospital, University of Sydney  
ST LEONARDS, NSW 2065  
Director, Centre for Advanced Reproductive Endosurgery (CARE)  
69 Christie Street  
ST LEONARDS, NSW 2065  
E: [alanlam@sydneycare.com.au](mailto:alanlam@sydneycare.com.au)  
T: +61 2 9966 9121  
F: +61 2 9966 9126

**Associate researcher/Investigator 2**

Associate Professor Michael Cooper  
Head of Gynaecology  
Royal Prince Alfred Hospital  
Missenden Road  
CAMPERDOWN, NSW 2050  
Park House Level 7  
187 Macquarie Street  
SYDNEY, NSW 2000  
E: [michael@mjwcooper.com.au](mailto:michael@mjwcooper.com.au)  
T: +61 2 9233 3546

**Associate researcher/Investigator 3**

Professor Jim Tsaltas  
Head of Gynaecological Endoscopy and Endometriosis Surgery, Monash Health  
Senior Infertility & IVF Specialist, Melbourne IVF  
Suite 119, 320 Victoria Parade  
EAST MELBOURNE, VIC 3002  
E: [jtsaltas@mivf.com.au](mailto:jtsaltas@mivf.com.au)  
T: +61 3 9416 1172  
F: +61 3 9416 4274

**Associate researcher/Investigator 4**

Dr Michael Wynn-Williams  
Director, Eve Health  
55 Little Edward Street  
SPRING HILL, QLD 4000  
E: [mwynn-williams@evehealth.com.au](mailto:mwynn-williams@evehealth.com.au)  
T: +61 7 3332 1999  
F: +61 7 3332 1990

**Associate researcher/Investigator 5**

Professor Sonia Grover  
Director, Department of Paediatric and Adolescent Gynaecology

The Royal Children's Hospital  
Research Fellow, Murdoch Children's Research Institute  
Honorary Clinical Professor, Faculty of Medicine, Dentistry and Health Sciences  
University of Melbourne  
Suite 4.3, Level 4,  
48 Flemington Road  
PARKVILLE VIC 3052  
E: [soniag@unimelb.edu.au](mailto:soniag@unimelb.edu.au)  
T: +61 3 9948 5005  
F: +61 3 8376 6246

**Associate researcher/Investigator 6**

Associate Professor Krishnan Karthigasu  
Clinical Associate Professor  
Department of Women's and Infants Health  
University of Western Australia  
Head of Department, Gynaecology Endoscopy  
King Edward Memorial Hospital for Women  
374 Bagot Road  
SUBIACO, WA 6008  
E: [krishkarthigasu@me.com](mailto:krishkarthigasu@me.com)  
T: +61 8 9389 8900

**Associate researcher/Investigator 7**

Associate Professor George Condous  
Obstetrics, Gynaecology and Neonatology  
Sydney Medical School, Nepean  
University of Sydney  
62 Derby Street  
KINGSWOOD, NSW 2747  
Director, OMNI Gynaecological Care  
Centre for Women's Ultrasound  
Level 2, Suite 201  
68 Derby Street  
KINGSWOOD, NSW 2747  
E: [george.condous@omnigynaecare.com.au](mailto:george.condous@omnigynaecare.com.au)  
T: +61 2 4734 4118

**Associate researcher/Investigator 8**

Dr Natalie Yang  
Acting Medical Director  
Department of Radiology  
Austin Health  
145 Studley Road  
HEIDELBERG, VIC 3084  
E: [yang.natalie@gmail.com](mailto:yang.natalie@gmail.com)  
T: +61 3 9496 5625

**Associate researcher/Investigator 9**

Dr Emma Readman  
Head of Unit, Endosurgery  
Mercy Hospital for Women  
163 Studley Road  
HEIDELBERG, VIC 3084  
E: [ereadman@melbpc.org.au](mailto:ereadman@melbpc.org.au)  
T: +61 3 9419 9699

**Associate researcher/Investigator 10**

Dr Valeria Lanzarone  
Obstetrics and Gynaecological Ultrasound Specialist  
Penrith Ultrasound for Women  
Suite 7 Nepean Private Specialist Centre  
1A Barber Avenue  
KINGSWOOD, NSW 2747  
E: [lanzaronev@gmail.com](mailto:lanzaronev@gmail.com)  
T: +61 2 4721 2195

**Associate researcher/Investigator 11**

Associate Professor Martin Healey  
Clinical Associate Professor  
University of Melbourne, Department of Obstetrics and Gynaecology  
Gynaecology Unit Head  
The Royal Women's Hospital  
Level 7, 20 Flemington Road  
PARKVILLE, VIC 3052  
E: [kathandmutt@bigpond.com](mailto:kathandmutt@bigpond.com)  
T: +61 3 9516 2896  
F: +61 3 9421 5932

**Associate researcher/Investigator 12**

Professor Kerry Sherman  
Deputy Head, Learning and Teaching  
Centre for Emotional Health  
Department of Psychology  
Macquarie University  
Balaclava Road  
NORTH RYDE, NSW 2109  
E: [kerry.sherman@mq.edu.au](mailto:kerry.sherman@mq.edu.au)  
T: +61 2 9850 6874  
F: +61 2 9850 8062

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## List of abbreviations

ACTA	Australian Clinical Trials Alliance
ALSWH	Australian Longitudinal Study on Women's Health
ANZARD	Australian & New Zealand Assisted Reproduction Database
CTN	Clinical Trials Network
MBS	Medicare Benefits Schedule
NDI	National Death Index
NECST	National Endometriosis Clinical and Scientific Trials
PBS	Pharmaceutical Benefits Scheme
PROMs	Patient reported outcomes measures
QoL	Quality of life
VCSF	VCS Foundation Ltd

## 1 Background and overview

Endometriosis is a common yet under-recognised chronic disease (Giudice, 2010, As-Sanie et al., 2019). Endometriosis occurs when cells similar to those that line the uterus grow in other parts of the body, usually around the pelvis. Although endometriosis is often effectively managed, it can lead to debilitating, chronic and persistent pelvic pain and compromised fertility. It can also significantly impact the social and economic participation and psychosocial health of those affected.

It is estimated that 11.4% (more than 730,000) Australian women and girls (in this proposal we use the term 'women' but respectfully acknowledge that not all people with endometriosis identify as women) are living with endometriosis; however, delays in diagnosis and a lack of definitive research on the domestic burden of disease suggest the number could be far higher (Commonwealth of Australia (Department of Health), 2018). Some research indicates the condition is more common than breast cancer, prostate cancer, and diabetes. It can affect women and girls, regardless of age, background or lifestyle (Fung et al., 2018).

Endometriosis has been historically under-recognised amongst both the medical community and the public and subsequently under-diagnosed. The delay between onset and diagnosis is, on average, between seven to twelve years. This is influenced by the fact that an invasive operation is required for formal diagnosis, but also due to stigma, as well as low education or miseducation about menstrual health (Abbott et al., 2003, Giudice, 2010). Therefore, many people living with endometriosis and pelvic pain are not receiving adequate treatment and management until they have had the condition for many years.

The causes of endometriosis remain unclear. It is likely that there is no single cause, and that genetic, biological and environmental factors may influence the condition. Although treatments are available, they are not always effective. There is currently no cure for endometriosis, and symptom recurrence following medical or surgical treatments is common. However, it is recognised that early assessment and intervention can lead to better long-term management, including lessening the impact of symptoms and improving quality of life, helping people affected by endometriosis to live normal healthy lives (Armour et al., 2019a, Rogers et al., 2017, Armour et al., 2019b).

### 1.1 Economic and social costs

There is increasing evidence of the extensive monetary, physical and psychological costs of delayed diagnosis and treatment. They are far reaching and include infertility, pain exacerbation, the development of pelvic pain syndrome, pharmacological dependence, negative impacts on educational attainment, work disruption and prolonged psychological distress (As-Sanie et al., 2019).

Endometriosis is reported to cost Australian society \$9.7 billion annually (Armour et al., 2019a, Australian Institute of Health and Welfare, 2019). Two thirds of these costs are attributed to loss in productivity with the remainder, approximately \$2.5 billion, being direct healthcare costs. Lost productivity for women experiencing endometriosis is estimated at 11 hours lost per week (Soliman et al., 2017, Nnoaham et al., 2011).

### 1.2 Impacts on fertility

About 30% of women with endometriosis have trouble getting pregnant (American Society for Reproductive Medicine, 2012, Carvalho et al., 2013). It is thought that the reasons are related to scarring of the tubes and ovaries from endometriosis; problems with the quality of the egg; problems with the embryo travelling down the tube and implanting in the wall of the uterus due to damage from endometriosis; and change of the organs in the pelvis, such as adhesions with scarred pelvic tissue and blockage of the fallopian tubes

### 1.3 Importance of timely diagnosis and treatment

Due to the progressive nature of endometriosis, early referral and management is critical in managing the pain and impact on areas such as fertility, quality of life, mental health and social and economic participation.

For those in rural and regional areas, treatment and management is exacerbated by diminished access to specialist care. Australian data from 2012 on the medical workforce (Australian Institute of Health and Welfare, 2014), for instance, indicates an average wait of up to 79 days for a specialist and up to 68 days for general medical services in regional areas of Victoria. Compared to major cities, outer regional areas have 19% less specialists and specialists in training.

Raising awareness is the first step to reducing diagnostic delay across age groups. Education about menstrual health is fundamental in younger age groups to break the cycle of diagnostic delay and flow-on effects for the next generation.

### 1.4 Adenomyosis

Like endometriosis, adenomyosis is a benign uterine disorder and is histologically defined by presence of endometrial tissue in the myometrium (muscle layer) of the uterus (Vannuccini and Petraglia, 2019, Abbott, 2017). Both endometriosis and adenomyosis may occur concurrently, with presentations including abnormal bleeding, pain symptoms or infertility. The prevalence of adenomyosis is difficult to determine, since histological confirmation is necessary following surgical biopsy or more commonly hysterectomy. For women wanting to retain their uterus, hysterectomy is not an option. Imaging technologies (e.g. transvaginal ultrasound and MRI), are used as a less invasive method of diagnosis and detection, although they have limitations. The variability of imaging quality and failure to achieve a consensus regarding criteria for diagnosis are principle issues with this non-invasive diagnostic approach.

Management options for adenomyosis depends on the presenting symptoms and will vary accordingly (Abbott, 2017, Van den Bosch and Van Schoubroeck, 2018). These include medical, surgical, radiological or combination treatments. Medical treatments can include non-steroidal anti-inflammatories, oral contraceptives, gonadotrophin-releasing hormone analogues, danazol, oral progestins and aromatase inhibitors. Surgical options include conservative methods (excisional or cytorreductive) to allow potential future fertility. If the woman does not desire future fertility and agrees in a shared decision-making approach for an extirpative management option, then hysterectomy is the 'gold-standard', providing relief from bleeding and no recurrence of disease. Radiological treatment options include high-intensity ultrasound or interventional radiological procedures such as uterine artery embolisation.

It has been identified that prospectively collected health data on management (medical, surgical or radiological) for adenomyosis presentations, including patient outcomes, long-term morbidity and fertility are currently unavailable. The recently published Australian Guidelines on Endometriosis management have highlighted adenomyosis as a priority area for research (RANZCOG, 2021).

## 2 Purpose of the NECST Registry Project

The aim of the National Endometriosis Clinical and Scientific Trials (NECST) Registry Project is to build a National Endometriosis Registry, housed in a contemporary for-purpose platform, that will underpin a comprehensive national program of clinical, basic science and translational research relevant to the needs of Australians with endometriosis, consistent with the research objectives in the National Action Plan for Endometriosis (Commonwealth of Australia (Department of Health), 2018). The NECST Registry is a core component of the NECST Network objectives that includes:

- i. Development of a national Clinical Trials Network that co-ordinates support for research organisations and conducts clinical trials for endometriosis treatments and services.

- ii. Development of an Australian Endometriosis Collaborative Research Framework to support co-ordinated patient recruitment, consistent data collection and **a national database** and bio-repository developed from clinical trials and research projects for national and international research projects specific to endometriosis.
- iii. Formation of a National Collaborative Network capable of responding to a targeted call for integrated endometriosis research focused on translational outcomes.

As identified above, endometriosis is currently an under-researched and often underdiagnosed and misunderstood disease impacting large numbers of people around the world and in Australia. The major benefit of this project, the establishment of the NECST Registry, and the associated analysis of data collected as baseline from people who enrol, is to provide an ongoing research resource and framework to facilitate the undertaking of high-quality research into endometriosis in Australia.

The overarching ultimate benefit sought by establishing the research framework and Registry is to facilitate high quality research that will improve the diagnosis, treatment and prognosis for people diagnosed with endometriosis. This will reduce the suffering of those affected including the burden of pain, infertility and loss of quality of life that can be due to endometriosis. These benefits should be realised most directly by people with endometriosis, but also by their families, employers, governments and wider society.

Researchers will also benefit from the establishment of this key piece of research infrastructure as it will facilitate access to and recruitment of eligible participants for research, facilitate standardisation of core data elements for comparison across research projects, facilitate cross linkage of participant clinical characteristics with biobanked research samples, and enable large scale data linkage of clinical details of people with endometriosis to other health datasets. By realising these benefits, the Registry aims to improve the quality of, and reduce the per project cost of, undertaking research into endometriosis in Australia.

### 3 Aims of this protocol

The NECST Registry will be a national resource of standardised patient data that will facilitate high quality research aiming to understand the causes of endometriosis, improve diagnosis and treatment outcomes, and reduce the burden of disease for patients with endometriosis-related symptoms or diagnosed with endometriosis.

#### **Aims:**

To establish a national Registry that will:

1. Collect and securely store demographic and health related information from consenting participants, who experience and/or seek management for endometriosis and/or endometriosis-related symptoms (e.g. chronic pelvic pain, fatigue, infertility, etc.) and any associated conditions (e.g. adenomyosis, fibroids, endometrial polyps etc.), utilising a minimum agreed and standardised core dataset. Such data will be collected at baseline enrolment and prospectively at regular intervals from participants, allowing longitudinal health outcomes data to be collected.
2. Make the data collected available to approved researchers undertaking related research, within the framework of requiring a formal request to access the data held in the NECST Registry and appropriate ethics approvals. Such data access may include:
  - a. Access to deidentified data elements collected in the core minimum data set for epidemiological analysis;
  - b. Access to contact details of consenting participants in the Registry, who meet the selection criteria for a related research study (including for example those known to have a biobanked specimen, including from histopathological diagnosis of any endometriosis lesions excised at time of planned surgical management, held in a repository within Australia that will support translational research and clinical trials) to invite them to participate in that study;

- c. Facilitation of the selection of consenting participants to undertake data linkage-based research using existing databases in Australia to enrich the available data on endometriosis. The Registry custodian would provide identifying data for such linkage direct to the linkage unit (not the researchers) and subsequently, after provision of linkage keys from the data linkage unit, provide the relevant clinical/demographic data (only) to the researchers. Such data sets for future linkage may include hospital separations (including emergency), National Death Index (NDI), Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS), Australian Institute Health and Welfare (AIHW) metadata, Australian Longitudinal Study of Women's Health (ALSWH), Australian Births, Deaths and Marriages registry and the Australian and New Zealand Assisted Reproduction Database (ANZARD).
3. Publish a de-identified baseline and regular statistical report, describing the number of and characteristics of Registry participants from the minimum baseline dataset.

## 4 Methods

### 4.1 Project setting

The NECST Registry will be stored and managed in a for-purpose, customised on-line platform built and IT managed under contract by VCS Digital, a division of VCS Foundation. VCS Foundation is a Victorian not-for-profit health promotion charity with over 30 years experience in delivery and management of population-based health registry services (e.g. National HPV Vaccination Program Register for the Commonwealth Department of Health and the Victorian and South Australian Cervical Screening Registries). The project/research management and data custodianship of the Registry will occur at the Jean Hailes for Women's Health (Jean Hailes Foundation), the lead agency coordinating the NECST Network and administering the MRFF grant supporting the realisation of the NECST Network and Registry. Investigators will be able to access, through unique log-ins and secure two factor authentication, relevant views of the NECST Registry online (as per defined user roles which only allow entering of data or updating of records and viewing of database reports of direct relevance to that clinician/investigator/their service).

In the establishment phase of the Registry (detailed in this project protocol), potential participants will be identified and approached to participate through clinical services of NECST Network members (physically located throughout Australia). Consenting participants will complete baseline survey data collection online in their own time prior to their appointment with their primary treating gynaecologist (if this is not possible, they may complete the survey online whilst attending their clinical service or on a printed paper copy). Future participant contact with the Registry project will occur primarily through emails (or their nominated preference for choice of contact method, which may include mail to a nominated physical address or a text message to their nominated mobile number), with phone support available at all times to answer any participant queries.

### 4.2 Participants

The population of core research interest is people resident in Australia diagnosed with endometriosis and those suffering from endometriosis-related symptoms. Notably however some of the key research questions of interest and importance in the field are understanding the reasons for the average delay of 7 – 12 years between symptom development and a diagnosis of endometriosis, during which time there is often not appropriate or effective treatment or symptom relief. Therefore, we are explicitly inviting those presenting with symptoms consistent with endometriosis to participate in the Registry rather than only including people with a confirmed diagnosis of endometriosis. People who are enrolled and subsequently receive an alternate diagnosis (e.g. adenomyosis etc.) will not be removed from the Registry (unless at their request), as they will be a potentially important resource for research into the timely and effective diagnosis of endometriosis as a comparator group.

Eligible participants are women aged 18 and over, residents in Australia with symptoms consistent with endometriosis. We recognise that children and women under 18 are also affected by



endometriosis but are not including them in this initial iteration of the Registry because there are currently no validated, appropriate endometriosis research survey instruments for use in this group. These are currently being developed as part of dedicated research studies.

Exclusion criteria for enrolment onto/participation in the NECST Registry are:

- Women unable to provide informed consent;
- Females aged under 18 years of age;
- Women who are not resident in Australia or planning to not reside in Australia for the foreseeable future;
- Women with insufficient English language ability to give informed consent and complete the baseline survey instruments (at this stage consent materials and survey modules are only available in English).

An inclusion criteria, for this establishment phase of the Registry, is referral to, or attendance at, a gynaecology service provider who is part of the NECST Network, for suspected or confirmed endometriosis. This is because this strategy optimises accurate identification of appropriate people to be invited to participate in a supported research environment and will maximise the depth of comprehensive clinical information available to populate the Registry in order to make it a useful research resource within a reasonable time period. As the Network grows over time, as other clinicians with significant populations of patients with endometriosis and relevant expertise and interest become aware of the Network and Registry through its activities and potentially through patient interest in being part of the Registry, the recruitment base will expand.

Network clinicians participating in this research currently see an estimated 10,000 women who would be eligible to join the Registry. We hope to recruit at least 250 women in year one, with year on year increases in recruitment numbers thereafter.

### 4.3 Participant recruitment

Screening of eligible women (determining if a woman is aged 18 years and over and has suspected or confirmed endometriosis) will occur prior to women receiving an invitation to participate from a clinician who is a member of the NECST Network and recruiting women to the Registry. Women may be identified by the network clinician and their research/administrative staff in two main ways 1) new referral received by the clinician for further diagnosis and/or care of a woman with suspected endometriosis and/or adenomyosis/symptoms consistent with endometriosis and/or adenomyosis and 2) existing patients of the clinician who have known or suspected endometriosis and/or adenomyosis.

Newly referred women will be invited to participate as part of their first visit to the clinician. Dependent upon the clinician's standard method of communicating with patients, most women aged 18 years and over will receive an invitation to complete the baseline information pre-visit electronically (i.e. via email with links to secure electronic data capture and online consent form) but more exceptionally on paper forms by post pre-visit or at the time of the visit (e.g. in waiting room). Administrative staff in the clinician's practice/service will manage the distribution of study recruitment materials to patients on the clinician's behalf. Patient information sheets and consent forms will explain the NECST Registry and its purpose and invite women to participate by consenting. Any woman with questions will have the opportunity to ask their clinician or research nurse/officer prior to signing the consent form on-line or on paper, as well have access to a research officer by phone as per the study information provided to her. Clinicians can also invite existing patients to participate following the same method of providing the study information, consent form and access to the baseline survey where consent is given either electronically or on paper. The primary treating clinician will have the final responsibility of ensuring full informed consent of the invited participant and ensure that consent is captured and confirmed.

### 4.4 Consent

All participants in the Registry are required to give written informed consent. Women will be clearly informed that their decision to participate or not will not impact upon their clinical care or relationship

with their provider in any way. Women will be informed that participation in the Registry is to facilitate research for improving understanding and hopefully improve diagnosis, management and treatment for women who may be diagnosed with endometriosis in the future. The woman is not consenting to a specific clinical research study or trial with an anticipated immediate clinical benefit. The consent comprises several components only the first of which is required. This minimum requirement is that the woman agrees to have her baseline survey data held in the Registry for deidentified research use. Consent components are:

1. Consent to complete baseline survey data and be a participant in epidemiological baseline research using these data which will report deidentified characteristics, impact of quality of life (via validated questionnaires, see section 5.1) and experiences of women with endometriosis or suspected endometriosis (due to symptoms of chronic pelvic pain, sub-fertility or other endometriosis-related symptoms) enrolled on the Registry;
2. Consent to allow treating clinician(s) to record results of her diagnostic tests and treatments on the Registry for research use;
3. Consent to receive future invitations to complete periodic follow up surveys (at 6 months, 12 months and annually);
4. Consent to be contacted to participate in future ethically approved endometriosis related research projects;
5. Consent to have data linked to other health data sets in future for ethically approved research into endometriosis;
6. Consent to have the identification number of any clinical specimens she may have deposited/deposit in future in a bio-bank recorded on the database by her clinician to facilitate future ethically approved research studies.

All women who consent to participate will keep a copy of their consent and information sheet which clearly informs them that they can opt off the Registry by withdrawing their consent at any time and how to do so. Women will be routinely followed up at regular intervals and invited to participate in ongoing data collection via surveys. This is primarily to provide ongoing data about their experience living with endometriosis for research purposes but also provides an opportunity to update contact details and remind women that they are part of the Registry and reiterate that they can withdraw consent any time.

#### **4.4.1 Consent process**

The consent process will be a two-step approach:

##### **Step 1: Pre-consent**

The participant will be asked to pre-consent (either electronically or paper) to allow their data to be uploaded to the NECST Registry, prior to completing their demographics, clinical presentation and medical history and PROMs (EQ-5D and/or EHP-30) questionnaires online. The electronic pre-consent will upload the participant's data into a "holding bay" within the NECST Registry until their index visit with their primary treating doctor. Answers provided by the participant to questionnaires and surveys will be made available for them to download and retain a copy for their records.

##### **Step 2: Consent at clinical visit**

At the participant's clinical visit, the clinician will go through the study and objectives of the NECST Registry. This will also be an opportunity for the participant to ask questions or have their concerns addressed. Following discussion, the participant will be asked to confirm their consent. The clinician will log the confirmation of consent, either electronically (via their individual login to the NECST Registry, under the participants record and will be location, date and time stamped) or on paper, by co-signing the consent form (will be scanned and uploaded onto the NECST Registry). Following this, the participant's record will become 'active' and uploaded onto the NECST Registry.

If the participant does not consent to take part in the NECST Registry, any data from questionnaires/surveys completed by the participant will be removed and deleted within the Registry.

The participant and their treating clinician may choose to print any data entered by the participant as a summary for their own record prior to this 'hard' delete.

## 5 Data collection

The initial online interface used by women for baseline survey data collection, which is then securely provided with her consent to the Registry in encrypted form, is the standard online survey tool REDCap. Women will be able to print out a copy of their consent, and if they so wish, print out and/or receive a summary of their survey answers by email. The baseline survey includes demographic information, symptom and medical history, and Quality of Life measures which may be relevant for diagnosis and management by the woman's clinician so have been designed so that the patient can allow an email alert to share these data with her clinician for potential inclusion in their clinical record. It is anticipated that it will take approximately 25 – 35 mins for the participant to complete their baseline data collection. Participants are also able to complete the baseline demographic, medical history and PROMs questionnaires over time, whereby participants can save their answers and return to the questionnaire later.

Once the patient has given consent to do so, information on consultation advice/diagnosis, any imaging, medical or surgical intervention and procedures will be entered into the relevant woman's data fields in the NECST Registry by the specialist provider using their unique log in and clinician view. Clinicians are able to search for their own patients and only add information to their own clinic patients' records. It is anticipated that data entry for the gynaecologist onto the Registry will take about 10 – 15 minutes to enter patient's pertinent details onto the system at diagnosis (key demographics, diagnosis and treatment modality). At any additional follow up visits, clinicians will enter data fields taking less than 5 minutes to complete. Given that the online Registry is an automated system, the majority of data fields will require minimal time expended to enter data. This is achieved through the use of standard modules for recording data, drop down menus and autocomplete text functions. Data will often be auto-populated by entering data into one specific cell that is then transposed automatically into other areas of the dataset. A key requirement in developing the NECST Registry Platform to support the Registry was that the process would minimise the time and burden spent by the clinician entering data.

To maximise data completeness, the research team will contact clinicians who are involved in the study annually to confirm the currency of data entered and where necessary provide support to update treatment given, patient outcomes and document any subsequent related treatments and/or referrals. On site record review and quality audits for data completeness and accuracy will be undertaken at least once per site every two years.

### 5.1 Data variables

The NECST Network has developed a comprehensive data dictionary through dedicated expert working groups focused on each Registry module (see attached Data Dictionary). These 7 modules underpin the data collection elements within the Registry. Each of these modules will contribute to the overall dataset in the NECST Registry; however, not all modules will be completed for each patient, since not all patients will require all interventions (decision is made by both the clinician and patient on the course of intervention appropriate for the patient) or necessarily provide consent for biobanking tissues or clinician reporting from medical records to check and confirm patient diagnosis and intervention(s) undertaken as entered into the NECST Registry during site review and quality audit checks every two years.

1. Demographic characteristics – Name, date of birth, Medicare number, Healthcare Identifier (HI), residential postcode, gender, ethnicity, language spoken at home, education and employment and marital status;
2. Clinical presentation and medical history characteristics – Presenting symptoms, menstrual symptoms, pain history and symptoms, endometriosis history, pregnancy, obstetric and fertility history, medication history, medical history and primary diagnosis;

3. Patient reported outcomes measures (PROMs) characteristics – Health-related quality of life (QoL) measure using the Euroqual-5D (EQ-5D) and endometriosis-specific QoL measure using the Endometriosis Health Profile-30 (EHP-30; only for participants who have received or receive a diagnosis of endometriosis);
4. Imaging (ultrasound and/or MRI) detection or pre-surgical mapping of endometriosis and/or adenomyosis;
5. Medical management interventions – type of hormonal, pain or other medications used, dose and duration, side effects and other types of complementary interventions utilised;
6. Surgical management (including Histopathology reporting) – type of surgery performed, complications, additional conditions identified at surgery, confirmation of endometriosis and/or adenomyosis and histopathology report;
7. NECST Network Biobanking – documentation of histopathology reports from samples excised at time of surgery for histopathological diagnosis and confirmation of endometriosis.
8. Environmental and lifestyle risk factors – to understand the effects that the environment, our lifestyle and behaviours have on conditions like endometriosis.

## 5.2 Data analysis: baseline statistical reporting and regular Registry statistical report

In our baseline publication and regular statistical report reporting the epidemiological and clinical characteristics of women enrolled on the Registry, all data will be analysed and presented as de-identified, grouped data. Descriptive statistics such as means, standard deviations, medians, inter-quartile ranges (for the continuous variables) and frequency (for the categorical variables) will be used. Cross tabulations and relevant statistical tests (e.g. chi squared) may be performed to describe demographic characteristics associated with an endometriosis patient diagnosis, acquisition of surgical and/or medical management.

No small cell sizes will be published where they could result in the possible identification of a participant e.g. using postcode level data against key characteristics. Geographical data and related classifications will use area levels appropriate to the number of participants e.g. state, Accessibility/Remoteness Index of Australia (ARIA), Socio-Economic Indexes for Areas (SEIFA), groupings larger than postcode to prevent small cell sizes arising. No individual level data that could identify non-participants e.g. family members will be reported.

## 5.3 Data storage security

In establishing the NECST Registry, we are explicitly developing and managing a research resource that will collect, securely store and use identified personal and health information from consenting participants. As such we are deeply aware of our ethical duty to maintain the privacy and security of the data that we hold. Data will be stored in a for-purpose registry platform configured and managed by VCS Foundation to support the NECST Network Registry using an existing proven digital health management system (canSCREEN™). The data is stored securely in Microsoft Azure in the cloud with access only available to authorised users. The application will run within a web browser. The underlying Azure platform is used for networking, security, identity management and environment monitoring and alerting. Best practice security measures are embedded in the architecture. Features of the system include role-based user privileges with only authorised users able to access participant records, multilevel authentication of users, encryption of all data at rest and in flight, and a full audit trail of all Registry activity. All system users are required to sign an agreement acknowledging the confidential nature of the data held on the Registry. The Registry is subject to penetration testing, security audits and monitoring.

Security of data will be ensured in the following ways:

- VCSF has privacy and security conscious policies that apply to all information handling practices including police checks of all staff, confidentiality agreements, building access and network security measures;

- All users must sign a confidentiality agreement before being provided log in based access to their view of the Registry;
- The NECST Registry data will be maintained by VCSF. All data will be made secure and will reside on a professionally maintained and physically secure servers hosted in Australian Microsoft Azure data centres;
- Connection to the NECST Registry 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;
- VCSF are the administrators of the NECST Registry infrastructure, VCSF personnel will not be able to view users login password, but are able to update authentication and sign-in details;
- Hardware and software configurations of the Registry system have been designed to provide data security that restricts user access to data based on authorisation, role and jurisdiction;
- All user data is stored in secure data centres and is replicated over secure links to a disaster recovery data centre. This design provides the ability to rapidly restore the Registry in the case of a catastrophic loss;
- User Controlled Privacy and Security Settings: Users may determine which of their respective designees can access different categories of data.

Clinicians who access the NECST Registry will only be able to save data in the NECST Registry application. The security features will not allow clinicians to save to desktop, USB device or cloud.

- Any paper-based information will be stored in a locked filing cabinet at Jean Hailes for Women's Health, East Melbourne (email and postal address will be provided with the questionnaires and Patient Information and Consent Form);
- After the data are entered the forms will be shredded prior to disposal in accordance with the disposal of medical information policy and ethical protocols. Validation checks of paper-based data forms will occur prior to disposal.

External data requests will be reviewed by the NECST data access committee following the data request protocol to ensure that all research has ethical and data provider approvals.

We do not plan to destroy data within the time period of the ethics application, with this application covering the establishment phase of a national Registry designed to be maintained into the foreseeable future.

#### **5.4 Intellectual property**

Custody of the data sits with the Jean Hailes Foundation, who are administrators of the MRFF grant and the lead organisation responsible for financial and administrative management. Each research team who utilise data in the NECST Registry or request access to women to participate in their research through the Registry will have ownership of the intellectual property created by their research.

#### **5.5 Governance structure of the NECST Network and Registry**

The NECST Network governance structure ensures that the NECST Registry runs efficiently; operates at all times within legal constraints, particularly with regard to ethical conduct, data security and privacy; is appropriately managed by people who have clear and identified roles and responsibilities; and has processes for data management, access, dissemination of information, engagement and commitment of all relevant stakeholders.

As the holders of the MRFF grant to establish the NECST Network and Registry, Jean Hailes Foundation is responsible for administration and management of the NECST Network and Registry. This includes responsibility for financial acquittals and reports, human resource management,

contract management and insurance. Jean Hailes Foundation are also the data custodians of the NECST Registry.

The NECST Network and Registry governance structure comprises of 2 groups:

**The NECST Strategic Governance Committee** provides oversight of research and management, including financial and organisational competence, strategic direction and performance of the NECST Network. They ensure all activities are conducted in a scientifically robust manner, and all clinical and health research is performed responsibly, ethically and in the interests of the wider community. This is performed in line with the MRFF Funding Principles, Research Governance Best Practice and adhering to the relevant codes of practice and ethics for research.

The Strategic Governance Committee consists of an independent Chair, an expert in financial/business management, a researcher with collaboration and research management and governance expertise, an academic clinician with extensive science and clinical trials expertise, an academic research nurse, a college nominee, and three patient/community representatives who have experience with endometriosis. The Committee meet four to six times a year.

**The NECST Advisory Committee** provides clinical and scientific leadership to the NECST Network and Registry. The Advisory Committee is overseeing the establishment and implementation of the NECST Network, including the development and launch of the NECST Registry. They feedback to the NECST Strategic Governance Committee about any governance issues. This group meets four to six times a year. The Advisory Committee consists of a lead clinician (gynaecological surgeon), senior research academics, epidemiology and biostatistician from participating centres in Australia, an expert in financial/business management, a researcher with research management and governance expertise and the Clinical Trials Network Manager. The NECST Advisory Committee will also deal with data access requests.

The governance structure will be reviewed prior to the end of the MRFF Grant (June 2021) to determine ongoing requirements for the Network pending funding and research activities. Following the establishment phase of the NECST Network Registry, the Advisory Committee will reappraise the need for further committees, revise the governance structure and advisory roles moving into the maturity phase of the NECST Network. The review will align in accordance to the Australian Commission on Safety and Quality in Health Care (ACSQHC) Strategic, Operational and Technical Principles and any changes would result in an ethics variation request/amendment.

## 6 Study privacy and confidentiality

### 6.1 Registry privacy and confidentiality

The researchers will respect the confidentiality and privacy of participants during consultations, the consent process and in relation to the patient stored data in keeping with the National Statement on Ethical Conduct in research. The consent process 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 of research and reporting. The NECST Registry data will only be used in the manner described in the consent.

NHMRC guidelines, approved under Section 95A of the Privacy Act 1988, allow the NECST Advisory Committee to request applicant investigators to submit a proposal to a HREC even if it has received written notification of ethics committee approval from the investigator's institution. It is therefore the preference of the NECST Advisory Committee that applications for release of identifiable data are submitted and reviewed by a HREC who has already approved data collection of core NECST Registry data variables.

The NECST Advisory and Strategic Governance Committees envisage that NECST Registry data will be of use to a large number of organisations, investigators and policy makers. Scenarios requiring data access may include:

- Analysis of aggregated NECST Registry data, which may or may not include specific subgroup analysis;
- Data linkage to external databases;

The NECST Advisory Committee will encourage generation of scientific knowledge based on the NECST Registry data. Requests for aggregated data or access to the database for research purposes will be required to be made in a standard format with a clear outline of the purpose and justification of the request, specifications of the requested data, signed agreement to protect the confidentiality and security of all data, attachment of the research protocol, and proof of ethics approval. Researchers will also be asked to provide a copy of any publications arising from the Registry data.

To ensure that the data and any limitations in scope or quality of the data provided has been properly understood by the user, pre-publication drafts of any derivative works must be submitted for review and comment by the NECST Advisory Committee.

## 7 Reporting

### 7.1 Reports

A regular statistical report will be published by the NECST Network reporting on the number of participants in the Registry and their characteristics and summarising their endometriosis related data in frequency tables (See statistical analysis section).

We will publish the first report after the first full year of data collection or after enrolling at least 200 participants, whichever comes later. It is envisaged that as the NECST Registry matures that more detailed de-identified statistical reports will be published. The research projects outcomes from research studies will be published in peer-reviewed journals and a copy of the result summary will be circulated to collaborative research groups and consumers. All data will be de-identified to maintain the confidentiality and privacy of participating individuals and hospitals.

Women enrolled on the Registry will receive communications by email and/or post at regular intervals for the purposes of maintaining contact and up to date contact details, completion of follow up surveys, and for the purpose of keeping women updated with the activities of the Registry including results of research. Such updates will be in the form of a newsletter or information sheet that will describe any key findings in lay language and links to publications. All women enrolled will be involved in the first research output, which is a descriptive baseline analysis of the characteristics of women with endometriosis/symptoms of endometriosis enrolled on the Registry, and all women will be provided with a summary of the findings through the newsletter.

### 7.2 Clinical research studies using the NECST Registry

The NECST Advisory Committee's aim is to undertake a number of prospective studies recruiting patients whose baseline endometriosis and related symptomatic data are already collected within the NECST Registry and who meet the research study criteria.

Patients consenting to take part in the NECST 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 process will be required for each study.

## 8 Ethics

Ethics approval (where the National Mutual Acceptance (NMA) agreement does not apply) and research governance (i.e. site specific assessment; SSA) will be sought at each of the participating gynaecology and fertility centres participating in this study.

## 9 Mechanisms implemented to monitor conduct of the study

Data analysts will be employed at sites nationally to monitor data entered onto the NECST Registry. Jean Hailes (data custodian) will be responsible for managing and overseeing the daily progress and conduct of the study adhering to good clinical practice guidelines.

The NECST Advisory 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:

- i. Data access responsibilities to ensure that privacy, confidentiality, equitable and ethical principles are maintained at all times.
- ii. Data quality and usage
  - a. Encourage the use of the data for appropriate relevant research;
  - b. facilitate access to data for projects with appropriate standards of scientific merit and public health importance
  - c. Data quality monitoring and use/release data of a sufficiently high level of quality;
  - d. Ensure release of de-identified aggregated data is sufficiently aggregated to protect privacy
  - e. Ensure any identifiable data are not released except with explicit consent for such release
  - f. Release of patient or clinician's contact details generated in a secure spreadsheet of Registry participants who have agreed to be contacted and meet the selection criteria for an approved study and provide it to the researchers so they can contact them. Detailed instructions including details of securely holding the data, not using them for any other purpose, and deleting the files once the recruitment phase of the study is completed.
- iii. Education – the NECST Network have developed the NECST Network 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 and e-learning tools for clinicians.

Awareness of cultural sensitivities Research procedures shall be appropriate to all participants as far as possible. The research team will have responsibility of being informed of, and take steps necessary to respect, the social and cultural sensitivity of all participants. When a consultation to acquire consent, 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.

## 10 Timetable

<b>Year 1</b>	Ethics approval application; Building, testing, progressive jurisdiction/site rollout of the NECST Registry; registration of Gynaecological clinicians (with expertise in endometriosis and reproductive endocrinology and infertility); training of clinical research associates in each jurisdiction/national data analyst.
June 2020 – May 2021	
<b>Year 2</b>	Continued testing and progressive jurisdiction/site rollout of the NECST Registry; baseline statistical reporting and dissemination of findings via



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June 2021 – May 2022	journal publication and conferences/workshops; regular meetings with the NECST Advisory and Strategic Governance Committee, and consumer group and conferences.
<b>Year 3</b>	Statistical report and dissemination of data, research studies utilising Database being submitted and approved.
June 2022 – May 2023	
<b>Year 4</b>	Ongoing research use applications for NECST Registry. Regular statistical report and dissemination of data via journal publication, meetings and conferences.
June 2023 – May 2024	
<b>Year 5</b>	Ongoing research use applications for NECST Registry. Regular statistical report and dissemination of data via journal publication, meetings and conferences.
June 2024 – May 2025	Apply to ethics to extend data capture until 2030.

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