Are Australian fertility clinics selling non evidence based interventions and if so, is it an indicator of financial conflicts of interest?

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Declaration

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at Macquarie University or any other educational institution, except where due acknowledgement is made in this thesis. Any contribution made to the research by others, with whom I have worked with at Macquarie University or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that the assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Ethics approval was not required as there were no human participants in this study.

Signed:

Date: 22 August 2019

Abstract

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Background and rationale
Adjunct services aim to improve fertility outcomes such as live birth rates. However, studies in the United Kingdom (UK) have found that adjuncts lack robust evidence for efficacy. This has raised concerns that financial interests of clinics are subordinating patient interests. Conditions where financial interests could unduly influence treatment decisions is a conflict of interest. Financial conflicts of interest may be an issue in Australia's lucrative fertility industry but with regard to adjunct services, there are no equivalent studies to show whether Australian clinics are also selling unproven interventions. The objective of this study was to determine whether Australian clinics are selling unproven interventions and if so, whether their sale could constitute a financial conflict of interest.

Method
Through a content analysis of Australian fertility clinic website texts, this qualitative study examined the adjunct treatments being offered and assessed them for efficacy. Websites for accredited Australian fertility clinics (n = 91) were located. After excluding duplicates and inaccessible sites, texts from the treatment pages of each of the remaining sites (n = 41) was captured to generate data on all interventions being offered by Australian clinics (n = 73). These services were coded in Nvivo to determine which were adjunct services and to facilitate evaluation against empirical evidence.

Results:

This study found that most adjuncts lacked the clinical evidence for efficacy. Of the 18 adjuncts investigated, only one was robustly supported by evidence but this evidence has since been called into question. These results show that Australian clinics are indeed offering expensive adjunct interventions with limited or no therapeutic benefit to patients so the practice does raise the possibility that financial interests are asserting undue influence on patient interests.

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List of abbreviations

ACCC	Australian Competition and Consumer Commission
AIHI	Australian Institute of Health Innovation
AMA	Australian Medical Association
APHRA	Australian Health Practitioner Regulation Agency
ART	assisted reproductive technology
ART guidelines	NHMRC Ethical guidelines on the use of assisted reproductive technology in clinical practice and research
EMSN	Extended Medicare Safety Net
FSA	Fertility Society of Australia
HFEA	Human Fertility and Embryology Authority
IVF	in-vitro fertilisation
MBA	Medical Board of Australia
MBS	Medicare Benefits Schedule
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
PGD	Preimplantation genetic diagnosis
PGS	Preimplantation genetic screening
RTAC	Reproductive Technology Accreditation Committee
VARTA	Victorian Assisted Reproduction Treatment Authority
WMA	World Medical Association

Chapter 1: Introduction

1.1 Background

Infertility, defined as "failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner" (Zegers-Hochschild et al., 2017, p. 401) and affects approximately 15% of women (Newman, Fitzgerald, Paul and Chambers, 2019). Many infertile people turn to assisted reproductive technologies (ART), such as in-vitro fertilisation (IVF), to help them have a baby. Latest estimates in Australia posits that 4.7% of all people who gave birth in Australia in 2017 had some form of ART treatment (Newman, et al 2019). The use of ART has been increasing steadily, culminating in the initiation of 74,357 cycles of IVF in Australia in 2016 (Fitzgerald, Paul, Harris, & Chambers, 2018). Of these many thousands of cycles, 13,517 babies were born and were still alive 28 days after birth (Fitzgerald et al., 2018). This means more than 80% of IVF cycles did not result in a baby, the outcome of greatest interest to patients. With such a high failure rate, many patients seek to maximise their chance of success by augmenting their IVF protocol with adjunct interventions, also known as adjuvants and add-ons. In this paper, I will refer to these as adjunct interventions, where possible, to avoid connotations of enhancement or therapeutic benefit.

The use of adjunct interventions has recently come under scrutiny because there is evidence that they may not work and have not been sufficiently assessed for safety, yet they are expensive and widely available. We do not have much information on their usage because most fertility services are provided in private practice, however, there are indications that adjunct treatments are widely used. Australia is the largest consumer of fertility services second only to Israel and since the fertility services industry is growing rapidly and generating large profits, we can hypothesise that adjuncts are also being used widely. Bioethicists are concerned that the sale of adjunct interventions reflects the rise of commercial interests in ART and unchecked financial conflicts of interest which can compromise patient care. The Fertility Society of Australia, (FSA), the national peak body representing stakeholders such as scientists, doctors, researchers and nurses in reproductive medicine, disagrees and denies that there are financial conflicts of interest in the ART industry (Fertility Society of Australia, 2016).

1.2 What are adjunct interventions?

Adjunct interventions are additional interventions and therapies available which are promoted as having the potential to enhance or improve any or all of steps in fertility treatment, most are employed to augment a specific part of the IVF cycle. A standard IVF cycle has several steps and begins with hormonal stimulation of the ovaries to mature then release eggs. The eggs are then collected, as is sperm, before in vitro fertilisation. The resulting embryos are placed in a culture medium to incubate for several days before being transferred fresh to the uterus, or frozen for later use. A blood test is done approximately two weeks after transfer to detect human chorionic gonadotropin (hCG) in the blood stream to confirm or rule out pregnancy. Adjunct interventions include drugs, procedures and the use of specialised equipment on patients, embryos, or gametes and aim to screen, diagnose or treat some aspect

that may be an impediment to successful implantation and pregnancy. Adjuncts can also be services added before and after the IVF cycle, for example during the preliminary testing stage, there are some standard diagnostic tests that most clinics conduct, then there are additional tests that are presented as beneficial, such as preimplantation genetic testing – structural arrangement (PGT-SR). Since they are not essential to IVF, adjuncts are generally sold as optional extras for an additional charge on top of the $3000 - $15 000 cost of IVF[1].

One example of an adjunct intervention is endometrial scratching, a deliberate mechanical injury to the endometrial lining, often performed as a biopsy with a small instrument such as a pipelle. The injury is said to trigger an inflammatory repair response that creates a more receptive environment for embryo implantation. Endometrial scratching adds hundred dollars to an IVF cycle. It also adds time, something many fertility patients are short of, since the scratch needs to be done several weeks to several days prior to the stimulated IVF cycle.

At the more expensive end of the cost spectrum is 'preimplantation genetic testing – structural arrangement', previously called preimplantation genetic screening (PGS)[2]. PGT-SR is used to screen for aneuploidy, like Turner and Down Syndromes. PGT-SR can reveal information about the structure and characteristics of genes but that information does not directly affect fertility or the capacity for gametes or embryos to develop, even when anomalies are detected. For example, aneuploid embryos are often deemed unsuitable for transfer but there have been successful pregnancy and births with aneuploid embryos, raising questions about the utility of the procedure and how results are interpreted (Gleicher, 2016). PGT-SR costs thousands of dollars in consultation and preliminary set up fees and an additional $400 - $900 for each embryo screened (see Appendices C and D for examples of costing). Like a standard IVF cycle, the cost varies a great deal between clinics.

1.3 The controversy of adjunct interventions

The promise of adjunct interventions is that they could resolve some issue that appears to be a barrier to pregnancy or the ability to carry a pregnancy to term, but recent studies and media reports have questioned their efficacy and safety, and therefore, whether their use is in the interests of patients. For example, a 2006 systematic review of randomised controlled trials (RCTs) for PGS showed that it significantly reduced the live birth rate[3] (Heneghan et al., 2016). Meanwhile, endometrial scratching does have RCTs and a recent systematic review showed that there was some evidence that the procedure improved pregnancy and live birth rates. However, reviewers found the quality of evidence low due to lack of randomisation, small numbers and other risks of bias that limit the reliability and generalisability of results (Nastri et al., 2015). The evidence that endometrial scratching improves fertility outcomes has since been challenged by a large, well designed, RCT that addressed many of the limitations of previous trials. The latest evidence shows no difference

[1] The cost of an IVF cycle varies widely between clinics. For example, bulk billing clinic, Adora (www.adorafertility.com.au), charges $0 out of pocket for a package including consultations, blood tests and ultrasounds, egg and sperm collection, embryo transfer and the IVF, intracytoplasmic sperm injection (ICSI) cycle or frozen embryo transfer cycle. Day surgery, anaesthetist fees and medication are extra and Adora estimates that cost is approximately $1000. An ICSI cycle at Monash IVF costs $9780.

[2] The change in terminology occurred in 2017 so many of the website texts and studies referenced in this paper refer to PGS. Where possible I will use the correct term but when referring to other texts, I will use the terms they use, including the outmoded 'preimplantation genetic screening' and 'PGS'.

[3] Heneghan et al do note that these RCTs investigated an older version of PGS and that a new PGS techniques seemed to provide better outcomes (Heneghan et al., 2016, p. 3). Even with this additional information, it would be reasonable to assume the cost of the previous version of PGS carried a similar cost.

in live birth rate between the endometrial scratch group and its corresponding no-intervention group (Lensen et al., 2019). Endometrial scratching was the adjunct intervention with the most robust, most promising evidence but this recent study by Lensen (2019) may mean that no adjuncts have robust evidence to support their efficacy.

Another issue with adjunct interventions is that they are expensive and may contribute to the financial burden experienced by many people undergoing fertility treatment without delivering a benefit. If it is the case that they do not improve fertility outcomes, questions are raised about the ethics of offering these interventions to patients when their cost can compound the distress experienced by patients.

In Australian society, as with other developed nations, it is socially accepted, and sometimes celebrated, that medicine is a lucrative profession. There is an accepted expectation that we pay doctors a fee for their service. It is also accepted that healthcare exists as a combination of government support, through our universal healthcare system, Medicare, and private sector complements and supplements to deliver care with more choice. It is also not uncommon to pay for expensive medical treatments, especially when specialist care is required.

What consumers also expect is that interventions offered, recommended and performed by doctors are interventions that are safe and effective, but this has been shown not to be the case with IVF adjunct interventions overseas. In the UK, studies have shown that ART clinics routinely make claims of benefit about adjunct interventions without offering evidence to support those claims (Spencer, Mahtani, Goldacre, & Heneghan, 2016). British research has also found that the adjunct interventions offered by their ART clinics are not supported by clinical evidence (Heneghan et al., 2016) and since they can add considerable expense to an already expensive treatment plan, there have been suggestions that they are being offered in the financial interests of clinics rather than for the benefit of patients. This area of research is lacking in Australia, and little is known about what adjunct interventions are available, how expensive they are and to what extent they are offered by Australian clinics.

1.4 Financial conflicts of interest in healthcare

The rise of commercialisation in ART brings with it the need examine how financial conflicts of interests are affecting clinical practice. Financial conflicts of interest, defined as a situation where there is a risk that a secondary interest may unduly influence a primary interest (Lo & Field, 2009), has been the subject of much research in other areas of healthcare, much of it centres around relationships with industry, 'Big Pharma' in particular. Though not specifically in reference to ART, these studies provide findings and trends to note since ART relies heavily on pharmacotherapy and there is evidence that Australian ART clinics have fostered ties with pharmaceutical companies. For example, several Australian clinics have provided links on their websites to information booklets produced by pharmaceutical company, Merck Serono (see for example the patient information booklets on the website for Queensland Fertility Group, 2018).

Research has shown that relationships with pharmaceutical companies has a pronounced effect on prescribing patterns in favour of the pharmaceutical companies (DeJong et al., 2016), that gifts from industry, even small tokens such as pens and keyrings, can influence clinicians (Dana & Loewenstein, 2003) and that physicians cannot always tell when they have been influenced or when their prescribing is not evidence based (Austad, Brendel, & Brendel, 2010; Haayer, 1982). Further, there is evidence that doctors believe they are

immune to the influence of pharmaceutical marketing, gifts and other incentives, while believing that their colleagues are not (Austad, Avorn, & Kesselheim, 2011; Lemmens, 2011; Spurling et al., 2010). What this means for financial conflicts of interest is that there are strong indications that clinicians and professional may not always be able to recognise a financial conflict of interest or that they are acting under an undue influence. There is also evidence that financial interests lead to over diagnosis and over treatment (Moynihan & Bero, 2017). There is nothing to suggest that these phenomena do not also apply to ART specialists.

Bioethics literature on conflicts of interest in ART has predominantly centred around the novel relationships created by the use of new technologies. The ability to create human embryos outside of the body, to form them using autologous or donated gametes and to have them be carried to term by gestational surrogates has raised a host of issues that ethicists have tried to anticipate. The literature has addressed conflicts of interest such as those between surrogates and the intended parents (Tanderup, Reddy, Patel, & Nielsen, 2015), between the clinician who is treating two competing patients, such as a donor and their recipient, and the conflicts of interests that arise during contractual arrangements between clinicians, patients, lawyers, psychologists and gamete brokers (Blake, McGowan, & Levine, 2015). There is also a body of literature that examines the conflicting interests of biological and non-biological parents, donors and the children conceived with ART (Applegarth, Kaufman, Josephs-Sohan, Christos, & Rosenwaks, 2016; see note 8 on p.13 of Chalmers, 2002; see s5.9 of NHMRC, 2017).

In contrast, there has been little research specifically focussed on financial conflicts of interest in ART. This is partly because the widespread use of ART is recent, so the focus has so far been on issues that are more obvious and immediate, like the other kinds of conflicts already described above. Financial conflicts of interest have gained attention with increasing commercialisation and that, too, is relatively recent so we are only beginning to identify the aspects that warrant investigation. The nature of relationships that exist within ART have also shaped what issues are given attention. For example, patients are in a situation where, if they want to question the commercial or financial arrangements of their clinics, they may feel they are jeopardising the care they will receive. Similarly, it is employees who are most likely to have first-hand knowledge of undue influences and witness improprieties (see for example section 3.2 in Gorton, 2018) but having to challenge employers and managers places employees, and other whistle-blowers, at risk. However, when given the protection of an independent investigation and the option of anonymity, some ART professionals have indeed made very serious allegations about unethical behaviour. For example, one anonymous professional told of instances where embryos had perished but clinics did not tell patients or deliberately misled them about what had transpired (Gorton, 2018). In another incident, a doctor knowingly transferred an expired embryo into a patient and told her it was viable (Gorton, 2018). There is no direct evidence or suggestion that these incidences were the result of financial conflicts of interest but they were raised in the context of the adequacy of self-regulation, something that is considered the equivalent of no regulation by its critics (Chalmers, 2002), in an environment of increasing commercial pressures (Blakely, Williams, Mayes, Kerridge, & Lipworth, 2017).

There is little published research specifically dealing with financial conflicts of interest in the Australian ART sector and none that consider the relationship between adjunct interventions and financial conflicts of interest. Only two articles were identified through extensive database and manual searches.

The first article, by Blakely, Williams, Mayes, Kerridge and Lipworth (2017), investigates conflicts of interest in Australian ART and presents findings from interviews with a small number of participants including ART clinicians, counsellors and researchers. The interviews revealed experiences of financial and business concerns competing with patient interests and influencing clinical practice. Examples include one participant who spoke of being directed to grow the business with unethical strategies such as recommending more patients have IVF, even when not clinically indicated, or creating situations where a patient will need to have further treatment (Blakely et al., 2017). Such actions do not conform to the *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research* (ART guidelines) issued by the National Health and Medical Research Council (NHMRC) (see for example sections 3.9 and 4.1 in NHMRC, 2017) and are a clear example of a manifestation of financial conflicts of interest. This is also the kind of data that has prompted questions about the adequacy of current regulation.

The second article, by Mayes, Blakely, Kerridge, Komesaroff, Olver and Lipworth (2016), explores the impact of commercialisation on the professional virtue of doctors and how conflict of interest policies attempt to ensure ethical conduct. Both Mayes (2016) and Blakely (2017) comment on the inadequacy of conflict of interest management strategies such as disclosure but their weakness also stems from what Mayes has identified as lack of awareness or unwillingness to address conflicts of interest (2016). For example, Mayes quotes Dr. Lyndon Hale, Director of Virtus Health, who recognises that he has the duelling priorities of patient care and business profitability but denies that the two responsibilities constitute a conflict of interest (2016). Mayes also points out that Monash IVF's code of conduct declares that all employees, which includes their IVF doctors, should recognise that their primary duty is to "the Company and its shareholders" (2016). This is a contravention of the widely held principle that patients are a doctor's first priority. It has been suggested that one way to protect patients from conflicts of interest is to actively cultivate virtue in our medical profession (DuBois et al., 2017; Mayes et al., 2016) but asking doctors to cultivate virtue without structural support shifts the burden to individuals and away from government and regulators.

While the existence of these financial interests are openly stated, Mayes (2016) and Blakely (2017) also show that parts of the medical establishment are hesitant to acknowledge financial conflicts of interest (Blakely et al., 2017; Mayes et al., 2016). These Australian-specific articles point to a possible divide between what ART practitioners and ethicist believe to constitute a conflict of interest. This highlights the need for further scholarship in this area, especially since international research has found that doctors are not adept at detecting, resolving or managing financial conflicts of interest.

1.5 The research question

With interventions that are expensive and have not been proven to be safe or efficacious, questions are raised about how they can be in the patient's best interests. Considering their cost, we also need to ask whether their availability and prescription indicates financial or commercial interests that would constitute a financial conflict of interest. It is difficulty to investigate these issues since there is little local knowledge available. Media reports (Ferguson et al., 2016) and other sources (Gorton, 2018) have established that Australian IVF patients are receiving adjunct interventions, however, there has been little research into the adjunct interventions available in Australian ART clinics so we do not know the extent of availability and use, and therefore the scope or scale of any problems.

This study aims to answer the question of whether, and to what extent, Australian ART clinics are offering patients non evidence-based adjunct interventions and analyse how the provision of these therapies might constitute a financial conflict of interest.

Chapter 2: Study Results

2.1 Methodology

This study composed of two parts. In Part I, a content analysis was conducted to collect data from Australian ART clinic websites to ascertain what adjunct interventions are being offered. Websites of ART clinics were examined to identify all fertility treatments, services and interventions being offered, then each intervention was assessed and classified according to whether they are adjunct interventions.

Websites were chosen as the corpus for Part I because studies have shown that many people, including IVF patients, start their search for health advice online so examining website texts shows us the same information that patients have access to (Haagen et al., 2003; Huang, Al-Fozan, Tan, & Tulandi, 2003; Weissman, Gotlieb, Ward, Greenblatt, & Casper, 2000). Examining website texts means we are looking at the same messages and information the clinics have chosen to present to the public about their adjunct services. Secondly, since all almost all Australian ART clinics have a web presence, this means results are generalisable to help us draw conclusions about patterns and trends across the industry. Finally, websites were chosen because conflicts of interest is a difficult topic to investigate by observation or other kinds of primary data collection. Observational studies are also unsuitable since consultations between doctor and patient will contain personal and sensitive information and the insertion of a researcher would disturb the privacy of the patient.

In Part II, a literature review of clinical evidence was conducted for each intervention to determine whether there is an evidence base for each intervention classified as an adjunct in Part I. The evidence search began with Cochrane database of systematic reviews. Cochrane reviews were chosen due to their reputation for high quality systematic reviews and because their reviews are updated regularly.

Levels of Evidence were assessed according to the NHMRC evidence hierarchy (2009) (see Appendix A for NHMRC Levels of Evidence). The NHMRC evidence hierarchy was chosen because it is Australian and from a reputable agency. Together, Parts I and II will answer the questions of what interventions are being offered by Australian ART clinics and whether they are evidence based.

2.2 Part I: Content Analysis

2.2.1 Methods

A list of current Australian clinics was made by collecting information from the webpages of the Reproductive Technology Accreditation Committee (RTAC) between January and May 2018. Since all Australian ART clinics must be accredited and licensed by the RTAC, every clinic licenced to operate in Australia is detailed on the RTAC website. However, there is no information on whether each clinics has a web presence.

All clinic names and addresses were collected from the RTAC webpages and recorded in a spreadsheet. Over the data collection period, it was noticed that clinics had been added to and removed from the RTAC list so the list was checked periodically and last checked in May 2018. Email to RTAC in May 2018 confirmed the list was current and up to date.

Inclusion and exclusion criteria

A Google search was conducted for each clinic's website. The URL was also noted in the spreadsheet. All websites were included for the next stage, the identifying of treatments, except:

- URLs that did not work: For example, pages that appear in Google search results but the website could not be accessed.

- Duplicates: Several of the larger companies had multiple branches, each with their own website. These texts were only collected once if the only difference was contact and location information. Websites of the same organisation, at a different locations, were included when they differed in more substantial ways, for example Melbourne IVF and IVF Australia are two arms of Virtus Health and each has very different branding and websites.

Identifying interventions

Each website was searched to catalogue interventions being offered. Texts were collected from the treatments and services pages of each website, then saved as static copies to contend with the ephemeral nature of web texts.

Files were imported to Nvivo for coding and analysis. Nvivo was chosen for its capacity to search, code and analyse large amounts of text.

Upon examining each webpage, when a treatment was identified, it was coded by the name of treatment. Some treatments had different names at different clinics, for example, some clinics referred to hyaluronic adhesion compounds, or transfer media, while others specified the brand name EmbryoGlue. Where treatments had multiple names, each name was coded and all codes were collected under the one node.

Once all webpages had been coded for treatments, a text search query was run for each treatment coded to capture any treatments missed by manual coding. All treatments being offered were then classified into one of the following four groups:

1. Medicare Benefits Schedule (MBS) items
2. Not an adjunct to IVF
3. Not medical
4. Adjunct interventions

The four categories were defined as follows:

1. MBS items: MBS items are procedures that carry a Medicare rebate. Since these are defined as "clinically relevant services [which are] generally accepted by the medical profession as necessary for the appropriate treatment of the patient" (MBS, 2018) they have been excluded from further investigation for evidence base[4].

2. Not an adjunct to IVF: These treatments and services include medical services but are not exclusively adjunct interventions for IVF. They have other applications for specific populations, such as treatment for depression or surgery for endometriosis. Some are ART but not IVF interventions.

3. Not medical: These refer to any treatment that does not require a doctor's prescription. In this study we are interested in treatments that can only be dispensed by a doctor in order to focus on the implications of doctors using non evidence-based treatments.

4. Adjunct interventions: Most of the remaining treatments fell into this category. Adjunct interventions are medical treatments offered with the aim of improving the outcome for a particular aspect of the IVF cycle, to contribute to the overarching goal of achieving a successful pregnancy and live birth.

2.2.2 Findings for Part I

In Part I, Australian clinics and their websites were identified and data was collected on the treatments and services they offered on their websites. The treatments were classified into several categories, including whether they qualified as an adjunct, and therefore, whether they will be investigated further in Part II.

2.2.2.1 Identifying clinics and websites

From the RTAC list of accredited clinics, 94 clinics were found and their details recorded. Using Google, a search was conducted for each clinic's website using the name of the clinic as the search term.

All clinics had a Google search result but not all pages were functioning. There were three clinics excluded from further analysis due to non-functioning websites; one site did not load, one site was under construction and there was one site where the institution's website remained but the page about IVF treatment had been removed. Of the remaining 91 websites, 46 were removed as duplicates, which left 41 sites for inclusion in further analysis.

[4] It should be noted that even though Medicare deems MBS items as being "generally accepted by the medical profession as necessary", MBS items are not uncontroversial. For example, endometrial scratching is currently being considered for inclusion for MBS coverage (Medicare Benefits Schedule Review Taskforce, 2018, p. 58; Nastri et al., 2015) based on the Cochrane systematic review by Nastri (2015) which concluded that the only robust evidence had substantial risk of bias. Natural cycle IVF also attracts a Medicare rebate under item number 1302 but the British National Institute for Health and Care Excellence (NICE) has a 'Do Not Do' Recommendation for natural cycle IVF: "Do not offer women natural cycle IVF" (NICE, 2013, p. 26)

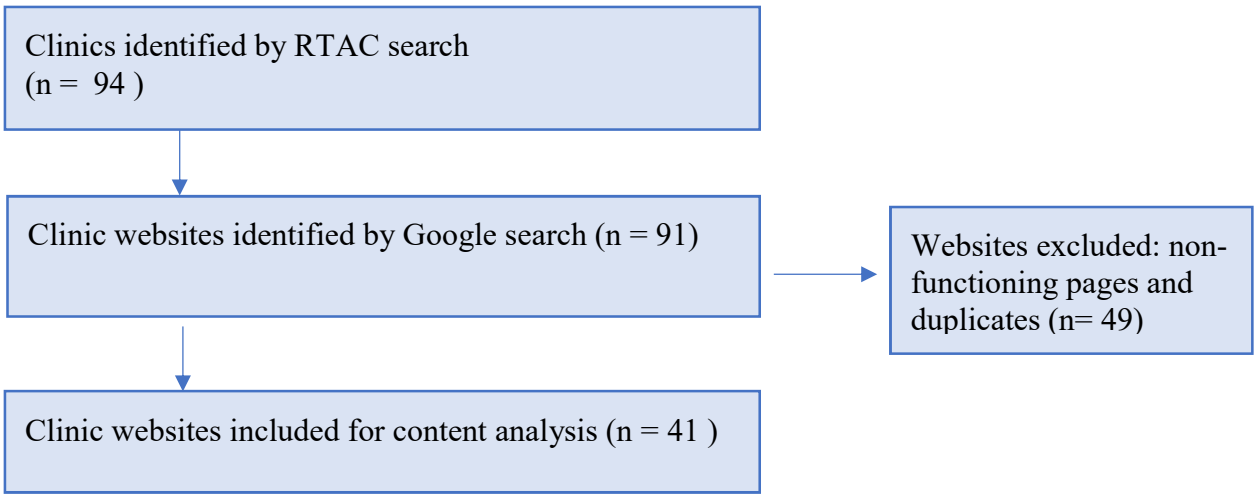

Figure 1: Selecting websites for inclusion for content analysis

2.2.2.2 Identifying and categorising treatments

Table 2.1 Treatments identified from all clinic websites

Items listed on MBS*	anti-sperm antibody testing, controlled ovarian hyperstimulation, egg freezing, embryo freezing frozen embryo transfer, fresh embryo transfer, hysterosalpingogram, intracytoplasmic sperm injection, intrauterine insemination, IVF, laparoscopy, ovulation monitoring, surgical sperm retrieval, natural IVF, ovulation induction, ovulation ultrasound, semen analysis, transvaginal or pelvic ultrasound
Not add-on to IVF	depression treatment, female microsurgery**, GIFT, gonadotropin, infectious disease testing, insulin sensitising, male microsurgery**, mild ovarian stimulation IVF, ovarian tissue freezing, semen freezing, thalassaemia screening, timed intercourse, tubal surgery, PCOS treatment, treatment for nervous system exhaustion
Not medical	acupuncture, chiropractic, dietetics, life coaching, massage, micronutrient therapy, multivitamins, naturopathy, "over 40s program", Quitline, relaxation, yoga, zinc, selenium, herbal supplements
Adjunct interventions	ovarian reserve testing, assisted hatching, digital high magnification, time lapsed imaging, endometrial scratching, hyaluronic adhesion compounds, sperm chromatin structure assay (SCSA), advanced sperm selection, PGT-SR or PGS, tubal flushing, post coital test, ultrasound guided transfer, endometrial receptivity assay, granulocyte macrophage colony stimulating factor, Natural Killer cell treatment, ovarian rejuvenation

* Some MBS items for ART only qualify for rebate when used in conjunction with other specific MBS items or in preparation for other MBS procedures. For example, ovulation induction only attracts a rebate when preceding an insemination procedure.

**This refers to non-specific "female microsurgery" and "male microsurgery" offered by several clinics that was available for a variety of conditions and circumstances. Some of these surgeries may be considered adjunct interventions but descriptions were often too broad and generic to identify a specific adjunct purpose.

2.2.2.3 Identifying adjunct interventions offered by RTAC accredited ART clinics

Table 2.2 Adjunct interventions offered by Australian clinics

Adjunct intervention	Number of websites (number of businesses)	Purpose of adjunct intervention	Example of cost
Ovarian Reserve Testing Eg "Egg timer test", Anti-Mullerian hormone (AMH) test and antral follicle count.	38 (10)	Help predict likely ovarian response to gonadotrophin stimulation in IVF. Also portrayed as a measure of a remaining egg supply and/or an indicator of fertility.	$75 - $100 for AMH testing
Assisted hatching	19 (9)	Help 'hatch' egg by piercing or thinning zona	$275 - $300
Digital high magnification, for IMSI	8 (5)	See sperm +6000x magnification, compared to standard 200-400x, to select best sperm based on morphology for ICSI	$300
Time lapsed imaging systems Eg EmbryoScope	33 (7)	To assess development of embryo to blastocyst stage without disturbing embryo and culture environment.	
Endometrial scratching	20 (7)	To trigger immune response that makes the endometrial lining more receptive to implantation	$200
Hyaluronic adhesion compounds eg EmbryoGlue®	10 (4)	Used as a transfer medium to increase chance of implantation	$500 for fresh embryo transfer, $300 for frozen
Sperm chromatin structure assay (SCSA) for DNA fragmentation testing eg HALO Sperm	25 (8)	To assess best sperm for ICSI	$150
Advanced sperm selection eg PICSI and SpermSlow®	9 (5)	Choose best sperm for ICSI	$433
PGD	30 (19)	Screening for single gene disorders	$2000-$10960 (feasibility study and set up cost) plus up to $925 per embryo
PGT-SR (PGS)	42 (14)	Screen for abnormal number of chromosomes.	$2000 - $8010 plus

			$385 - $875 per embryo
Tubal flushing with various contrast media eg poppy seed oil or Lipiodol	11 (5)	Clear debris causing blockage of fallopian tubes	
Post coital test	1 (1)	To detect the presence of motile sperm or assess motility of sperm.	$160
Ultrasound guided transfer	6 (5)	Ultrasound guided catheter for embryo transfer rather than 'clinical touch' – i.e. reliance on clinician's senses and judgement of when catheter is in correct position before depositing embryo.	
Endometrial receptivity assay (ERA)	2 (2)	To determine endometrial receptivity for best window for implantation.	ERA Cycle $350+ Cost of drugs+ Ultrasound $210+ Biopsy $200+ Biopsy sample analysis $750
Granulocyte macrophage	8 (2)	Culture supplement meant to more closely mimic natural conditions during embryo growth after fertilisation before transfer	$250
Natural Killer cell treatment by intralipid infusion	5 (3)	Intralipid (soya oil) infusion to aid implantation	
Ovarian rejuvenation	1 (1)	Platelet rich plasma (PRP) injections to promote healing and attract stem cells to the site.	
Polarised light imaging eg PolScope™	2 (2)	PolScope uses polarised light to study genetic material in the egg, in particular examining meiotic spindle to evaluate egg maturity to aid identification of best eggs for fertilisation	$375 plus $150 consultation fee

Table 2.2 shows the 18 adjunct interventions that were identified. Table 2 also gives a brief description of the intended purpose of each treatment and some information on cost. Not all clinics published costs for all services so cost could not be located for all treatments.

Table 2.2 also shows that adjunct interventions, especially when used in combination, can add significant expense to an IVF cycle. Despite the treatments being widely advertised, pricing information for most treatments was only displayed by a small number of clinics. Most clinics did mention costs with an invitation to contact the clinic for more information. For PGT-SR, the cost varied more than other interventions and were often packaged (eg cost for up to X number of embryos or capped). Appendices C and D are samples of cost schedules from two clinics.

2.2.2.4 Australian clinics and the adjunct interventions they offer

See Appendix B for Table 2.2 Australian clinics and the adjunct interventions offered on their websites

Table 2.3 shows how many websites are offering adjunct interventions and how many different adjunct interventions each website offers.

Of the 91 clinic websites identified, 84 (92%) offered at least one adjunct intervention and nine (9.8%) clinics offered none. Of the nine clinics that offered no adjunct interventions, two were public hospital clinics, four are in remote or rural locations and two are low cost 'no frills' services. One clinic offers ART but not IVF. Although the 91 clinic websites includes duplicates, I have based this calculation on the entire body of websites available to consumers to emphasise the widespread message being communicated to patients and those seeking information. It shows that anyone searching clinic websites for information would almost certainly be presented with a positive message about the use and availability of adjunct interventions.

Most clinics only advertise a few adjunct interventions. This means that most of the website text was not focussed on adjunct interventions. However, Table 2.3 below shows that offers of adjunct interventions is pervasive. Together, ART clinic websites form a large body of information that almost always includes mention of adjuncts as a possible avenue of improving ART outcomes. This is what consumers encounter when they search online for information.

The most commonly offered adjunct interventions were PGT-SR, which is also the most expensive of the treatments (see Table 2.2). PGT-SR was offered by 14 different businesses across 42 websites, the cost of which would add thousands of dollars to an IVF cycle.

The number of adjunct interventions offered by a website did not correspond with the size of the business. For example, Genea and Monash, both market leaders, offer only two adjunct interventions each on their websites.

2.3 Part II: Evaluation of clinical evidence

In Part II, we are using the results from Part I to determine which interventions to investigate further. The interventions included in Part II have all been classified as adjuncts. Part II will determine whether there is empirical evidence to support their use.

2.3.1 Methods

To investigate claims that adjunct interventions are not evidence-based, searches were conducted for evidence for each adjunct and evaluated for whether it improved outcomes. The main outcome of interest was live birth rate but other significant outcomes were also noted.

Inclusion and exclusion criteria

Searches performed on the Cochrane Database of Systematic Reviews were conducted between October 2018 and May 2019. Each intervention was searched by name. Results were assessed for relevance by Review title.

Other searches were conducted on PubMed and Medline between December 2018 and May 2019, by name of intervention. Studies were initially filtered by title and abstract to identify studies meeting the following inclusion and exclusion criteria.
Inclusion criteria:

i) Intervention used as part of IVF[5]
ii) On human participants
iii) Reporting live birth or pregnancy rate

Exclusion criteria:

i) Not used in conjunction with IVF
ii) Trials conducted on non-human animals
iii) Not in English
iv) No full text available (eg conference abstracts)

Papers were then read to understand review authors' conclusions about the evidence for improved outcomes and quality issues of the included studies. Only outcomes for pregnancy and live birth rates were noted. Live birth is the most relevant outcome for fertility patients but not all studies reported on live birth rates so pregnancy rates were chosen as next most relevant outcome. Other important outcomes such as harms were not regularly or adequately assessed, recorded or reported so the decision was made to confine this project to an examination of whether the treatments helped patients achieve pregnancy or live birth.

2.3.2 Findings for Part II

2.3.2.1 What kind of evidence do adjunct interventions have?

Table 2.4 Levels of evidence for adjunct interventions offered by Australian ART clinics

NHMRC Level of evidence	Evidence available	No. of adjunct interventions (%)	Adjunct interventions
I	Adjuncts with systematic reviews of level II studies	14 (82%)	Ovarian reserve testing, assisted hatching, digital high magnification, time-lapsed imaging, endometrial scratching, hyaluronic adhesion compounds, SCSA, Spermslow, PGT-SR / PGS, polarised light, tubal flushing, post coital, ultrasounds guided transfer, granulocyte macrophage colony stimulating factor.
II	Adjunct with RCT	1 (5.5%)	Natural Killer cell treatment by intralipid infusion
III	Adjuncts with prospective cohort study	2 (11%)	Natural Killer cell treatment by intralipid infusion, Endometrial Receptivity Array
IV	Adjunct with other observational studies	1 (5.5%)	Ovarian rejuvenation

[5] This is to distinguish from interventions used for ART but not necessarily for IVF. For example, ovarian reserve testing is a common procedure, also known as 'the egg timer test', which is advertised as a way to estimate "fertility potential" by looking for number of eggs and often used to "predict" fertility. The egg timer test is often marketed as a gauge of currently fertility to help people make fertility decisions such as freezing eggs for future use.

Summary of Table 2.4: Evidence available for each adjunct

The results for Part II show that 14 of the 18 (82%) adjunct interventions have systematic reviews of RCTs and other NHMRC Level II evidence, which means the systematic reviews are of NHMRC Level 1 evidence and, assuming reviews are robust, the systematic reviews provide reliable analysis of the studies they examine.

The remaining three interventions had lower levels of evidence, such as observational studies, and several had only small groups or single case studies. For this thesis, a systematic review of research for these three interventions was not included for various reasons. For example, there is relatively little research to review for ovarian rejuvenation since it is still highly experimental. So far, the literature is predominantly observations of single cases or small groups and are not studies designed to show that the intervention is related to the effect.

2.3.2.2 Adjunct interventions and outcomes

Table 2.5 Does the adjunct improve pregnancy or live birth rate?

	Evidence of improved clinical or ongoing pregnancy rate	Evidence of improved Live birth rate
Ovarian reserve testing	No	No
Assisted hatching	Yes, moderate quality	No
Digital high magnification	Yes	No
Time lapsed imaging systems	No	No
Endometrial scratch	Yes, moderate quality	Yes, moderate quality
Hyaluronic adhesion compounds	Yes, moderate quality	Yes, moderate quality
Sperm chromatin structure assay	No	No
Advanced sperm selection techniques	No	No
PGD	No	No
PGT-SR / PGS	No	No
Tubal flushing	Yes, moderate – low quality evidence	Yes, moderate – low quality evidence
Post coital test	No	No
Ultrasound guided transfer	Yes, low quality	Yes, low quality
Granulocyte macrophage colony stimulating factor	No	No

Of the interventions with systematic reviews, four interventions had evidence to support improved lived birth rate, however the evidence was of low to moderate quality due to risks of bias. Cochrane systematic reviews assessed quality using the GRADE approach. The intervention with the most robust evidence was endometrial scratching but limitations, such as small cohorts in the individual trials and the inability to rule out effects from other

procedures, meant that our confidence that the effect was caused by exposure to endometrial scratching was lowered. As noted in Table 2.6 below, a more recent RCT for endometrial scratching addressed many of the limitations of previous trials and found no improvement in live birth rate. Five interventions had evidence of improved clinical pregnancy rate. The systematic reviews found that these were also of low to moderate quality. Low to moderate quality evidence means that more research is required and the intervention should not be used routinely.

Adjunct interventions and their evidence

Table 2.6 Adjunct interventions with systematic reviews

	Number of RCTs (participants)	Systematic Review	Quality of evidence, limitations of trials, risks and other comments.
Time lapsed imaging systems	9 (2955)	Armstrong (2019). Time-lapse systems for embryo incubation and assessment in assisted reproduction.	RCTs were all of low or very low quality so review authors found it difficult to draw conclusions about the benefits and harms. Due to the low quality of evidence, the review found it unclear whether time lapsed imaging systems made any difference compared to conventional incubation and assessment for pregnancy, live birth, miscarriage or stillbirth rates.
Hyaluronic adhesion compounds eg EnbryoGlue®	16 (3687)	Bontekoe (2014). Adherence compounds in embryo transfer media for assisted reproductive technologies.	Only 6 of the 16 studies reported on live birth rate. The metanalysis found evidence that live birth rate was improved with the use of hyaluronic acid (HA) adhesion compound but this result is mostly attributed to one large RCT. The remaining studies that reported on live birth rate were of lower quality evidence with much smaller sample sizes. The most robust evidence was for improvement in clinical pregnancy rate but method of determining pregnancy was unclear in several studies. Effect on risk of harms could not be identified due to the small number of studies that reported on adverse effects.
Ultrasound guided transfer	21 (6214)	Brown (2016). Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women.	Evidence is of low quality but review authors estimate that chance of live birth or ongoing pregnancy is increased by 5-10% when embryo is transferred with ultrasound guidance and there is an association with increased clinical

			pregnancy rate. 4/ 21 trials reported live births. Risks reported were multiple pregnancy, ectopic pregnancy and miscarriage. Difference between intervention and no intervention was difficult to detect due to small sample sizes.
Assisted hatching	31 (5728)	Carney (2012). Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI)).	Only 9/31 studies reported on live birth rate and there was no evidence that assisted hatching improved live birth rate. However, there was moderate quality evidence to show that assisted hatching increased the chance of achieving a clinical pregnancy but the review authors caution that the results only just reached statistical significance. 14 trials reported on miscarriage, rate was similar is both the intervention and control groups.
Sperm chromatin structure assay (SCSA) for DNA fragmentation testing, eg Halosperm®	21 (2227+)*	Cissen (2016). Measuring Sperm DNA Fragmentation and Clinical Outcomes of Medically Assisted Reproduction: A Systematic Review and Meta-Analysis	Studies included had significant limitations. Evidence points to poor capacity for SCSA to predict which couples have a higher or lower chance of conceiving and shows that low sperm DNA fragmentation does not mean more pregnancies. Harms were not reported in this review. * Number of participants = 2227+. Two studies did not report number of participants.
PGD	0	Franssen (2011). Reproductive outcome after PGD in couples with recurrent miscarriage carrying a structural chromosome abnormality: a systematic review	There were no RCTs or comparison studies so two systematic reviews were conducted on a total of 25 studies (595) to compare outcomes for couples who conceived naturally v couples who had IVF. One study from the PGD review accounts for 49 of the 126 in PGD group but did not report on live birth rate. The review concludes that there is insufficient evidence to show that PGD improves live birth rates in couples with repeated miscarriage and chromosomal abnormality. Miscarriage rate was reported but data insufficient to indicate effect.

Ovarian Reserve Testing	20 (6088)	Lensen (2018): Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI)	The evidence did not find that tailoring gonadotropin dosage to ovarian reserve test results led to improved rates of live birth or ongoing pregnancy. The quality of evidence included in the review ranged from very low to moderate. Decreased dosage in some women may reduce OHSS but size of the effect not clear.
Advanced sperm selection techniques. Eg PICSI and SpermSlow®	2 (581)	McDowell(2014) Advanced sperm selection techniques for assisted reproduction	Only low quality evidence with significant limitations was available. Only 1 of the two trials reported on live birth rates. Insufficient evidence to show difference in any outcomes between techniques or when compared to conventional ICSI.
Tubal flushing	13 (2914)	Moyihiddeen (2015)Tubal flushing for subfertility	Low quality evidence shows flushing with oil soluble contrast media may increase chance of pregnancy and live birth compared to no intervention. Insufficient evidence to draw conclusions about other outcomes.
Endometrial scratching	14 (2128)	Nastri (2015) Endometrial injury in women undergoing assisted reproductive techniques.	Systematic review found moderate quality evidence that endometrial injury between day 7 of previous cycle and day 7 of the current embryo transfer cycles was associated with increased rates for live birth and clinical pregnancy. There was also evidence that endometrial scratch performed on day of egg retrieval is associated with reduced rate of clinical pregnancy and ongoing pregnancy. Low quality evidence showed no difference in rate of miscarriage. Very low quality evidence reported increase in pain complaints. Review authors caution that individual studies are small and underpowered and had methodological issues that created a high risk of bias. **2019 Update**: A team led by one of the Nastri review authors

			conducted a large pragmatic, multi-centre open label RCT with 1364 participants (Lensen et al., 2019) found that endometrial scratching did not result in a higher rate of live birth. Live birth rate was the same for both the intervention group and the control group (21.6%). Lensen's study addressed many of the quality issues raised by the systematic review eg by ensuring this study was sufficiently powered and biases introduced by methodology were mitigated or avoided.
Post coital test	1 (444)	Oei (1995) When is the post-coital test normal? A critical appraisal.	No significant difference between cumulative pregnancy rate with intervention v no intervention. Confounding not sufficiently dealt with to make comparisons and draw firm conclusions about benefits or risks. Even after taking into account limitations, predictive value of the post coital test was found to be poor.
Granulocyte macrophage colony-stimulating factor (GM-CSF)	1 (1621 patients, plus 161 embryos)	Siristatidis (2013) Granulocyte macrophage colony stimulating factor supplementation in culture media for subfertile women undergoing assisted reproduction technologies: a systematic review.	No statistically significant differences were found in implantation and pregnancy rates. Some indication of improvement in other outcomes, such as embryo quality However, no statistically significant differences were found in implantation and pregnancy rates in all apart from one large multi-centre trial, which reported favourable outcomes, in terms of implantation and live birth rates.
Digital high magnification	9 (2014)	Teixeira (2013) Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction.	Evidence included in this review was of low and very low quality. Only 1 of the 9 RCTs reported on live birth rates and showed no difference between intervention group and control and effect on clinical pregnancy was "very uncertain". Evidence showed no benefit regarding miscarriage, no evidence of effect on other adverse outcomes.

PGT-SR / PGS	9 (1589)	Twisk (2006) Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection.	PGS at the time significantly decreased ongoing pregnancy and live birth rates in women of advance maternal age and those with recurrent IVF failure. This review is 13 years old and did note that PGS techniques were evolving but no large RCTs or systematic reviews have been published since.

Summary of Table 2.6: Results from systematic reviews

Table 2.6 summarises the findings of systematic reviews including comments about the quality of the evidence assessed in the reviews. All reviews come from the Cochrane database of systematic reviews apart from Cissen 2016 for SCSA and Charalampos 2013 for the use of granulocyte macrophage colony stimulating factor. Systematic reviews of 14 interventions found evidence for improved pregnancy rate for five interventions and live birth rate for four interventions. However, the quality of the evidence reviewed was, at best, of moderate quality and had been downgraded due to risks of bias.

The overwhelming majority of studies reviewed had significant quality issues and insufficiently addressed risks of bias. Common issues include heterogeneity between cohorts and study designs, incomplete outcome data, and small sample sizes and lack of power. This means that the evidence they present is less reliable. If doctors wish to use these interventions, ethical principles demand that patients give informed consent after considering information including the lack of scientific evidence to demonstrate the intervention will bring any benefit.

Despite the fact that these interventions are being used in ART, many studies did not report on live birth rates. Most reported on clinical, rather than ongoing, pregnancy rate. This pattern may be due to time constraints and the desire to publish sooner since reporting on ongoing pregnancy and live birth rates would necessitate more time and follow up.

2.4 Summary of Results

The results from Parts I and II show that almost all Australian ART clinics are offering adjunct interventions but that almost all adjunct interventions lack a clinical evidence base. Adjunct services can also be expensive even though most treatments have no evidence to show that they have a benefit over no intervention or that they will increase the chance of taking home a baby. In fact, many studies did not record or report live birth as an outcome.

For the few interventions with evidence to support improved pregnancy or live birth rate, the evidence was not of high quality. This was the case across all interventions. Review authors repeatedly cited problems such as fundamental flaws in study design and insufficiently powered studies. This means that the body of evidence for all the adjunct interventions being offered by Australian ART clinics does not actually support their use.

Chapter 3: Discussion

In this chapter, the results are examined in the broader context of the Australian ART industry and the argument is made that provision of adjunct treatments is reflective of financial conflicts of interest in the industry. This is followed by brief critique of the current Australian regulatory framework.

3.1 Australian ART clinics are offering non-evidence based adjunct interventions.

The results of this study confirmed that non evidence based interventions are being offered by most Australian ART clinics. 84 of the 91 (92%) Australian clinics offered between one and nine adjunct interventions on their websites. Across all clinics, 18 different adjunct interventions were identified, 14 of which had undergone systematic review. Only four of these reviewed interventions showed evidence that they improved live birth rate, the most important outcome for ART patients, while five showed improved pregnancy rates. Importantly, the evidence showing these improved fertility outcomes was of low to moderate quality, so although the meta analyses showed statistically significant results, the included studies were not without important limitations and biases. All of the systematic reviews included studies with low and very low quality evidence, often due to poor study design, small sample sizes and risks of bias. Many of the included studies did not report on live birth rate, often due to a lack of follow up. Studies also did not sufficiently address adverse events or risks of harm. Further research involving sufficiently powered RCTs was called for by most of the systematic review authors. In all, none of the interventions had good quality evidence to demonstrate efficacy and safety.

The lack of evidence for interventions offered by Australian clinics mirrors the situation in other countries. For example, in Britain, the Human Fertility and Embryology Authority (HFEA) has recently responded to similar concerns by rating adjunct services with a 'traffic light' system where green means that there is more than one high quality randomised controlled trial to show efficacy, amber means that there is a small body of research with unclear conclusions and further research is required, and red means there is no good quality evidence to show that an intervention is effective in improving fertility outcomes (HFEA, , n.d.). The HFEA website has ratings for 11 interventions, including eight of the interventions offered by Australian clinics, and none of these have been given a green light. Five have been designated red, five are rated amber, one is both red and amber. Applying the same criteria, Australians too would find that none of adjunct interventions would meet the standard to receive a green light. Despite this lack of evidence base, adjunct interventions are being advertised widely and, it would be fair to assume, have been incorporated into practice by the clinics offering them.

3.2 Adjunct interventions can be expensive

The most commonly offered intervention was PGT-SR, offered by 41 clinics respectively—despite the lack of evidence that it improves pregnancy or live birth rates. As shown in Table 2.2, the cost of PGT-SR can be thousands to set up, then additional hundreds per embryo screened. No doubt some of the cost can be attributed to the need for expensive facilities, equipment and specialised staff to administer, process and analyse samples, but the range of pricing indicates the difference may be accounted for by difference in the profit component

between clinics. There is evidence that profit is a conscious growth strategy employed by Virtus Health, one of Australia's biggest ART companies. In recent financial reporting, Virtus Health explained that growth of profit was partly due to the expansion of pathology services such as PGT-SR. CEO Sue Channon said; "[w]e saw a 27.3% increase in pre-implantation genetic diagnosis and screening services [in the last 6 months], with one in five IVF patients now utilising this technology (Virtus Health, 2018b)." PGT-SR was originally introduce to screen for genetic anomalies that compromise the viability of embryos for patients with a particular profile of repeated failed cycles and complex fertility issues, but it is now marketed more widely with some clinics suggesting that it is suitable for all patients. One clinic indicates that PGT-SR is "recommended" for people who "[w]ant to increase their chance of a successful IVF cycle" and includes the note "PGD/PGS is open to all patients and is offered under clinical guidance depending on your particular circumstances. However, patients can opt for genetic testing from the outset of their treatment (City Fertility, 2019)."

Although not all adjunct interventions are as expensive as PGT-SR multiple tests can add a sizable amount to the overall cost of treatment. In this regard, it is noteworthy that nine of the adjunct services identified for this paper are diagnostic, or include a diagnostic component to the intervention (ovarian reserve testing, digital high magnification, SCSA, advanced sperm selection, PGT-SR, post coital test, endometrial receptivity assay, natural killer cell treatment), and it was common for clinics to offer packages of testing. For example, the Fertility Centre (2019) tells patients that the "first step" is to complete the 'Couples Fertility Assessment' which is a panel of tests including non-essential adjunct tests such as SCSA, another test that has no evidence to support an improvement in fertility outcomes.

It is also important to be aware that other expensive adjunct interventions are emerging. For example, ovarian rejuvenation (which was excluded in Part II due to the lack of systematic review) involves injecting the ovaries with autologous platelet rich plasma which purports to stimulate tissue regeneration. Claims include the reversal of menopause (Pantos et al., 2016; Sfakianoudis et al., 2019). Studies so far are few and have very small cohorts; Pantos (2016) had eight participants, Sfakianoudis (2019) had three. However, this has not tempered one clinic's enthusiasm. Demeter presents a video on its website of their fertility specialist, Dr David Knight, enthusiastically talking about "one of the newest and most exciting techniques that may be going to take the IVF world by storm…", explaining that menopausal women have had their egg production restored and "[o]ver 75% now have the option of natural pregnancy or in vitro fertilization" (Demeter Fertility, 2018). These are sensational and misleading statements that require a number of qualifications and clarifications that are not forthcoming. Although Demeter did not offer information on cost, an online search found two clinics in Greece, where much of the research and case reports on ovarian rejuvenation originates, offering the procedure for €1600 ($AU2600) and €2000 ($AU3295) (MediPass, 2017).

3.3 Financial conflicts of interest

The combination of a lack of evidence for adjunct interventions and their costs (either in isolation or in combination) has led bioethicists to query whether financial conflicts of interest may explain the widespread availability of adjunct interventions. This is a sensitive topic for some because the suggestion of a financial conflict of interest equates to an accusation of impropriety or a judgement of their morality (Rosenbaum, 2015). More specifically, claims that doctors have financial conflicts of interest are interpreted as accusations money might be more important to them than the wellbeing of patients (Mayes et

al., 2016). For others, financial interests in healthcare provision are acknowledged but constructed as unavoidable and unresolvable because in today's commercial climate, clinicians are often required to wear "different hats" (Blakely et al., 2017). In the next section, financial conflicts of interest are defined, then related to the use of adjunct interventions to show how financial conflict of interest might drive the sale of non-evidence-based adjunct interventions.

Definition of conflict of interest

A conflict of interest is a set of circumstances where a so called "secondary interest" could improperly influence a so-called "primary interest" (Lemmens, 2011). This definition is widely accepted internationally and can be found in medical codes of conduct such the *International Code of Medical Ethics* from the World Medical Association (WMA)(2006b), the *Good medical practice: a code of conduct for doctors in Australia* issued by the Medical Board of Australia (MBA) (2014), the *Code of Ethics* issued by Australian Medical Association (AMA) (2016) and in the *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research* (ART guidelines) produced by the NHMRC (2017). There are three elements to a conflict of interest: the primary interest, the secondary interest and the conflict itself.

The primary interest

The primary interests of a doctor are determined by the "proper goals" of their professional role, which are generally accepted to be the promotion of the health, wellbeing and safety of their patient (Oakley, 2014). This understanding is expressed not only in the abovementioned codes and guidelines, but it is also explicitly stated in the Declaration of Geneva, more commonly known as the modern day Hippocratic Oath. The Declaration states that the patient's health is a doctor's first consideration (World Medical Association, 2006a). In a draft revision of the Declaration, the notion of the patient's health has been expanded to encompass the "patient's health and wellbeing" and an additional clause has been proposed to state to the importance of patient autonomy. Primary interests are therefore often expressed as the obligation to promote or ensure the patient's health and wellbeing, or to protect the rights of the patient, such as their right to be involved in decision making about their treatment.

The secondary interest

In any clinical context, there can be multiple secondary interests (McCoy & Emanuel, 2017). They can include personal interests such as wanting to earn money, give preferential treatment to family and friends, progress one's career or be a scientific pioneer. They can also include "other-oriented" interests such as promoting research and innovation in order to benefit future patients. Secondary interests are not necessarily problematic and some are desirable (Thompson, 1993). Others are not morally important in and of themselves but lead to other important outcomes. For example, the interest in operating an ART clinic in a profitable manner can ensure the viability of the business which in turn safeguards other important interests such continuity of care for patients.

The conflict

The final element of a conflict of interest is the existence of the conflict itself. A conflict of interest means only that a set of circumstances exists where there is a risk that a secondary interest could unduly influence a primary interest. There is no requirement or suggestion that any improper act has occurred, nor is there any imputation of intention, or moral judgement

(Beauchamp & Childress, 2001; Emanuel & Thompson, 2011). Critically, conflicts of interest exist whether or not actual bias or harm has occurred (McCoy & Emanuel). This is important because, despite assurances that the existence of a conflict of interest is not inherently unethical, some medical practitioners still perceive an implicit moral judgement in acknowledging a conflict of interest and see disclosure of a conflict of interest as an admission of inappropriate behaviour (Emanuel & Thompson, 2011; Mayes et al., 2016). This may be the misapprehension under which the FSA issued its denial of financial conflicts of interest in Australian ART.

3.4 Interests and conflicts of interest in the provision of adjunct ART interventions

Adjunct interventions and ART doctors' interests

It seems reasonable to assume that in ART, as in medicine more generally, the "primary interest" of clinicians is to promote their patients' health, wellbeing and autonomy. With respect to adjunct interventions, fulfilment of this primary interest would include, where possible, providing interventions that are known to be effective or safe. There are, however, arguments that support the view that the provision of non evidence-based interventions is consistent with concern for patients' health, wellbeing and autonomy. Fertility specialist, Dr Lynn Burnmeister, for example, argues that she offers adjunct interventions to maximise her patients' chances of success: "If someone is not getting pregnant, you're going to try other things. You can't keep doing the same, same, same…[if] you read an article and it looks like something may work, and it's not going to cause your patient any harm, of course you want to try" (Whyte, 2017). If a doctor, after weighing the best available information, thinks the possible benefits outweigh the risk of harms, it may be in the patient's best interest to recommend the use of an experimental adjunct.

Another reason given by clinicians for providing non evidence based interventions is that patients demand them (Balendra, 2016"The Baby Business," 2016; Blakely et al., 2017; Scott, Knight, & Gartry, 2019). Doctors report that patients ask for interventions they have read about online or heard about through their networks and insist on trying them and clinicians acquiesce for various reasons, including to prevent them having treatment elsewhere or to maintain the patient's hope (Blakely et al., 2017). Since one component of a physician's primary interest is to demonstrate respect for patient autonomy, honouring a patient's request, even for an unproven adjunct, may be justifiable if the patient is properly informed of both the possible risks and benefits.

Importantly, "proper" information in this context would need to include information about the biases present in many of the studies that appear to support adjunct information. The provision of information would also have to take into account the fact that ART can be a highly emotional process, driven by powerful biological and social influences. These can influence patients' decision making about the use of adjunct interventions even when presented with empirical evidence. This dynamic is evident in an anecdote in which an IVF patient who was aware of the recent evidence against endometrial scratching, still wanted the intervention:

"It's funny, because even though the endometrial scratching has been shown not to work, there's a huge part of me that just wants to do it just exactly the same (Scott et al., 2019)."

The provision of information in this context would also need to account for the psychological forces that lead to the "therapeutic misconception"—a phenomenon in which people believe that participation in a clinical trial will benefit them (and/or not harm them) specifically, even when they've been told they may be randomised to a placebo control group, and can include denial that the trial could expose them to harm (Appelbaum, Roth, Lidz, Benson, & Winslade, 1987). These caveats aside, it does seem possible that offering adjunct interventions—including those that are not evidence-based—could be consistent with ART doctors' "primary interests" in promoting their patients' health, wellbeing and autonomy.

Whether or not one agrees that the provision of adjunct interventions is consistent with ART doctors' primary interest, there is little doubt that it can also be driven by secondary interests—most notably by the desire for doctors or clinics to make money. As described above, adjunct interventions can be highly lucrative with some services adding thousands of dollars to an IVF cycle and with some clinics setting prices with a substantial profit margin built in.

Adjunct interventions as a source of conflict of interest

If we accept that the sale of adjunct interventions contributes to the income of both individual doctors and ART clinics, then it follows that there is a risk that a secondary interest (in this case making money) could unduly influence a primary interest (in this case promoting the patient's health, wellbeing and autonomy). According to the definition provided above, there is, therefore a financial conflict of interest when doctors or clinics sell adjunct interventions. While this does not mean that the doctors or clinics are actually allowing this secondary interest to override their primary interest, this possibility does need to be taken seriously.

In the UK, the investigative journalism program, Panorama, suggested that unproven interventions were being sold for the financial gain of the clinics rather than for the benefit of patients (Cohen & McAuley, 2016). Posing as a couple seeking fertility intervention, Panorama journalists visited a high profile London IVF clinic. After a blood test, the female journalist was advised that her Natural Killer cells level was high, and this meant that her immune system would attack an embryo, for which she should have treatment by intralipid infusion. The doctor showed her evidence that women treated with intralipid infusions had an increased pregnancy rate from 9% to 46%. This vignette was juxtaposed with commentary from Cambridge University's Professor Ashley Moffat, a Natural Killer cells expert, who said that the doctor had misrepresented Natural Killer cells and, despite their name, they "certainly don't kill the embryo, they're not even in contact with the embryo" (Cohen & McAuley, 2016). There is also no evidence that "treating" levels of Natural Killer cells has any effect on fertility outcomes. Of Natural Killer (NK) cell testing and treatment, Professor Robert Winston has said: "I have scoured the research literature and I can find no good randomised controlled trials which clearly show that NK cells, elevated or not, treated or not, make any measurable difference to the real outcome in fertility treatment and IVF" (2019). The program concluded that since the interventions had no clinical indication, had no evidence to support its use, and lacked any other benefit to the patient, that it was logical to query whether it was motivated by financial interests of the doctor or clinic.

There are concerns that similar commercially-motivated practices are happening in Australia and that pressure is being placed on Australian ART patients to "optimise" their IVF treatment with unnecessary and unproven adjunct interventions. In 2016, the Australian Broadcasting Corporation (ABC)'s *4 Corners* program produced an episode called *The Baby*

Business (Balendra, 2016; "The Baby Business," 2016) which questioned the use of adjunct interventions and suggested they were unnecessary and expensive additions. One IVF specialist interviewed, Professor Gab Kovacs, referred to adjunct interventions as "snake oil" and argued that adjunct interventions are offered by clinics and clinicians partly for marketing purposes; to differentiate themselves from other clinics as a means of attracting patients. Some of my results support this proposition. The nine clinics that offered no adjunct interventions had one thing in common; they had no need to engage in competitive marketing. Two of the clinics were public hospital clinics. Two others were the low-cost clinics that differentiate themselves by being 'no frills'. One clinic was an ART clinic that does not offer IVF, and the remainder were remote or rural clinics where the nearest competition could be hundreds of kilometres away, for example, Fertility Great Southern in Denmark WA is 400km away from its nearest competitors in Perth.

In addition to concerns about adjunct interventions, the Australian ART industry has attracted scrutiny for other ethically questionable behaviours that appear to be driven by commercialisation. In the 4 Corners program, another specialist, Professor Rob Norman, argued that unnecessary interventions are widespread and estimates that 40-50% of women undergoing IVF do not need IVF at all (Balendra, 2016; "The Baby Business," 2016). This assertion is supported by evidence. An Australian study showed that amongst a group of 1376 women aged between 28 and 36 women with a history of infertility, more than 40% eventually had a baby without ART treatment (Herbert, Lucke, & Dobson, 2012). While Gab Kovacs is a strong proponent of IVF (telling the ABC that one of his patients received 37 cycles) even he admitted that stimulated IVF cycles are the key driver of income for ART clinics (Balendra, 2016"The Baby Business," 2016) and there is evidence to support this claim in Virtus Health's bonus program for clinicians who perform high volumes of cycles. Virtus IVF specialists can earn uncapped bonuses in the form of ordinary shares starting at $80000 worth if they can average 299 IVF cycles per year over a 4 year period[6] (Virtus Health, 2018a).

Advertising practices have also come under scrutiny. For example, the Australian Competition and Consumer Commission (ACCC) recently conducted an investigation into the false and misleading claims made by fertility clinics on their websites about their success rates (ACCC, 2016). The ACCC noted that one of the practices was to use jargon to mask facts. Clinics based success rates on clinical pregnancies or the number of embryos created, rather than live births—distinctions that may not be understood by lay people. This not only illustrates another way in which commercial imperatives can distort behaviour, but also alerts us to how unlikely it is that patients will understand the information presented to them about adjunct interventions. If Australian clinics and regulators are not forthcoming with independent advice written in lay language, any patients who do conduct their own research regarding add-ons may be examining evidence without understanding the important differences between fertilisation and implantation, clinical and ongoing pregnancy, or that a live birth can mean a very fragile baby born at 20 weeks' gestation or weighing only 400 grams.

[6] Incentives start at $80 000 worth of shares and increase by $25 000 worth of shares for every 25 more cycles. Incentives previously required an average of 400 completed cycles per annum over four years but in 2017, it was dropped to 300 after three consecutive years where no specialists met the minimum number of cycles to qualify for this reward. In 2018, 2 specialists qualified. For those who do not meet these targets, there is an additional 'loyalty option' which rewards those who reach 200+ cycles in a financial year and qualify for $10 000 worth of ordinary shares with a sliding scale for every 50 extra cycles performed.

Commercial influences on Australian ART have also come under scrutiny because of the structure of the industry, which is dominated by a handful of large corporations. The world's first publicly listed fertility business was Virtus Health, which entered the stock market in 2013, quickly followed by Monash IVF in 2014. Virtus raised $472 million dollars in their initial public offering, while Monash raised $315.6 million. It is reported that Virtus services approximately 40% of the Australian market, while Monash follows with approximately 30% (Sier, 2017). These companies all have the financial interest of providing a return to their shareholders. This obligation is made explicit in Monash IVF's code of conduct which states that, for all employees, the "primary responsibility is to the Company and its shareholders…" (Mayes et al., 2016). The goal of satisfying shareholders can affect the way doctors treat patients, as seen in the example of Virtus Health incentivising the number of IVF cycles performed. Rewarding volume in this manner implies that clinicians should strive to increase the number of patients they see or the number of cycles each patient undergoes. One of Blakely's interviewees relayed this exchange that may sum up the few avenues available for a clinician to achieve increased cycles:

... the bankers got up and said "we want to grow the business, and we're going to sell it again in three years' time". And so one of the doctors got up and said, "what do you mean by grow the business, do you mean get patients from other units to come and have IVF with us, do you mean to put patients inappropriately on IVF, or do you mean to have patients have less successful cycles so that they have more treatment cycles?" And the banker said 'all of the above'. (Blakely et al., 2017, pp. 3-4)

Another substantial financial issue is the heavy subsidising of IVF by public funding in the form of Medicare rebates. Under Medicare, medically infertile patients can receive rebates for unlimited cycles. There is no cap on age even though maternal age is a major factor in the success of fertility treatments. Since cost has been shown to be the biggest barrier to access to IVF (Daar, 2008) these rebates clearly facilitate access for many people. However, there is evidence that Medicare subsidies are being abused by ART clinics who use them to justify higher fees and increased servicing (Assisted Reproductive Technologies Review Committee (ARTRC), 2006; van Gool, Savage, Viney, Haas, & Anderson, 2009). In 2004, the Extended Medicare Safety Net (EMSN) was introduced to reduce out of pocket costs for people who have greater than average need for medical care. Under the EMSN, eligible IVF patients could receive up to 80% of their out of pocket costs in rebates once they met annual household healthcare spending thresholds. The difference in Medicare spending between 2003 and 2005, that is, before and after the introduction of the EMSN, was a 117% increase - from $50 million to $108.4 million (ARTRC, 2006). The data showed that the increase was due to a spike in service utilisation and healthcare providers increasing their fees. The data also showed the increases were most pronounced for ART items, which supports the theory that ART clinics exploited the availability of more rebates. Once EMSN rebates were capped for ART and related obstetric services, the government found an "immediate and extensive" reduction of 42% in EMSN spending (van Gool, 2015).

Taken together, there is clear evidence of strong commercial imperatives, as well as evidence that clinicians and clinics are acting on these imperatives in ways that are not consistent with their primary interests. There is, therefore, clear evidence not only of conflict of interest, but also of resulting unethical behaviour in the provision of ART in general and adjunct interventions in particular.

3.5 Adequacy of current regulatory arrangements

The Australian ART sector is self-regulated but sits within a nest of complementary legislation, guidelines and industry codes, such as the Family Law Act (Cth 1975) and practitioner registration requirements set out by the Australian Health Practitioner Regulation Agency (APHRA). The self-regulatory framework assigns responsibility for accreditation, licensing, auditing of clinics and the setting of standards to the Reproductive Technology Accreditation Committee (RTAC). RTAC is a subcommittee of the FSA and sets the industry's practice standards through its *Code of Practice for Assisted Reproductive Technology Units* (the Code), which includes the stipulation that ART clinics must comply with relevant legislation and the NHMRC ART guidelines. The Code also informs the *Reproductive Technology Accreditation Committee Scheme,* which dictates the practices that are assessed and audited in order for clinics to receive and maintain accreditation.

Current regulations recognise the need for conflicts of interest to be managed but there is no oversight to ensure that the need is met. The NHMRC ART guidelines has a brief section on conflicts of interest, which state that "[c]linics should ensure that the clinical team discloses any interests, including any commercial, financial or personal interests, relating to the services provided by the clinic or any treatment or procedure recommended by the treating clinician(s). Disclosure of interests is necessary in order to assess any relevant conflicts…" (2017). The NHMRC guidelines also require that clinics have documented processes and procedures for disclosure of interests. In contrast, the FSA Code includes no duties or obligations explicitly regarding the management of conflicts of interest, and the assessment of whether clinics have conflict of interest processes in place is not part of the accreditation or auditing process. This, in turn, means that there is currently no industry-wide routine collection of data regarding the management of financial conflicts of interest. Thus, when the FSA denies that there are financial conflicts of interest in the ART industry, it does so without this kind of data to support its assertions.

If RTAC had a conflict of interest policy, it is plausible that the initial management strategy would be disclosure. As acknowledged by the NHMRC and others, disclosure does not resolve conflicts of interest (NHMRC, 2017) but it remains an important first step. Disclosure also recognises that financial interest might be a material consideration for patient decision making. For example, knowing that your clinician works for an organisation that has a threshold number of interventions that qualifies them for a bonus might prompt a patient to seek a second opinion or change clinics. It is important to bear in mind that for disclosure to have its full effect, there might be a need for public reporting and oversight by an external independent body (2016). This oversight would need to focus not only on the prevalence and patterns of conflicts of interest, but also on the extent of use of unproven interventions. The recent Independent Review of Assisted Reproductive Treatment (Gorton, 2019) has acknowledged VARTA's inclusion of adjunct use in the reporting clinics are required to do in order to satisfy conditions for registration in Victoria. Such reporting will assist in quantifying the use of these interventions and enable monitoring of appropriate and inappropriate use and long term outcomes that could be a public health issue.

Since one of the criticisms of disclosure policies is that they lack external or independent oversight, it may be illuminating to examine the disclosure practices of other industries that do have external or independent governance. In other industries, there are customer-provider relationships that are, in some aspects, analogous to the patient and provider relationship in ART, because they are fiduciary in nature and can leave customers vulnerable. Unlike ART,

there is legislation protecting the customer or consumer, or measures in place to require specific standards are met to secure informed consent. For example, the NSW Property, Stock and Business Agents Act (2002) (the Act) regulates the conduct of professionals such as real estate agents. The Act includes several sections requiring disclosure of financial interests such as commissions and bonuses. The Act is prescriptive to the degree that it specifies what constitutes disclosure. Like ART, real estate and property services also have industry bodies however, legislation creates an externally imposed frame around what is permissible and required when dealing with duties to disclose.

Another crucial component of conflict of interest management is the provision of unbiased information to current and potential patients. In Australia, there is currently no independent organisation that provides information on adjunct interventions, so there is no reliable source of impartial advice about their efficacy and safety. Examination of the FSA Code finds broad references to providing patients with information, in the context of obtaining informed consent, but does not specifically address the use of adjunct or experimental procedures. Again, looking at other industries may be prudent. The Australian Health Practitioners Regulation Agency (AHPRA) administers the boards that register their practitioners. The primary purpose of these boards is to "protect the public" (AHPRA, 2017). AHPRA's Medical Board of Australia (the Board) has codes, guidelines and policies and has issued guidelines for those who perform cosmetic surgery. In acknowledgment of what can be deeply personal and emotional decision making, with substantial consequences for the wellbeing of the patient, the Board's guidelines have a strong emphasis on obtaining informed consent, managing conflicts of interest and assessing the prospective patient to ensure that they are suitable candidates for surgery. Some of the recommendations of the guidelines are that patients must have received psychological or psychiatric support before surgery, that information be presented in certain ways and that there is a cooling off period. While these particular rules may not be suitable for ART, what is of note here is that these guidelines are set by an independent Government organisation which also provides recourse and has the authority to de-register practitioners who do not comply with regulations.

The only comparable Australian ART body is the Victorian Assisted Reproduction Treatment Authority (VARTA) is a statutory organisation that co-regulates ART in Victoria and its website, although created for Victorian audiences with references to Victorian legislation, provides one of the most comprehensive independent Australian resources for ART (Victorian Assisted Reproductive Treatment Authority, 2019). Even so, its information regarding the use of adjunct interventions is limited and refers Australians to the HFEA website where they land on the page featuring the traffic light ratings. The traffic light system is written in lay language and provides a clear message that most commonly offered adjunct services are not evidence based but, as previously noted, only eight of the HFEA rated treatments are ones that Australian clinics are advertising on their websites. The VARTA page also directs viewers to Australian organisation Choosing Wisely (Choosing Wisely, n.d.), which provides healthcare information to consumers and suggests questions for patients to ask about any treatments offered but is silent on adjuncts in ART. Another Australian resource is the Your Fertility website (2018) which offers fact sheets and other information about fertility and fertility treatment, but again, it is not a complete source of information and only has limited information about adjunct treatments.

Other common measures for dealing with conflicts of interest, such as recusal or eliminating the financial interest are more challenging. For example, it would be unfeasible and needlessly punitive to prohibit a clinician, who also owns the business, from seeing patients.

However, there are actions that can be employed to diffuse the risk inherent in a conflict of interest. These may include independent consent processes, group decision making, so that any innovative or unusual proposals are made in conjunction with peers, or standardising treatment protocols with the guidance of assessment and treatment recommendations similar to those issued by NICE (2013) which, informed by the latest research, explicitly state both the circumstances when an intervention is appropriate and when an intervention should not be offered. In this regard, it is noteworthy that the NHMRC guidelines state that "[t]he provision of ART must be underpinned by policies that support effective and efficient practices that minimise interventions not supported by evidence of successful clinical outcomes" (NHMRC, 2017).

One broader question that remains to be answered is whether a self-regulating system can ever adequately address the issue of conflict of interest. The FSA Board and the RTAC are overwhelmingly comprised of industry members so there is stakeholder concern that current arrangements lack the necessary level of independent oversight for this increasingly commercialised industry (Blakely et al., 2017; Gorton, 2018). In the current framework, there is no independent body to ensure compliance with the ART guidelines or legislation, or even to assess whether the Code aligns with the them.

3.6 Limitations of this study

The most important limitation of this study are the possible issues caused by ambiguity in how interventions are named or referred to on clinic websites and in journal publications. Many of the interventions were referred to by multiple names; some were advertised under commercial brand names, while others were described as their process or the drugs used, others were included under broad categories such as "fertility assessment" therefore some interventions may have gone unidentified both during data collection and in searches for evidence.

Ambiguity about interventions also introduced uncertainty in interpreting results. The systematic review for PGS (Twisk et al., 2006) makes an important distinction between older methods and new, with a considerable risk of loss of embryos attributed to older PGS techniques, but Australian clinic websites did not make clear distinctions so it was not possible to tell if the current Australian offers of PGS were the same, older, techniques that were the subject of the systematic review.

Ambiguous naming coupled with limited knowledge about medical treatment may have led to some interventions being incorrectly categorised, or not categorised, as MBS items, and therefore not investigated further as adjunct treatments. Relating interventions to MBS item numbers often required interpretation that would have benefitted from a better understanding of medical terminology and procedures. Some procedures qualified for rebates only under certain circumstances, or in conjunction with other MBS services, so it was not always clear whether an intervention could be assigned to the MBS group.

These limitations would not have made significant impact on the overall finding that adjunct interventions are offered extensively across the Australian ART industry and lack the evidence base to support their routine clinical use.

3.7 Areas for further investigation.

This study has demonstrated that non evidence based interventions are frequently offered to Australian patients as part of clinical "care". Adjuncts are, however, also the subject of research and these practices warrant further investigation. There have, for example, been reports of the testing of adjunct treatments on paying patients (Blakley et al, 2017). Such anecdotes are corroborated the publication of resulting journal articles. For example, Keane (2017) conducted a retrospective analysis of patient clinical data spanning 2008 to 2015 at West Australian clinic, Pivet, to investigate the addition of growth hormones to IVF protocols. Growth hormones are an adjunct that is not advertised on the Pivot website but Keane's study (2017) is evidence that it was offered to patients for at least seven years. The patients paid for this adjunct as part of their IVF treatment but their clinical data has been used for research that may have had commercial benefit for Pivet. Recruiting paying patients as participants in research is a highly contentious issue, in part because it is believed to exacerbate the therapeutic misconception, so these practices require further investigation. There are also questions about reporting bias, whether participants are properly consented and the line between treatment and research. The number of IVF clinics with their own Human Research Ethics Committees (NHMRC, 2019) seems to indicate that in-house research on patients is a common occurrence and that such research might not meet the standards usually expected of biomedical researchers.

There are also other aspects of the use of adjunct interventions that would benefit from investigation. An examination of patient experiences of adjunct interventions would be an illuminating contribution to this topic and would enable scrutiny of the assurances and claims made by the FSA and individual clinics and clinicians. Information from the perspective of patients will also illuminate a discussion on informaed consent which can add to an analysis of whether financial interests are being prioritised over the wishes and the wellbeing of patients. Patient experience would also help us characterise the relationship between the patient and the service provider to inform a discussion about whether patients are vulnerable and taken advantage of, or whether they are savvy consumers not requiring special protections. The use of adjuncts andany commercial arrangements would also benefit from some analysis; there were some indications that clinics had relationships with pharmaceutical brands and diagnostic services and it would be valuable to know the nature and extent of those relationships and whether they influence the adjunct interventions on offer and how aggressively they are marketed. Likewise, it would be worthwhile to generate empirical data on any other performance-based financial bonuses and rewards that might encourage the use of adjunct interventions. Examination of websites also found that there are opportunities to further analyse website texts, especially regarding the claims of benefit made about adjunct treatments in comparison to the evidence available for them, how these claims are situated amongst other information, including their imagery and language, contribute to the message about adjunct interventions. Further, it would be prudent to also periodically assess more of the interventions listed in Table 2.1 since, as the example of endometrial scratching has shown, further studies can unseat previous evidence.

Chapter 4: Conclusion

In this study, it was established that most Australia ART clinics are offering adjunct interventions to patients but that these are predominantly non evidence based. For the few adjuncts that did have evidence to support claims about improved fertility outcomes, the evidence was not robust. Since these interventions are unlikely to be of benefit to patients, and some can add thousands of dollars to the cost of an IVF cycle, their use in IVF, especially at such scale, suggest that their use is driven, at least in part, by financial interests. The risk that that financial interests could be influencing clinical decision making makes this a conflict of interest.

The Australian regulatory framework for ART does not adequately protect patients and consumers from such conflicts of interest, but there are several steps that could be taken to improve this situation including disclosure of interests, transparency and peer review and restructuring of practice to diffuse the risk inherent in conflict of interest. There are, however, questions about whether any such remedies would be effective in an industry that is self-regulated and there may be a need for broad regulatory reform if patients are to be adequately protected from perverse commercial imperatives.

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Appendices

Appendix A

NHMRC Designations of levels of evidence according to type of research question

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation of some other method)	A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation of some other method)
III-2	A comparative study with concurrent controls: Non-randomised, • experimental trial Cohort study• Case-control study• Interrupted time series • with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, • experimental trial Cohort study• Case-control study•
III-3	A comparative study without concurrent controls: Historical control study• Two or more single arm • study Interrupted time series • without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control • study Two or more single • arm study
IV	Case studies with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case studies

Appendix B

Table 2.3 Australian clinics and the adjunct interventions offered on their websites

State	Clinic	Adjunct interventions offered	n =
ACT	Canberra Fertility Centre	assisted hatching	1
ACT	Compass Fertility	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	3
NSW	Genea Canberra	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	City Fertility Centre – Sydney	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg EmbryoGlue, granulocyte macrophage colony-stimulating factor culture medium eg BlastoGen and EmbryoGen, ovarian reserve testing, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), physiological intra-cytoplasmic sperm injection (PICSI), tubal flushing eg poppy seed oil or lipiodol	9
NSW	Demeter Fertility	adhesion compounds eg Embryoglue, endometrial receptivity array (ERA), ovarian rejuvenation or plasma rich platelet injection, ovarian reserve testing, tubal flushing eg poppy seed oil or lipiodol, ultrasound guided transfer	6
NSW	Fertility First	preimplantation genetic diagnosis (PGD), tubal flushing eg poppy seed oil or lipiodol	2
NSW	Genea - Kent St	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	Genea – Coffs Harbour	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	Genea – Illawarra	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	Genea – Lismore	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	Genea – Liverpool	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	Genea – Newcastle	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2

NSW	Genea – Northwest	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	Genea – Orange	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	Genea – RPAH	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
NSW	Hunter IVF	digital high magnification, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury, natural killer cell testing and treatment, preimplantation genetic diagnosis (PGD),	6
NSW	IVF Australia – Central Coast	assisted hatching, digital high magnification, time lapsed imaging incubation eg embryoscope,	3
NSW	IVF Australia – Eastern Sydney	assisted hatching, digital high magnification, time lapsed imaging incubation eg embryoscope,	3
NSW	IVF Australia – North Shore	assisted hatching, digital high magnification, time lapsed imaging incubation eg embryoscope,	3
NSW	IVF Australia – Western Sydney	assisted hatching, digital high magnification, time lapsed imaging incubation eg embryoscope, PolScope	4
NSW	Monash IVF – Mosman	ovarian reserve testing, preimplantation genetic screening (PGS)	2
NSW	Monash IVF – Bondi Junction	ovarian reserve testing, preimplantation genetic screening (PGS)	2
NSW	Monash IVF Parramatta	ovarian reserve testing, preimplantation genetic screening (PGS)	2
NSW	Next Generation Fertility	Website no longer exists: “Page not found”.	0
NSW	Primary IVF	PGS	1
NSW	Reproductive Medicine Albury	none	0
NSW	Reproductive Medicine Wagga	none	0
NSW	Royal Hospital for Women	Public hospital website. ART / IVF page removed.	0
NSW	The Fertility Centre – Liverpool	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), ovarian reserve testing, preimplantation genetic diagnosis (PGD)	3
NSW	The Fertility Centre – Wollongong	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), ovarian reserve testing, preimplantation genetic diagnosis (PGD)	3
NT	Westmead Fertility Centre	preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	2
QLD	Repromed Darwin	ovarian reserve testing, preimplantation genetic diagnosis (PGD), ultrasound guided transfer	3
QLD	Cairns Fertility Centre	none	0

QLD	CARE Fertility Green Slopes	ovarian reserve testing, tubal flushing eg poppy seed oil or lipiodol	2
QLD	CARE Fertility Toowoomba	Website not working: page does not load.	0
QLD	City Fertility Centre – Brisbane	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg Embryoglue, granulocyte macrophage colony-stimulating factor culture medium eg BlastoGen and EmbryoGen, ovarian reserve testing, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), physiological intra-cytoplasmic sperm injection (PICSI), tubal flushing eg poppy seed oil or lipiodol	9
QLD	City Fertility Centre – Gold Coast	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg Embryoglue, granulocyte macrophage colony-stimulating factor culture medium eg BlastoGen and EmbryoGen, ovarian reserve testing, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), physiological intra-cytoplasmic sperm injection (PICSI), tubal flushing eg poppy seed oil or lipiodol	9
QLD	City Fertility Centre – Sunnybank	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg Embryoglue, granulocyte macrophage colony-stimulating factor culture medium eg BlastoGen and EmbryoGen, ovarian reserve testing, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), physiological intra-cytoplasmic sperm injection (PICSI), tubal flushing eg poppy seed oil or lipiodol	9
QLD	Coastal IVF	assisted hatching, preimplantation genetic diagnosis (PGD)	2
QLD	Fertility Solutions Bundaberg	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), endometrial scratch or endometrial injury, natural killer cell testing and treatment, ovarian reserve testing, preimplantation genetic diagnosis (PGD), physiological intra-cytoplasmic sperm injection (PICSI)	7
QLD	Fertility Solutions Sunshine Coast	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), endometrial scratch or endometrial injury, natural killer cell testing and treatment, ovarian reserve testing, preimplantation genetic diagnosis (PGD), physiological intra-cytoplasmic sperm injection (PICSI)	7
QLD	Life Fertility Centre	ovarian reserve testing, ultrasound guided transfer	2
QLD	Monash IVF Auchenflower	ovarian reserve testing, preimplantation genetic screening (PGS)	2

QLD	Monash IVF Gold Coast	ovarian reserve testing, preimplantation genetic screening (PGS)	2
QLD	Monash IVF Rockhampton	ovarian reserve testing, preimplantation genetic screening (PGS)	2
QLD	Monash IVF Townsville	ovarian reserve testing, preimplantation genetic screening (PGS)	2
QLD	MyIVF	none	0
QLD	Primary IVF Brisbane	PGS	1
QLD	QFG Cairns	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, time lapsed imaging incubation eg embryoscope, physiological intra-cytoplasmic sperm injection (PICSI)	4
QLD	QFG Everton Park	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, time lapsed imaging incubation eg embryoscope, physiological intra-cytoplasmic sperm injection (PICSI)	4
QLD	QFG Gold Coast	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, time lapsed imaging incubation eg embryoscope, physiological intra-cytoplasmic sperm injection (PICSI)	4
QLD	QFG Mackay	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, time lapsed imaging incubation eg embryoscope, physiological intra-cytoplasmic sperm injection (PICSI)	4
QLD	QFG Sunshine Coast	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, time lapsed imaging incubation eg embryoscope, physiological intra-cytoplasmic sperm injection (PICSI)	4
QLD	QFG Toowoomba	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, time lapsed imaging incubation eg embryoscope, physiological intra-cytoplasmic sperm injection (PICSI)	4
QLD	QFG Townsville	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, time lapsed imaging incubation eg embryoscope, physiological intra-cytoplasmic sperm injection (PICSI)	4
QLD	Queensland Fertility Group	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), time lapsed imaging incubation eg embryoscope, time lapsed imaging incubation eg embryoscope,	3

QLD	The Fertility Centre	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), ovarian reserve testing, preimplantation genetic diagnosis (PGD)	3
SA	The Fertility Centre Sunshine Coast	sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), ovarian reserve testing, preimplantation genetic diagnosis (PGD)	3
SA	City Fertility Centre – Adelaide	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg Embryoglue, granulocyte macrophage colony-stimulating factor culture medium eg BlastoGen and EmbryoGen, ovarian reserve testing, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), physiological intra-cytoplasmic sperm injection (PICSI), tubal flushing eg poppy seed oil or lipiodol	9
SA	Fertility SA	preimplantation genetic screening (PGS)	1
SA	Flinders Fertility	endometrial scratch or endometrial injury, preimplantation genetic screening (PGS)	2
SA	MyIVF – South Australia	none	0
TAS	Repromed	ovarian reserve testing, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), ultrasound guided transfer	4
TAS	Fertility Tasmania	ovarian reserve testing, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), preimplantation genetic screening (PGS), ultrasound guided transfer	5
TAS	TasIVF Hobart	time lapsed imaging incubation eg embryoscope, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	3
VIC	TasIVF Launceston	time lapsed imaging incubation eg embryoscope, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	3
VIC	Ballarat IVF	endometrial scratch	1
VIC	City Babies	none	0
VIC	City Fertility Centre Bundoora	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg Embryoglue, granulocyte macrophage colony-stimulating factor culture medium eg BlastoGen and EmbryoGen, ovarian reserve testing, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), physiological intra-cytoplasmic sperm injection (PICSI), tubal flushing eg poppy seed oil or lipiodol	9
VIC	City Fertility Centre Melbourne	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg Embryoglue, granulocyte macrophage colony-stimulating factor culture medium eg BlastoGen and EmbryoGen, ovarian reserve testing, preimplantation	9

		genetic diagnosis (PGD), preimplantation genetic screening (PGS), physiological intra-cytoplasmic sperm injection (PICSI), tubal flushing eg poppy seed oil or lipiodol	
VIC	Genea Melbourne	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
VIC	Melbourne IVF	digital high magnification, time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury, natural killer cell testing and treatment, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	6
VIC	Melbourne IVF Mt Waverley	digital high magnification, time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury, natural killer cell testing and treatment, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	6
VIC	Monash IVF Bendigo	ovarian reserve testing, preimplantation genetic screening (PGS)	2
VIC	Monash IVF Clayton	ovarian reserve testing, preimplantation genetic screening (PGS)	2
VIC	Monash IVF Frankston	ovarian reserve testing, preimplantation genetic screening (PGS)	2
VIC	Monash IVF Geelong	ovarian reserve testing, preimplantation genetic screening (PGS)	2
VIC	Monash IVF Mildura	ovarian reserve testing, preimplantation genetic screening (PGS)	2
VIC	Monash IVF Richmond	ovarian reserve testing, preimplantation genetic screening (PGS)	2
VIC	Monash IVF Sale	ovarian reserve testing, preimplantation genetic screening (PGS)	2
VIC	Monash IVF Sunshine	ovarian reserve testing, preimplantation genetic screening (PGS)	2
VIC	No 1 Fertility	digital high magnification, time lapsed imaging incubation eg embryoscope, preimplantation genetic diagnosis (PGD), physiological intra-cytoplasmic sperm injection (PICSI), ultrasound guided transfer	5
VIC	Primary IVF Preston	PGS	1
VIC	Reproductive Services Royal Women's Parkville	none	0
WA	Concept Fertility Centre	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg Embryoglue, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS), physiological intra-cytoplasmic sperm injection (PICSI), post coital test, tubal flushing eg poppy seed oil or lipiodol	7

WA	Fertility Great Southern	none	0
WA	Fertility North	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury, endometrial receptivity array (ERA), granulocyte macrophage colony-stimulating factor culture medium eg BlastoGen and EmbryoGen, ovarian reserve testing,	5
WA	Fertility Specialists South	assisted hatching, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	3
WA	Fertility Specialists WA	assisted hatching, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	3
WA	Genea Hollywood Fertility	time lapsed imaging incubation eg embryoscope, endometrial scratch or endometrial injury	2
WA	PIVET Medical Centre	assisted hatching, sperm DNA fragmentation testing / sperm chromatic structure assay (SCSA), adhesion compounds eg Embryoglue, preimplantation genetic diagnosis (PGD), preimplantation genetic screening (PGS)	4
WA	Primary IVF	PGS	1
WA	The Keogh Institute for Medical Research	none	0

Appendix C

Example of fees: Fees Structure from Fertility North

FertilityNorth
GynaeNorth

Fee Structure

Procedure Type	Cost	Out of Pocket	EMSN* Out Of Pocket	Payment Due
Tracking Cycle				
Cycle Tracking (There may be extra costs for drugs during this cycle)	**$265.00**	Medicare Rebates Do Not Apply		Day 2 Bloods
Ultrasound	**$210.00**	$126.45	$126.45	Payable to U/S Clinic
Pregnancy Monitoring	**$140.00**	Medicare Rebates Do Not Apply		1st Attendance
Ovulation Induction				
OI Cycle (There may be extra costs for drugs during this cycle)	**$350.00**	Medicare Rebates Do Not Apply		Day 2 Bloods
Ultrasound	**$210.00**	$126.45	$126.45	Payable to U/S Clinic
Pregnancy Monitoring	**$140.00**	Medicare Rebates Do Not Apply		1st Attendance
AIH / IUI				
Artificial Insemination**	**$1,750.00**	$1,221.05	$1,080.30	Day of Treatment
IVF Cycle *Please see 'Non Fertility North Fees' for information on anaesthetist & JHC fees*				
IVF** (Including Embryoscope or Blastocyst Culture)	**$7,570.00**	$4,376.20	$2,641.10	Day of Embryo Transfer
TVOA (Egg Collection)	**$420.00**	$118.70	$48.35	On Receipt of Invoice
	Nil Out of Pocket Expense for Patients with Private Health Cover			
ICSI Cycle *Please see 'Non Fertility North Fees' for information on anaesthetist & JHC fees*				
ISCI** (Including Embryoscope or Blastocyst Culture)	**$8,120.00**	$4,570.90	$2,727.65	Day of Embryo Transfer
TVOA (Egg Collection)	**$420.00**	$118.70	$48.35	On Receipt of Invoice
	Nil Out of Pocket Expense for Patients with Private Health Cover			
MoNa (Modified Natural Cycle)				
IVF	**$5,260.00**	$1,764.90	$680.83	Day of Oocyte Retrieval
ICSI	**$5,810.00**	$1,959.60	$767.38	Day of Oocyte Retrieval
Mini-IVF / ICSI				
IVF	**$6,103.00**	$2,607.90	$849.43	Day of Oocyte Retrieval
ICSI	**$6,653.00**	$2,802.60	$935.98	Day of Oocyte Retrieval
FET Cycle				
FET Cycle** (There may be extra costs for drugs during this cycle)	**$2,700.00**	$1,823.40	$1,061.15	Day of Treatment
Frozen Embryo Transfer - Failed Thaw	**Cycle will be bulk-billed in the event of a failed thaw**			N/A
Oocyte Retrieval Cycle *Please see 'Non Fertility North Fees' for information on anaesthetist & JHC fees*				
Oocyte Retrieval Cycle	**$6,825.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
TVOA (Egg Collection)	**$420.00**	Medicare Rebates Do Not Apply		
PLEASE NOTE: Medicare and Private Health Funds do not cover Fertility Preservation. You wil be billed for the anaesthetist & JHC Admission fees				
Thaw of Oocytes, ICSI & Transfer	**$1,595.00**	Medicare Rebates Do Not Apply		Day of Embryo Transfer
Pre-Implantation Genetic Testing - Aneuploidy				
PGT-A Fee	**$2,000.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
PGT-A Testing Fee (per embryo)	**$500.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
Pre-Implantation Genetic Testing - Monogenic (Single Gene Diseases)				
PGT-M Feasibility Test (per case)	**$1,810.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
Courier Charge	**$325.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
PGT-M Fee	**$2,200.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
PGT-M Testing Fee (per embryo)	**$800.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
Non-Clinician Cancelled Cycle				
Global (IVF / ICSI / MoNa / Mini / FET / AIH / AID)	**$1,200.00**	Medicare Rebates Do Not Apply		At Cancellation

***EMSN** - Extended Medicare Safety Net. This applies to patients who have already accrued $2133.00 in out of pocket expenses per calendar year in addition to their Original Medicare Safety Net.

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FertilityNorth
GynaeNorth

Fee Structure

Procedure Type	Cost	Out of Pocket	EMSN* Out Of Pocket	Payment Due
Surgical Sperm Collection *Please see 'Non Fertility North Fees' for information on anaesthetist & JHC fees*				
Open Surgical Sperm Retrieval Testicular Epididymal Sperm Extraction (TESE)	**$550.00**	$134.05 Nil Out of Pocket Expense for Patients with Private Health Cover	$134.05	Day of Procedure
Surgical Sperm Collection Laboratory Fee	**$150.00**	Medicare Rebates Do Not Apply		Day of Procedure
Surgical Sperm Collection				
Sperm Retrieval (PESA / TESA)	**$550.00**	$232.55	$232.55	Day of Procedure
Surgical Sperm Collection Laboratory Fee	**$150.00**	Medicare Rebates Do Not Apply		Day of Procedure
Surgical Sperm Collection *Additonal fees for the Urologist (Dr Barrett), anaesthetist & hospital admission will apply to this procedure*				
Micro TESE Laboratory Fee	**$1,000.00**	Medicare Rebates Do Not Apply		Day of Procedure
Endometrial Receptivity Analysis (ERA)				
ERA Cycle (There will be extra costs for drugs during this cycle)	**$350.00**	Medicare Rebates Do Not Apply		1st Attendance
Ultrasound	**$210.00**	$126.45	$126.45	Payable to U/S Clinic
ERA Biopsy	**$200.00**	Medicare Rebates Do Not Apply		Day of Procedure
Biospy Sample Analysis	**€ 750.00**	Medicare Rebates Do Not Apply		Direct to Testing lab
Cryopreservation				
Sperm Freezing - Cost per Sample	**$80.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
Oocyte Freezing - Cost per Egg Collection	**$100.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
Embryo Freezing - Cost per Egg Collection	**$100.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
Ongoing Sperm /Oocyte /Embryo Storage (from anniversary of initial storage)		**$380.00** for 1 year **$210.00** for 6 months **$110.00** for 3 months **$40.00** for 1 month		Paid via Direct Debit Arrangement
Export of Sperm / Oocytes / Embryos / Ovarian Tissue *(Admin & Processing Fee)*	**$210.00**	Administration Fee for Export to Clinics Within WA, Interstate & Overseas		On Receipt of Invoice, Prior to Export
Import of Sperm / Oocytes / Embryos / Ovarian Tissue *(Courier Charge)*	**$800.00**	Courier Charge for Collection from an Interstate or Overseas Clinic Only		On Receipt of Invoice
Advanced Science				
Semen Analysis	**$70.00**	$34.50	$34.50	Day of Appointment
HALO Sperm (DNA Fragmentation Test)	**$150.00**	Medicare Rebates Do Not Apply		Day of Appointment
MAR Test (Anti-Sperm Antibodies)	**$30.00**	$5.90	$5.90	Day of Appointment
Trial Prep	**$30.00**	Medicare Rebates Do Not Apply		Day of Appointment
Microfluidic Sperm Separation (IVF/IUI)	**$200.00**	Medicare Rebates Do Not Apply		Day of Embryo Transfer
Microfluidic Sperm Separation (ICSI)	**$250.00**	Medicare Rebates Do Not Apply		Day of Embryo Transfer
Assisted Hatching	**$300.00**	Medicare Rebates Do Not Apply		Day of Embryo Transfer
Mechanical Endometrial Injury (MEI)	**$200.00**	Medicare Rebates Do Not Apply		Day of Treatment
G-CSF Intrauterine Installation Procedure	**$250.00**	Medicare Rebates Do Not Apply		Day of Treatment
Male Factor Pack	**$25.00**	Medicare Rebates Do Not Apply		Day Pack Taken
Non-Attendance at Lab Appointment	**$55.00**	Medicare Rebates Do Not Apply		On Receipt of Invoice
Non Fertility North Fees				
Anaesthetist Fee†	**Up to $480**	Nil Out of Pocket Expense for Patients with Private Health Cover		Day of Admission or Receipt of Invoice
Joondalup Hospital Admission Fee	**$1,244.00**	Nil Out of Pocket Expense for Patients with Private Health Cover		Day of Admission to JHC

***EMSN** - Extended Medicare Safety Net. This applies to patients who have already accrued $2133.00 in out of pocket expenses per calendar year in addition to their Original Medicare Safety Net.

† **Patients with Private Hospital Cover:** The cost of your egg collection (TVOA), JHC admission and anaesthetist fee will either be billed directly to your health insurance provider or, will be billed directly to you by Joondalup Private Hospital and/or the anaesthetists private rooms. In this instance, you will be issued a receipt which can be used to claim back your admission and anaesthetist fees from your health insurance provider. The amount you can claim is dependant on your level of cover, we advise you to confirm this with your private health fund. Eligible patients may also claim their TVOA and anaethetist fees via medicare. ** Part of the cost of IVF / ICSI & FET can be claimed from medicare ONLY if the patient is infertile for medical reasons.

† **Self Funded Patients**: Hospital admission fees will be billed directly to you by Joondalup Private Hospital. Anaesthetist fees will be billed directly to you by either Joondalup Private Hospital or the anaesthetist's private rooms. TVOA will be billed directly to you by the Dr's private rooms.

Please note that these prices are subject to change at anytime, however all fees stated on a signed payment of procedure form will be honoured.

Appendix D

Example of fees: Fees Schedule from Concept Fertility

12.4.2
FEE SCHEDULE **Effective Date: 14/03/19**

Concept Fertility Centre

TAILORED IVF TREATMENT PROGRAMME **No up front fees**				
Description of service	**Cost**	**Medicare Rebate**	**Expected Medicare Safety Net Rebate**	**Expected out of pocket costs from**
Oocyte Collection For Initial IVF rebated procedures in a calendar year (Item 13200)	**$8,255.00**	$3,028.00 +$355 ICSI* *MBS item 13251	$1,675.00	$3,550.00
Oocyte Collection For Subsequent IVF rebated procedures in a calendar year (Item 13201)	**$8,255.00**	$2,826.00 +$355 ICSI* * MBS item 13251	$2,430.00	$2,990.00
Additional services extra to Tailored IVF Treatment				
Embryo /oocyte freezing	**$760.00**	$0	$0	$760.00
Oocyte Collection For Surrogacy	**$,6900.00**	$0	$0	$6,900.00
Oocyte Collection For Medical Reasons	**$6,900.00**	$2,826-$3,028	From $,1675.00	$1,630.00
Oocyte Collection For Social Freeze	**$6,900.00**	$0	$0	$6,900.00
Cancelled IVF Cycle Prior to Oocyte Collection (Item 13202)	**$640.00**	$395.00	$64.00	$180.00
Failed Oocyte Collection	**$5,265.00**	$2,826-$3,028	From $1,675.00	$15.00
Failed Oocyte Fertilisation	**$5,900.00**	$2,826-$3028	From $1,675.00	$650.00
Semen Preparation	**$155.00**	$0	$0	$155.00
TAILORED FROZEN EMBRYO TRANSFER **No up front fees**				
Description of service	**Cost**	**Medicare Rebate**	**Expected Medicare Safety Net Rebate**	**Expected out of pocket costs from**
FET (Item 13218)	**$2,510.00**	$710.00	$702.00	$1,090.00

INTRA UTERINE INSEMINATION (IUI) PROCEDURES				
Description of service	**Cost**	**Medicare Rebate**	**Expected Medicare Safety Net Rebate**	**Expected out of pocket costs from**
IUI (Item 13203)	**$720.00**	$410.00	$105.00	$195.00
Semen Preparation (Item 13221)	**$155.00**	$40.00	$20.00	$90.00
Counselling session (AI)	**$190.00**	$0	$0	$190.00
Cancelled DI/AIH (Item 13203)	**$550.00**	$410.00	$105.00	$25.00
Donor Sperm	**$700.00**	$0	$0	$700.00
Catheter	**$160.00**	$0	$0	$160.00

OOCYTE RECIPIENTS				
EITHER Known Recipient / Anonymous Recipient				
Description of service	**Cost**	**Medicare Rebate**	**Expected Medicare Safety Net Rebate**	**Expected out of pocket costs from**
Embryology	**$2170.00**	$0	$0	$2170.00
Plus additional costs				
Assignment Fee	**$600.00**	$0	$0	$600.00
Clinical service fee	**$760.00**	$0	$0	$760.00

SURROGACY Charges are in addition to IVF treatment programme and any additional services required				
Description of service	**Cost**	**Medicare Rebate**	**Expected Medicare Safety Net Rebate**	**Expected out of pocket costs from**
Patient Management	**$2750.00**	$0	$0	$2750.00
Subsequent Surrogacy Cycle	**$550.00**	$0	$0	$550.00

ADDITIONAL SERVICES				
Description of service	**Cost**	**Medicare Rebate**	**Expected Medicare Safety Net Rebate**	**Expected out of pocket costs from**
Blastocyst culture of embryos	included in **Tailored** IVF, **Tailored** ICSI & **Tailored** FET programmes			
Initial Sperm Freezing and first five years storage	**$300.00**	$0	$0	$300.00
Continued storage – Sperm (after first five years)	**$250.00**	$0	$0	$250.00
Continued storage – Oocytes (after first ten years)	**$250.00**	$0	$0	$250.00
Continued storage –Embryos (after first ten years)	**$250.00**	$0	$0	$250.00
Sperm/Embryo Importation	**From $200.00**	$0	$0	$200.00
Imported Sperm/Embryo Storage	**$290.00**	$0	$0	$290.00
Sperm/Embryo Export handling fee	**$150.00**	$0	$0	$150.00
Counselling Session	**$190.00**	$0	$0	$190.00
Medications / Script fees	**From $25.00**	$0	$0	$25.00
Post Coital Test (consumables)	**$160.00**	$0	$0	$160.00
Blood test	**From $20.00**	From $13.00	$0	$5.00
Ultrasound	**From $75.00**	From $29.00	$0	$45.00

FROZEN OOCYTE TRANSFER				
Description of service	**Cost**	**Medicare Rebate**	**Expected Medicare Safety Net Rebate**	**Expected out of pocket costs from**
FOT (Item 13218)	**$2,510.00**	$710.00	$702.00	$1,090.00

PRE-GENETICS* only applicable to Frozen Embryo Transfer cycles				
Description of service	**Cost**	**Medicare Rebate**	**Expected Medicare Safety Net Rebate**	**Expected out of pocket costs from**
PGS – per embryo (cap at 6 embryos $4850)	**$800.00**	$0	$0	Up to $4850
PGD(Translocation)	**$5,350.00**	$0	$0	$5,350.00
PGD and chromosome screening	**$7,800.00**	$0	$0	$7,800.00
Feasibility Studies	**$3,160.00**	$0	$0	$3,160.00
Cancelled PGD Cycle (External Testing Laboratory)	**$950.00**	$0	$0	$950.00

IMPORTANT INFORMATION: TAILORED IVF TREATMENT PATIENTS Day case procedures in Concept Day Hospital incur theatre and accommodation fees. These charges will apply to patients with no private health cover or who are insured with a Concept unapproved health fund. Please note there are no Medicare rebates.	
Oocyte Collection** Day Hospital theatre & accommodation fee**	**$960.00**
Embryo Replacement** Day Hospital theatre & accommodation fee**	**$730.00**
Epididymal Aspiration Day Hospital theatre & accommodation fee**	**$960.00**