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Patient and professional perspectives about using in vitro fertilisation add-ons in the UK and Australia: a qualitative study

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ABSTRACT

Objectives In vitro fertilisation (IVF) add-ons are additional procedures offered alongside an IVF cycle with the aim of improving live birth rates. They are controversial because of the paucity of evidence to support their efficacy and safety, alongside the additional financial cost they often pose to patients. Despite this, they are popular. However, there is limited qualitative research regarding their use. The aims of the VALUE Study were to understand the decision-making process surrounding using or recommending add-ons; report sources of information for add-ons; and explore concerns for safety and effectiveness when considering their use.

Design 'VALUE' is a qualitative semistructured interview study using inductive thematic analysis of anonymised transcriptions.

Setting Participants were recruited from a broad geographical spread across the UK and Australia from public and private clinical settings.

Participants Patients (n=25) and health professionals (embryologists (n=25) and clinicians (n=24)) were interviewed. A purposive sampling strategy was undertaken. The sampling framework included people having state-subsidised and private cycles, professionals working in public and private sectors, geographical location and professionals of all grades.

Results Patients often made decisions about add-ons based on hope, minimising considerations of safety, efficacy or cost, whereas professionals sought the best outcomes for their patients and wanted to avoid them wasting their money. The driving forces behind add-on use differed: for patients, a professional opinion was the most influential reason, whereas for professionals, it was seen as patient driven. For both groups, applying the available evidence to individual circumstances was very challenging, especially in the sphere of IVF medicine, where the stakes are high.

Conclusions There is scope to build on the quality of the discourse between patients and professionals. Patients describe valuing their autonomy with add-ons, but for professionals, undertaking informed consent will be critical, no matter where they sit on the spectrum regarding add-ons.

Trial registration osf.io/vnyb9.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ VALUE drew on information-rich sources from a broad geographical spread across the UK and Australia.
⇒ Professionals and patients from both public and private clinical settings were interviewed, including participants whose in vitro fertilisation treatment had and had not given them a baby.
⇒ Some study authors have previously written quantitative and opinion pieces about add-ons; these potential biases have been acknowledged and managed by including authors who have no affiliation with the add-on debate and by involving qualitative research experts at every stage.

INTRODUCTION

The advent of in vitro fertilisation (IVF) in 1978 was a breakthrough for people experiencing infertility, but current live birth rates per cycle initiated are more or less static. In 2019, fewer than 26% of women had a baby with each cycle.[1 2] The decline in fecundability with advancing female age makes IVF a time-sensitive treatment and this, in combination with limited state funding, means that many patients often pay for IVF themselves. The pressure to improve IVF outcomes has led to a search for additional or adjunct procedures known as 'add-ons'. Add-ons range hugely in scope and variety. They can be grouped broadly into five categories: (1) add-ons for eggs, sperm and embryos; (2) incubators; (3) medications, including intravenous infusions; (4) operative procedures and (5) alternative therapies (online supplemental table 1). Add-ons have been widely introduced without evaluation and are usually an additional cost to patients.[3] IVF clinics that offer them have been described as 'mercenary' or 'exploitative'.[4–10] The lack of evidence and concerns

about informed consent has further highlighted the debate about their merit.[11 12]

For health professionals, a frequent rationale for offering add-ons is a simple response to market forces because patients demand them.[13–15] Almost three-quarters of those undergoing IVF choose to use at least one add-on.[14 16] However, there is limited research exploring the attitudes and beliefs of patients and professionals about their use. Qualitative research is limited and has not comprehensively included women who have had failed treatment, the views of fertility clinic staff or considered a range of add-ons.[14 17–19]

We developed a qualitative semistructured interview study (the VALUE Study) for both patients and health professionals (embryologists and clinicians) in the UK and Australia. The research team was multinational with members working in both countries. We sought to understand whether the views of professionals and patients would differ between the two settings, or whether they would be harmonious given that the process of IVF is broadly the same in both countries. The main difference between the two countries is in relation to funding for IVF treatment. In the UK, there is variable state-funded access to IVF according to strict criteria determined by individual integrated care boards which have superseded clinical commissioning groups. In Australia, there is access to a government-funded rebate to cover approximately half of the cost of IVF. The aims of VALUE were to: understand the decision-making process regarding using or recommending add-ons; report sources of information for add-ons; and explore concerns for safety and effectiveness when considering their use.

METHODS

The VALUE Study was an in-depth, semistructured interview study exploring the driving factors behind the use of IVF add-ons by patients, clinicians and embryologists. The interview schedule was iteratively developed with our patient and public involvement (PPI) group. The PPI process included patients, clinicians and embryologists with two PPI groups in both the UK and Australia. PPI sessions were conducted separately in the UK and Australia due to subtle differences in demographic questions.

The protocol for the VALUE Study was published prospectively.[20] Inclusion criteria for patient participants were: adult women, men or couples (18+ years of age); who had undergone IVF or intracytoplasmic sperm injection (ICSI) in the past 2 years (any number of cycles); publicly funded (National Health Service (NHS) funded in the UK, or Medicare in Australia) or privately funded; using either autologous oocytes and sperm, or donor oocytes and sperm; and who had considered using, or had used, one or more add-ons as part of their treatment. Inclusion criteria for clinicians were registered doctors involved in the care of patients or couples undergoing assisted reproduction. Doctors could be consultant fertility specialists, staff-grade fertility specialists or general practitioners who specialised in reproductive medicine and worked in fertility clinics. Inclusion criteria for embryologists were: registered embryologists involved in decisions regarding the assessment of embryos, who have direct interaction with patients or couples undergoing IVF or ICSI. The exclusion criteria for all three groups were: those who were non-fluent English speakers owing to the financial cost and logistics of arranging appropriate translation assistance during interviews. Those who were donating oocytes or sperm therefore not undergoing assisted reproduction themselves. An amendment was made to the protocol to exclude those patients in active treatment as it was recognised that the interview may represent an additional psychological burden.

The interview schedules can be viewed in online supplemental material 1. In both countries, participants were recruited via broad-ranging social media advertising. In addition, the British Fertility Society, and the Association of Reproductive and Clinical Scientists sent emails to their members highlighting the study, and the charity Fertility Network UK advertised VALUE on its website. In Australia, some participants were recruited via an established Research Panel at the University of Melbourne. Snowball recruitment was used across both countries. A purposive sampling strategy was undertaken, whereby participants were selected for in-depth interview when they were deemed likely to be information rich due to their experiences.[21] The sampling framework included people having state-subsidised and privately funded cycles, professionals working in the public and private sector, geographical location and professionals of all grades.

Interviews were conducted by SCA and EV (UK) and SL and LC (Australia) between January and May 2021. Semi-structured interviews took place remotely using recorded video-conferencing software, were transcribed verbatim and then anonymised (tables 1 and 2, and online supplemental tables 2 and 3).

Concurrent iterative analyses of all transcripts were undertaken using Dedoose to organise coding (SocioCultural Research Consultants, Manhattan Beach, California, USA). Embryologist and clinician transcripts were coded together, with the patients occupying a different coding tree because it was reasoned that the responses from professionals were likely to be different. Recruitment of participants ceased once data saturation was achieved through thematic and code saturation which was continually discussed and debated iteratively.

Two separate thematic analyses took place.[22 23] An inductive approach was adopted, whereby themes were generated from the data, as opposed to being mapped to a preconceived coding scheme. Before commencement of coding, the coders (SCA, EV, DW and SL) immersed themselves in the data through repeated readings of transcripts, and initial thoughts were noted. Coders embarked on the analytical phase together to combine codes into broader themes and subthemes, which were discussed,

Table 1 Characteristics of patient participants

	Interviews UK (n=11)	Interviews Australia (n=14)	Totals (n/%)
Gender			
Male	0	2	8
Female	11	12	92
Age (years)			
25–30	1	1	8
31–35	4	4	32
36–40	5	6	44
41–45	1	3	16
Relationship status			
Single	1	0	4
With partner	10	14	96
Gender of partner			
Female	1	3*	16
Male	10	11	84
Treatment undertaken			
IVF/intracytoplasmic sperm injection (ICSI) one–two cycles	4	8	48
IVF/ICSI three–four cycles	6	3	36
IVF/ICSI ≥five cycles	1	3	16
Intrauterine insemination (IUI) (any number of cycles)	2	2	16
Number of embryo transfer procedures			
None	1	2	12
One–two	3	5	32
Three–four	4	4	32
≥Five	3	3	24
Cumulative period undergoing fertility treatment (IVF/ICSI, IUI, ovulation induction)			
1–2 years	3	6	36
3–4 years	5	5	40
5 years or longer	3	3	24

*Two are female partners of male participants
IVF, in vitro fertilisation.

Table 2 Characteristics of professional participants

	Interviews UK (n=24)	Interviews Australia (n=25)	Totals (n/%)
Profession			
Clinician	11	13	49
Embryologist	13	12	51
Years working in assisted reproduction			
1–5	3	1	8
6–10	5	5	21
11–15	6	6	24
≥15	10	13	47
Seniority embryologist (n=25)			
Scientific director	6	3	36
Laboratory manager	1	0	4
Senior-qualified embryologist	4	5	36
Qualified embryologist	2	3	20
Missing	0	1	4
Seniority clinician (n=24)			
Consultant Obstetrician and Gynaecologist and fertility specialist	7	12	79
Staff-grade fertility specialist	1	0	4
Clinical fellow/ trainee reproductive medicine	3	1	17

debated and named. The wider research team then commented on and debated the themes and subthemes, which were settled upon by a consensus, with only minor changes in the naming of one theme.

Strategies were employed to ensure transparency, credibility and quality of the research process, especially considering our own professional and research backgrounds.[24]

The imperative to be reflexive and open about our own and others' perceptions throughout each stage of VALUE was acknowledged given some members of the research team (SCA, CMF, SL, AP and AHB) had published papers about add-ons, while others (EW, EV, MP, LC) had had no previous research with them. We also acknowledged the research team's experience with fertility services, both on a personal and professional level. The most senior qualitative researcher (EW) double-coded 12 transcripts, and high agreement between coders was reached, supporting the validity of the results. Regular meetings took place to appraise the sample size, data collection, analyses and research reflexivity.

Patient and public involvement

The interview schedule was iteratively developed with a PPI group in both countries. PPI panels included patients who had recently undergone IVF, clinicians involved in assisted reproduction and embryologists. Each participant was provided with a draft set of study materials to comment on. A series of questions about the coordination

Table 3 Themes and subthemes

	Themes	Subthemes
Patient thematic analysis	Patient 1: vulnerability	1.1 Desperate for success 1.2 Add-ons lend hope and a sense of control 1.3 Safety and efficacy ranked lower than hope
	Patient 2: power of the trusted professional opinion	2.1 Must be in my best interest 2.2 Unaware add-on was optional 2.3 Supports patient autonomy 2.4 Informed consent important
	Patient 3: the evidence doesn't apply to me	3.1 Tension between EBM and bespoke care 3.2 Power of personal testimonies
	Patient 4: acceptability of add-on	4.1 Risks perceived as low 4.2 Costs worth it: stakes are high
	Patient 5: role of previous experience	5.1 Previously used and had success 5.2 Previous unsuccessful cycle
Professional thematic analysis	Professional 1: treating desperation	1.1 In absence of anything else, it is reasonable to offer add-ons 1.2 Allows patients to exhaust every avenue 1.3 Hope vs false hope
	Professional 2: the patient shopper	2.1 Patients drive use following personal research 2.2 Allows patients autonomy to choose provided informed consent undertaken 2.3 Not being cutting-edge risks losing patients
	Professional 3: tensions within evidence-based practice	3.1 Continuum of approaches to the evidence 3.2 Being evidence based in IVF is challenging
	Professional 4: potential for harm	4.1 Add-on potentially harmful 4.2 Discomfort with performing some lab-based add-ons
	Professional 5: success, not profits	5.1 Genuine desire to help and avoid wasting patients' money 5.2 Other clinics exploit patients 5.3 Discomfort in charging for add-ons 5.4 Add-ons increase workload for clinic

EBM, evidence-based medicine; IVF, in vitro fertilisation.

and practical running of the study were also posed. As a result of PPI, various adaptations were made to the participant materials which are reflected in the final protocol.

RESULTS

A total of 25 patients (11 UK and 14 Australia), 25 embryologists (13 UK and 12 Australia) and 24 clinicians (11 UK and 13 Australia) were interviewed (tables 1 and 2). Interviews lasted an average of 69 min (patients) and 45 min (professionals). There was a demographic spread of patient (online supplemental table 2) and professional (online supplemental table 3) participants from across the UK and Australia. However, no participants were recruited from Northern Ireland, and within Australia, participants were recruited from five of the eight states and territories (online supplemental tables 2 and 3). Patient participants included both those who had become parents via assisted reproductive technology (ART) (n=16, 64%), and those for whom ART had not been successful (n=9, 36%) (online supplemental table 2). Analyses identified five key themes for patients and professionals (table 3), which are compared and contrasted below.

Desperation and the compulsion to treat it

Patients were vulnerable and had a strong sense of desperation. Desperation was illustrated with several examples of 'bargaining', with patients willing to suffer theoretical hardships offered by professionals if it meant a successful outcome: 'If they'd said, I don't know, stand on your head for an hour and that would work, I would have done that. You know, it, it just leaves patients very vulnerable, I think' (UK patient 4). Decision-making in the context of desperation gave rise to examples of being willing to try any add-on, no matter how small the additional chance of success. One participant compared her situation with a patient she cared for in her role at work: 'We had a little boy, he went off to China for some weird therapy because of a 1% chance it might work, and I could never understand that. But I kind of do now, because you get to a point, you're so desperate why wouldn't you? If you have that 1% chance of it working, you'd throw that 1% at it' (UK patient 11). The goal of parenthood for IVF patients was profoundly important, and fertility treatment often left them feeling out of control, powerless and at the mercy of chance. Opting to use add-ons was a

Table 4 Patient quotes

Theme	Participant	Illustrative quotations
Patient theme 1: 'vulnerability'	UK patient 7	'Because if someone's offering me something and they, they say, well, it could work but it might not work, you cling on to the it could work. So, yeah, I'd probably still go ahead with it. But, you know, looking back now, it [evidence of effectiveness] does matter. But, you know, it doesn't make a difference when you're, kind of, in the flows of it and there were lots of emotions flying around.'
	Australia patient 11	'If a doctor wants to offer some hope because they genuinely think that might work for you, wonderful, but I don't think you can give people false hope because it will make the doctor feel better. You know, if a doctor, there's no point doing it just to make the doctor feel better about giving a patient hope. They've got to truly believe it would actually work.'
Patient theme 2: 'power of the trusted professional opinion'	Australia patient 3	'And he said that's got nothing to do with it, you're just throwing money down the drain. You might as well just stop [dehydroepiandrosterone], and it was really blunt, and I did actually just stop. And then he said, [clinician quotes study regarding melatonin]. And he said, you're wasting your money on that too. And I said, okay terrific, so I stopped both of them [DHEA and melatonin], which was fine, I suppose it saved me some money.'
	UK patient 2	'I thought that was just standard, to be honest. I didn't realise that [time-lapse imaging] was an option. I mean, it came up, sort of, itemised on our bill so maybe I should've guessed from that that I could've taken it off.'
	UK patient 5	'…I think it's a bewildering, overwhelming world of stuff that lay people wouldn't necessarily understand. And yes, it doesn't seem fair that they include them [add-ons] as standard when people can't make the active choice, based on research, whether to go ahead or not.'
Patient theme 3: 'the evidence doesn't apply to me'	Australia patient 5	'So I think a lot of these, even the ERA test, the endometrial scratching, a lot of them are actually not proven to guarantee success. It's just, I think because everybody's different, everybody responds differently to treatment, I don't think there's ever going to be a definite answer, scientifically proven answer, for every single person.'
Patient theme 4: 'acceptability of add-on'	Australia patient 6	'I also looked at the dangers of PGT testing. So, let's say wrong results come back. And it was only quite low, so I was okay with that. I also looked at the risk of it being, like, what if it will harm the embryo unnecessarily and actually make the embryo unusable? But I think the risk of that is also quite low, so I was comfortable with that.'
	UK patient 6	'Cost was a massive thing for us. We ended up re-mortgaging our house to pay for our treatment…'
Patient theme 5: 'role of previous experience'	Australia patient 13	'But that said, one thing that did work really well for us, which was not noted down, was, a song called [name]. We played that before we went to the clinic, and that worked for our first daughter. And then the second time around… Of course, the same cocktail of different, different combinations. We also played that song again on the way on the way to the insemination clinic, and it worked two times [laughter]. For our friends, we said, we know you don't like this music at all, but put this song on on the way to the IVF clinic, and see if it works, and it did. Three for three, scientifically proven [laughing]. You should play this. I'm just throwing it out there, so there's… That's three for three.'

ERA, endometrial receptivity array; IVF, in vitro fertilisation; PGT, pre-implantation genetic testing.

way of bringing about purpose and control (table 4, UK patient 7).

In addition, add-ons provided renewed hope by offering a bespoke addition to the cycle that may bring about a successful IVF outcome. Safety and efficacy were minimised in favour of hope: 'I couldn't care less, you could've told me the risk was really high, and honestly, I just couldn't have cared. Because if you could guarantee me a baby, if it was a 100% guarantee, I just had to chop off my left arm, I would have been, no worries, just chop it off. If it was 100% guarantee, so, the risk, even if there was risks, I couldn't have cared less, what any of, probably, the side-effects or risks were' (Australia patient 3). Nearly all patients indicated that it was unacceptable for a clinician to offer an add-on based on false hope, with many citing they held doctors to a higher standard of honesty (table 4, Australia patient 11).

For professionals, some expressed that hope from using an add-on was beneficial to patients, whereas other felt that hope was false, burdensome and left patients vulnerable to exploitation: 'Disadvantages are that it [the add-on] might give them false hope, and I think it's really important not to do that. We've got to be honest. Let's not take hope away, but we've got to be honest with people' (UK clinician 5). Professionals acknowledged the desperation their patients experience, particularly after unsuccessful cycles. Add-ons offered the patient a change to the subsequent cycle, and in the absence of any other evidence-based interventions, were a reasonable option: 'I think for the rest of the add-ons, it's really when the

Table 5 Professional quotes

Theme	Participant	Illustrative quotations
Professional theme 1: 'treating desperation'	Australia embryologist 12	'I think having add-ons gives them that slight feeling that they have opened all the doors. They have explored all the avenues. And then maybe they will be able to, you know, complete their IVF journey at least with the satisfaction that they know they have tried everything. They have given it all.'
Professional theme 2: 'the patient shopper'	UK embryologist 9	'But I think patients as well are becoming a lot more informed and a lot more are aware of what is available. And certainly I, I think a proportion of patients, you know, if they are not able to have certain add-ons at a particular clinic they can probably take their business elsewhere as well.'
Professional theme 3: 'tensions within evidence-based practice'	Australia clinician 6	'Everyone talks about how expensive IVF is and, you know, that it's $10 000 a cycle. And many people say it has a low success rate, which is not true. So, if a patient has a certain amount of money, there is no question that the greatest likelihood of getting pregnant is the more IVF they have, the more cycles they have, the more eggs that are collected, the more embryos that are made. So, when patients are wasting their money on totally charlatan, unethical treatments, they are using their pool of money towards something that is not making them pregnant. For example, something like embryo biopsy that might double the cost of the cycle. Where, in fact, they would have been better off having two cycles.'
	Australia clinician 8	'To have a proper randomised trial that can prove efficacy, let's say improving the chances from 2% to 3%, that's a 50% increase, but to actually have that show significance in a randomised control trial would be impossible to do. It's not a trial that you can do because it requires thousands and thousands of patients. Nobody can run such a trial. So, uh, our ability to prove efficacy of any add-on is very limited.'
	Australia embryologist 8	'And all the scientific journal papers are skewed, as well, depending on the clinic, depending on who's studying it, and depending on who's, who's publishing it. I think the results vary too much at this stage with a lot of different add-ons.'
Professional theme 4: 'potential for harm'	UK clinician 1	'…there will be the case where you will damage some embryos in the process of biopsying them for example. And you will, you'll have some abnormal, you'll, you may be damaging the occasional normal embryo. And I always say to patients about mosaicism, just because the results are abnormal doesn't mean to say that that baby's abnormal. So, you may be causing harm, but that's a discussion we have with them.'
Professional theme 5: 'success not profits'	Australia clinician 10	'I can't begin to tell you the anger that I see in my rooms when for whatever reason I say to them, well, natural killer cells are elevated, or you have tissue compatibly, or you have a balance translocation of your chromosomes which is why you're not getting pregnant. But nobody has done these tests and they've had IVF treatments without success. And they're very angry that they've wasted all this money on previous cycles.'
	Australia embryologist 9	'I actually feel quite angry sometimes when you hear of patients that have gone to other clinics and been sold all this stuff that's really, you do wonder if it's doing more harm than good. And you just think if, your problem is, is quite simple, cut away all of that and just focus on the basic science that we know is working, save your money. I think, I, I do think that there is a bit of exploitation going on.'
	UK embryologist 10	'But there's other add-ons that, they don't cost any money to the clinic, like assisted hatching. That, the cost for the lab is zero. Obviously, you can always factor in the knowledge of the embryologist, the equipment calibrations, blah, blah, blah. But the cost is essentially to buy anything. So, for that one, for example, there shouldn't be a charge at all.'

IVF, in vitro fertilisation.

consultation turns into a sort of, consultation of desperation. Like the patients had several failed cycles, and her NHS funding is just about to finish or perhaps she has just one cycle left with the NHS. I think that's the point when, if we can improve something, if we can change something in a treatment protocol without essentially incurring extra cost then it's, sort of a, why not? Sort of consultation' (UK clinician 8). Add-ons also offer their patients the opportunity to feel that they and the clinic have tried their best, even if the cycle ends in disappointment. It was also believed to absolve patients of regret at not having 'tried everything' (table 5, Australia embryologist 12).

Professionals versus patients: who is driving add-on use?

The driving forces behind the use of add-ons differed between patients and professionals. For patients, a professional opinion was felt to be the most influential reason for opting to use them. Such recommendations held a lot of sway and were hard to disregard. Patients described how the add-on was in their best interest and a bespoke element of care: 'That all came from the clinic. I hadn't heard of either of them before, natural killer cells or the ERA [endometrial receptivity array] testing. And it was more a, we're going to do this. We're testing this and then when the results came, they were like, we're going to do this. We're changing this, do these medications. Obviously, we had the choice, but for us it was a no-brainer. If that's what your specialist is telling you to do, then we're doing it' (Australia patient 1).

The power of the professional opinion was not limited to clinicians. Some participants described how important the opinions of their nurse or embryologist were: 'And I remember the nurse had said to us, you know, if it failed, would you consider that you've done everything that you've possibly could? And then we were like, all right, yeah, no, we should go with the options that you've given us…' (UK patient 7). The importance of the professional

opinion also holds when the recommendation is to reject an add-on, providing patients with the freedom to stop considering it (table 4, Australia patient 3).

The power of the professional opinion sometimes extended to patients not realising the optional nature of add-ons, on the basis that if it had been offered, then it must be an essential element of care. Learning about the additional cost was sometimes only revealed when they came to pay (table 4, UK patient 2). While the professional opinion was important, patients also expressed the desire for autonomy with add-on choices: 'For my fifth transfer I wanted to try something. I'd had four failed and I think I was quite happy to try it, so they agreed to do the scratch' (Australia patient 11). The need for adequate counselling about the risks to make an informed decision was deemed important by over two-thirds of participants (table 4, UK patient 5).

Contrasting 'power of the trusted professional opinion' is the professional theme 'the patient shopper'. Professionals described the well-informed patient, who had undertaken extensive reading online and had clear preferences regarding add-ons: 'You know, it, it used to be the case that they [patients] would leave their brain at the door and just walk in and do as they're told. And now I think, I absolutely don't think that's the case with a large proportion of patients. I think they come in through the door knowing what they want and often having researched it' (UK embryologist 2).

Professionals described the importance of listening to patient requests about add-ons but caveated this with the need to maintain the core ethical principle of informed consent: 'When they come and talk to me about growth factor, I show them that paper, and say, look, it really has not shown any benefit, it costs as much as another IVF cycle. You know, if you wanted to use it, that's fine, but there's been a proven study, that hasn't shown a benefit from it, it's enormously expensive, and, and you'll, you'll get much more chance if you do another IVF cycle' (Australia clinician 9). Being able to offer add-ons provides professionals with the benefit of appearing modern and innovative. The patient shopper drives add-on use which clinics respond to in the hope of attracting new clients and keeping those who might go elsewhere, possibly for less ethical treatment (table 5, UK embryologist 9).

Add-ons and evidence

For both patients and professionals, applying the available evidence to individual circumstances was very challenging. Patients overwhelmingly appreciated the importance of evidence to inform healthcare decisions, but when it came to decisions about themselves, tailored care took precedence. Their clinician's opinion and personal experience trumped evidence from randomised controlled trials (RCTs), which were felt to not represent their unique clinical circumstances (table 4, Australia patient 5). There also was a tension between evidence-based medicine and personal testimony read online. They described how the blog of an unknown IVF patient, especially one with a similar set of circumstances to them, was very compelling: '…that's why the Janet from Birmingham comes in useful. Because she will say, I've done five cycles with rubbish eggs, rubbish embryos, everything was terrible, but then I did that [add-on], and look what happened. And so, for me, that individual story of, similar to me, for instance, has done this, tried that, and it's worked, is a lot more helpful, even though it's one person, than knowing what happened to a hundred. When you read that Janet from Birmingham did this and got pregnant, you're, like, oh, my god, it's going to work for me. So, I'd say, I can honestly say that is the most powerful, powerful influencer of all' (UK patient 5).

For professionals, there was also tension with respect to the importance of robust evidence to guide the recommendation or use of add-ons; professional attitudes vary across the spectrum from a reliance on robust evidence from RCTs, to the willingness to use add-ons even in the absence of evidence. Those who subscribed to the former appeared to believe that patients have a largely common set of problems that explain their infertility, and when cycles failed, this was due to chance, one major factor being aneuploidy within the embryo. Thus, their preference was to repeat cycles without add-ons in the hope that pregnancy would eventually occur. They were also concerned that add-ons might exhaust funding better spent on an additional cycle of IVF (table 5, Australia clinician 6). These practitioners were critical of add-ons which they felt lacked evidence of efficacy and described changing their clinical practice in response to RCTs: 'I've prescribed growth hormone, I don't know, not more than a half dozen times in my life but, [fertility clinic] did a study which I think was called the [name of study] and that sort of refuted any perceived benefits so I stopped doing that' (Australia clinician 13).

Professionals at the other end of the spectrum often believed that patients (especially those with multiple failed cycles) have specific problems that may be identified through extensive diagnostic testing and remedied by add-ons. They held the available evidence with scepticism, which was criticised for being underpowered thus ruling out the identification of efficacy in subgroups, and for 'cherry picking' good prognosis patients (table 5, Australia clinician 8). They described feeling uneasy about the ethics of conducting RCTs on technologies already available and described suspicion of research groups' objectives and publishing journals' political stance on add-ons (table 5, Australia embryologist 8). In the absence of compelling evidence from RCTs, their practice was based on scientific plausibility and on evidence gleaned from their own clinic's data: 'It's even difficult to prove something that's ineffective because the trials that are required are often very expensive, large and might not be applicable to a particular patient. So, if you group all patients together in a trial you may not find evidence of effectiveness, but if you looked at some subgroups perhaps you would. So, a trial is not real life. You know, evidence-based medicine, you have to take

the best evidence and then apply it to a patient in front of you who may not be the same as patients in the trial' (Australia clinician 8). Many professionals occupied points between these two extremes; however, even the staunchest advocates for the necessity of robust evidence described being willing to provide add-ons under specific clinical circumstances.

Consideration of risks

Add-ons were acceptable to patients, particularly in the context of a professional recommendation, because they were perceived as low risk and worth the cost (table 4, Australia patient 6). Although the additional cost was a burden, the goal of parenthood was more important and therefore worth the financial strain. For some, using add-ons left them in significant debt, with participants remortgaging their home or borrowing money to fund them (table 4, UK patient 6). The substantial cost of IVF was used as an 'anchor' to reference and justify the relatively low cost of add-ons: '….it just got to the point because they were all, it's not thousands of pounds each one, is it? It's like, the scratch is, I don't know, a couple of hundred pounds. None of it was so expensive that it was, that it made you think. It seemed like a drop in the ocean I guess to the thousands of pounds that we'd already paid' (UK patient 9).

In contrast to the patients, professionals held concerns about the potentially harmful nature of certain add-ons, particularly assisted hatching, pre-implantation genetic testing for aneuploidy (PGT-A) and immunological therapies (table 5, UK clinician 1). For one embryologist, the requirement to undertake PGT-A was the catalyst to change employer: 'And I felt very uncomfortable. The way we presented it was, you know, those are things that might help, but we're not sure that they will. But what we do know, or what we used to say is that we did know that it wouldn't do any harm. And I now feel uncomfortable about that as well, particularly about PGT-A, because you're really putting embryos in a very sort of stressful situation, with no evidence that what you're doing will make a difference to the outcome to the patient. And you're mutilating the embryo. And also, you're taking cells that might not be representative of what the fetus's cells will be like. So, this is one of the ones that I felt most uncomfortable with, and part of the reason why I left where I was working' (UK embryologist 1).

Role of previous experience

Use of an add-on in a previous successful cycle was an important driver for patients. Deviating from a 'tried and tested' formula was difficult as it was impossible to tease out whether it was the add-on that had led to success: 'I'm glad we used the scratch, very glad, because whilst I can't say it was what caused us to conceive, I can't say it didn't. If I was in the position where I needed to do IVF again, I would definitely pay for it every time' (UK patient 6). For some, this becomes a superstition, even when it can be rationalised that the add-on is unlikely to be helpful (table 4, Australia patient 13).

Success, not profits

Analyses showed professionals wanted the best outcomes for their patients alongside a genuine desire to avoid wasting their money. Yet, there were some who would never offer add-ons because of the lack of evidence and at the other end of the spectrum, there were those who felt that not offering add-ons was a failure to 'optimise all variables' (table 5, Australia clinician 10).

Holding their patients' best interests at heart was expressed universally; however, they observed that some other clinics used add-ons unethically for financial gain, including clinics they had previously worked for (table 5, Australia embryologist 9).

Professionals expressed discomfort at charging patients for add-ons in various contexts including when they were used routinely (eg, time-lapse incubation of embryos), or when the cost of the add-on technology had already been met by the clinic (table 5, UK embryologist 10). Professionals described the paradox of charging for add-ons that are believed to be effective while also charging for add-ons that were not. Many argued that add-ons were only ever offered in a 'success, not profit' context by expressing how they increase the burden on clinics. Keeping track of individual add-ons increased complexity in the laboratory and heightened workload around managing patients' expectations: 'It is a bit time consuming, to be honest, to go through the list of adds-on with patients, in particular, the ones that are very well, you know, brainwashed by Google, and they know everything, and they just start from the beginning. And so it is, it does add time to the consultation' (UK clinician 6).

DISCUSSION

The VALUE Study provides new insights and understanding into how patients and professionals make decisions about IVF add-ons. Patients describe the importance of hope, which is ranked higher than considerations of efficacy, safety and cost to frame their choices, particularly after previously unsuccessful cycles. Choosing an add-on offers a sense of control, with the possibility of overcoming problems encountered previously. The driver for add-ons from a professional perspective is ascribed to patients; however, patients not only describe the power of the professional opinion, but also acknowledge that seeking add-ons is a quest for hope sought after learning of success stories online.

VALUE's findings are at odds with the debate surrounding add-ons, which often portrays professionals within fertility services as having commercial incentives.[4–6] We found no 'smoking gun' to suggest that professionals saw add-ons as a means of generating revenue; however, there was an acceptance that unethical practices do exist, with examples of embryologists being uncomfortable performing some laboratory-based add-ons, believing

them to be potentially harmful to embryos. We show here the significant tension that exists between traditional evidence-based medicine and IVF in the era of add-ons. However, even for the staunchest advocates of evidence-based medicine, there were caveats where add-ons would be offered. For patients, the stakes are so high, that evidence concerning efficacy and safety, although important, is not the most important factor when deciding upon an add-on, alongside a belief that the evidence does not reflect their unique clinical circumstances.

VALUE explores the patient–professional decision-making dyad regarding add-ons for the first time. When compared with other high-stakes, time-critical clinical situations, such as cancer treatment decisions, we find that there is a distinct difference. For routine cancer care, shared decision-making is rarely implemented.[25] In contrast, we found that people undergoing IVF are often actively engaged with clinical decisions, consuming information online and supported by professionals to exercise autonomy regarding add-ons.

There is limited qualitative evidence exploring the patient and professional perspective surrounding add-ons. One semistructured interview study analysed how professionals legitimise the use of one add-on: time-lapse imaging.[17] The authors suggest that professionals create legitimation arguments for its use, downplaying the values of traditional evidence-based medicine to evaluate its worth.[17] VALUE goes further to show that professionals occupy a spectrum of approaches to the evidence, which furthermore guides their clinical practice. Previous studies have found hope to be of critical appeal for patients and important for persevering against adversity.[18 26] VALUE offers a broader explanation as to the appeal of add-ons, including the role of desperation and hierarchy of hope over other priorities. Regarding patients, this is the first study that offers the perspective of those who have had and not had success from IVF, including those who considered, but did not use add-ons.

VALUE's strengths lie in its robust design and development which included the opinions of patients and professionals. We interviewed a broad range of participants spread across two countries. Some study authors have previously written quantitative and opinion pieces about add-ons. These potential biases have been acknowledged and managed by including authors who have no affiliation with the add-on debate and by involving qualitative research experts (EW and MP) at every stage. Other limitations include the generalisability of our findings to other countries. Despite differences in reproductive care in the UK and Australia, VALUE has shown that the participant experience is similar. This may reflect the comparable availability of add-ons in both settings.

This study has shown that the IVF add-on debate is more complex than it may appear at first glance. While we cannot avoid the impact of the power dynamic between doctors and patients, describing clinicians as predatory and patients as naïve is not helpful and may be unproductive. Across the spectrum of all professionals, there was a strong drive to deliver the best care for their patients, but what was perceived as 'best' varied according to their approach to the available evidence on add-ons. For patients, the decision to use an add-on was complex and included more than just a discussion with a clinician.

VALUE provides evidence that to best support patients in making decisions about add-ons, there needs to be a balance between the professional advice, the evidence and the needs of the patient who often wants to do everything possible to improve their chances of success. This involves professionals understanding what is important to the patient, and how to best communicate evidence surrounding efficacy and safety. Finally, with access to digestible information about the evidence base, costs and possible risks, informed consent will continue to provide the ethical cornerstone to these discussions.

One of the challenges regarding add-ons is how to fund and undertake well-designed RCTs in order to provide greater certainty about benefits and harms. This requires a coordinated effort and may benefit from a focused approach by an international taskforce. The widespread uptake of add-ons in spite of a lack of evidence goes against the fundamental tenets of evidence-based medicine where research informs practice. In the largely privatised sphere of IVF, policymakers and regulators will continue to be challenged about how to monitor and regulate the use of add-ons.

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Contributors SCA, EV, SL, CMF, AP, AHB and MP were involved in the design of VALUE and publication of the protocol. SCA, EV, SL and LC undertook participant interviews. Analysis was undertaken by SCA, EV, SL and EW. SCA wrote the initial draft, which was edited by all authors. All authors had full access to the anonymised dataset and accept responsibility for publication. SCA is the guarantor for this research.

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Competing interests SCA is a consultant gynaecologist and subspecialist in reproductive medicine and surgery. She is an editor for *Cochrane Gynaecology and Fertility*, and *Human Fertility*. In the past 12 months, she has been an invited speaker for ESHRE, receiving expenses for travel. She has no financial relationships or affiliations with any commercial companies. EV is an obstetrics and gynaecology registrar; from 2020 to 2022, she was a National Institute for Health and Care Research (NIHR) Academic Clinical Fellow with the University of Bristol. She currently works as a Clinical Fellow in an NHS Reproductive Medicine Unit, at University College London Hospital. She has no financial relationships or affiliations with any commercial companies. SL is a clinical triallist and methodologist, employed by the University of Melbourne. She has a strong interest in randomised controlled trials and systematic reviews and is an editor for the Cochrane Gynaecology and Fertility Group. She has no financial relationships or affiliations with any commercial companies and has received research funding from only government and not-for-profit organisations. LC has no conflicts of interest to declare. CMF is a professor of obstetrics and gynaecology, University of Auckland, New Zealand. She is a fertility specialist, clinical director of Gynaecology and Fertility Plus, Auckland District Health Board, New Zealand and coordinating editor of the Cochrane Gynaecology and Fertility Group. She has no financial relationships with any commercial companies or fertility clinics. She is an invited speaker for ESHRE 2022, receiving expenses for travel. AP is the editor in chief of *Human Fertility*, trustee of the Progress Educational Trust and chairman of the advisory committee of the UK National External Quality Assurance Schemes in Andrology (all unpaid). In the last 24 months, he has undertaken paid consultancy, speaker fees or contributor fees from Cryos International, Cytoswim, Exseed Health and Merck Serono Limited, but all monies associated with these are paid to the University of Sheffield. MP is a behavioural scientist employed by the University of Melbourne. She is president-elect for the Australian Society for Psychosocial Obstetrics and Gynaecology and is on the editorial board for *Journal of Psychosocial Oncology Research and Practice*. She is an invited speaker for ESHRE 2022, receiving expenses for travel. She has no financial relationships or affiliations with any commercial companies and has received research funding from only government and not-for-profit organisations. AHB is an NHS consultant in reproductive medicine, honorary chair and clinical lead for Leeds Centre for Reproductive Medicine, Leeds Teaching Hospitals NHS Trust. He is also a consultant at CARE Fertility, Leeds, and chair of the CARE Fertility UK Innovation and Research Board. He is Fellows' Representative, RCOG Council for Northern, Yorkshire and Humber, a trustee of the British Fertility Society (BFS) and a member of the WHO Guideline Development Group on Infertility. He is a director of Balance Reproductive Health and a member of the advisory board on PCOS and weight reduction, NovoNordisk Pharmaceuticals, for which he has received speaker's fees for attending meetings. EW is a chartered psychologist (academic) employed by the Universities of Aberdeen and Bath and with an Honorary Research Fellowship at Bath Spa University. She has a strong interest and expertise in qualitative methods as applied to health services research. She has no financial relationships or affiliations with any commercial companies and has received research funding from only government and not-for-profit organisations.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval This study involves human participants and ethical approval was obtained from the Universities of Sheffield (036268), Bath Spa (BSU-20-205) and Melbourne (2057434.1). Participants gave informed consent to participate in the study before taking part.

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REFERENCES

1 Newman JP, Chambers GM. *Assisted reproductive technology in Australia and New Zealand 2019*. Sydney: National Perinatal Epidemiology and Statistics Unit, the University of New South Wales, 2021.
2 HFEA. Fertility treatment 2019: trends and figures HFEA. 2021. Available: https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2019-trends-and-figures/
3 Armstrong S, Atkinson M, MacKenzie J, *et al*. Add-Ons in the laboratory: hopeful, but not always helpful. *Fertil Steril* 2019;112:994–9.
4 McAuley J. *Panorama: Inside Britain's Fertility Business*. 2016.
5 Belli E L-W. *Pregnancy: Calls to regulate 'cruel' IVF add-ons*. BBC, 2022.
6 Tsigdinos P. The big IVF add-on racket. *The New York Times* 2019.
7 Heneghan C, Spencer EA, Bobrovitz N, *et al*. Lack of evidence for interventions offered in UK fertility centres. *BMJ* 2016;355:i6295.
8 Harper J, Jackson E, Sermon K, *et al*. "Adjuncts in the IVF laboratory: where is the evidence for 'add-on' interventions" *Hum Reprod* 2017;32:485–91.
9 Repping S. Evidence-based medicine and infertility treatment. *Lancet* 2019;393:380–2.
10 Cochrane. Special collection: in vitro Fertilisation. 2019. Available: https://www.cochrane.org/news/special-collection-vitro-fertilisation-effectiveness-add-ons
11 Authority CaM. Fertility treatment: A guide for clinics. 2021. Available: https://www.gov.uk/government/publications/fertility-treatment-a-guide-for-clinics: Competition and Markets Authority
12 Human Fertilisation and Embryology Authority. Fertility 2022 - Julia chain, chair of the HFEA. 2022. Available: https://www.hfea.gov.uk/about-us/news-and-press-releases/2022-news-and-press-releases/fertility-2022-julia-chain-chair-of-the-hfea/
13 HFEA. *The responsible use of treatment add-ons in fertility services: a consensus statement*. 2019.
14 HFEA. Pilot national fertility patient survey Hfea.Co.UK. 2018. Available: https://www.hfea.gov.uk/media/2702/pilot-national-fertility-patient-survey-2018.pdf
15 Lensen S, Chen S, Goodman L, *et al*. IVF add-Ons in Australia and New Zealand: A systematic assessment of IVF clinic Websites. *Aust N Z J Obstet Gynaecol* 2021;61:430–8.
16 Lensen S, Hammarberg K, Polyakov A, *et al*. How common is add-on use and how do patients decide whether to use them? A national survey of IVF patients. *Hum Reprod* 2021;36:1854–61.
17 Perrotta M, Geampana A. The trouble with IVF and randomised control trials: professional Legitimation narratives on time-lapse imaging and evidence-informed care. *Soc Sci Med* 2020;258:113115.
18 Perrotta M, Hamper J. The crafting of hope: Contextualising add-Ons in the treatment Trajectories of IVF patients. *Soc Sci Med* 2021;287:114317.
19 Iacoponi O, van de Wiel L, Wilkinson J, *et al*. Pressure and pragmatism: how fertility clinic medical directors view IVF add-Ons. *Reproductive BioMedicine Online* 2022;45:169–79.
20 Armstrong SC, Lensen S, Vaughan E, *et al*. VALUE study: a protocol for a qualitative semi-structured interview study of IVF add-Ons use by patients, Clinicians and Embryologists in the UK and Australia. *BMJ Open* 2021;11:e047307.

21 Patton MQ. *Qualitative research & evaluation methods: integrating theory and practice*Fourth edition. ed. Thousand Oaks, California: SAGE Publications, Inc, 2015: 806.
22 Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3:77–101.
23 Kiger ME, Varpio L. Thematic analysis of qualitative data: AMEE guide No.131. *Med Teach* 2020;42:846–54.
24 Shenton AK. Strategies for ensuring trustworthiness in qualitative research projects. *EFI* 2004;22:63–75.
25 Hahlweg P, Härter M, Nestoriuc Y, *et al*. How are decisions made in cancer care? A qualitative study using participant observation of current practice. *BMJ Open* 2017;7:e016360.
26 Franklin S. *Embodied progress: a cultural account of assisted conception*. London: Routledge, 1997: 252.