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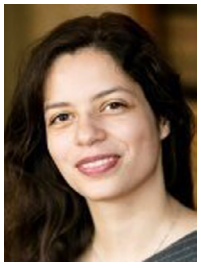
ARTICLE

Passion, pressure and pragmatism: how fertility clinic medical directors view IVF add-ons



BIOGRAPHY

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KEY MESSAGE

The add-on debate points to broader changes in the organization of the IVF sector, which touch on key aspects of practising (reproductive) medicine, including the patient–doctor relationship and responsibility for clinical decision-making, and the relationship between regulator and IVF clinic and between scientific evidence and clinical practice.

ABSTRACT

Research question: What are the views of the medical directors of fertility clinics on IVF add-ons?

Design: A total of 93 UK clinics were emailed with an invitation for their medical director to participate. Ten IVF clinic medical directors were interviewed to discuss their views on the use of IVF add-ons. Some of the interviewees were medical directors of an IVF clinic with multiple branches across the UK, meaning the total number of clinics accounted for in this study was 35 out of the 93 contacted. Thematic analysis was used to analyse the data.

Results: The participants consisted of seven males and three females, with six from solely private clinics and four with NHS and private patients. Four themes were identified: clinical decision-making and the patient–doctor relationship; regulations and the add-on traffic light system; research and evidence; and commercialization and financialization of the IVF sector.

Conclusions: UK IVF medical directors had a wide variety of views and experienced different pressures to offer IVF add-ons. The add-on discussion touches on core aspects of professional identity and the meaning of medical practice. The add-on debate points to broader changes in the organization of the IVF sector, which affect key aspects of practising (reproductive) medicine, including the patient–doctor relationship and responsibility for clinical decision-making, and the relationship between regulator and IVF clinic and between scientific evidence and clinical practice.

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INTRODUCTION

IVF add-ons have been defined by the Human Fertilisation and Embryology Authority (HFEA) as 'optional additional treatments' that are not essential for an IVF/intracytoplasmic sperm cycle (ICSI) cycle but can be offered in addition to standard fertility treatment, usually at an additional cost (*Human Fertilisation and Embryology Authority, 2020*). They include a collection of emerging technologies, longstanding techniques and reappointed treatments. However, their use has been the subject of debate. Critics of add-ons have highlighted their frequent clinical use despite the lack of high-quality randomized controlled trials (RCT) and follow-up studies, both to show benefit and to rule out harms (*Harper et al., 2017*), as well as the potential commercial motivations for their provision (*Farquhar, 2019*; *Stein and Harper, 2021*). Add-ons are frequently marketed on clinic websites without clear reference to a robust evidence base and the pricing of these treatments varies significantly (*Lensen et al., 2021a*; *van de Wiel et al., 2020*).

The evidence base for add-ons is also a subject of contention. Some have asserted that RCT should not be the only study design to be considered when assessing the evidence base (*Macklon et al., 2019*). Critics have responded that the capacity of non-randomized studies to assess add-ons is misunderstood and overstated (*Wilkinson et al., 2019a*). Another important driver for add-ons is patient demand, which is itself driven by direct-to-consumer advertising from the clinics themselves (*Lensen et al., 2021a*; *Nardo et al., 2015*; *Stein and Harper, 2021*). The tension between respect for patient autonomy and preference for evidence-based practice has been described (*Wilkinson et al., 2019b*; *Zemyarska, 2019*). Given the complex and conflicting body of evidence for add-ons, and the limitations of available patient information, there are concerns about whether the conditions for legitimate informed consent are satisfied (*Competition and Markets Authority, 2021*; *Lensen et al., 2019*). There have been requests for specific outlines on what should be explained to patients, yet others have asserted that patients already have an adequate understanding of the risks and are free to choose their own treatment path (*Zemyarska, 2019*).

To provide some guidance to patients and clinicians in the UK, the HFEA created a traffic light system for add-ons, where a green, amber or red rating is assigned to each add-on depending on whether the evidence suggests it increases live birth rate (LBR). Presently, and controversially in the eyes of some (*Macklon et al., 2019*), there are no green add-on treatments (*Human Fertilisation and Embryology Authority, 2020*). Attitudes differ towards the regulation of add-ons (*Ledger, 2017*; *Murdoch, 2017*; *Rutherford, 2017*).

Progress in this debate is unlikely without a nuanced understanding of the views of patients and clinicians. Some recent work has surveyed patients about add-ons, including the reasons why people use them (*Lensen et al., 2021b*). There is relatively little information about the views of practising clinicians, however. We sought to remedy this by interviewing medical directors of IVF clinics in relation to their views on the use of add-ons. A thematic analysis of the conducted interviews will provide insight into the opinions and decisions of clinicians.

MATERIALS AND METHODS

Ethical approval was obtained from the UCL Ethics Committee (reference 9831/001, 24 February 2020). It was made clear to the participants that only OI would be aware of what was discussed at the interviews, and that these would then be anonymized. The other co-authors were not aware of the identity of participants.

In order to recruit participants impartially, all the IVF clinics from the HFEA website were contacted. The medical director and relevant contact information was located on the websites, and emails were sent to individual clinics and clinic chains with an invitation to participate. There were 13 replies, but only 10 interviews were conducted due to cancellation as clinics were facing disruption from COVID-19. Some of the medical directors were the head of a chain of clinics, meaning a total of 35 clinics were accounted for in this study. The participants consisted of seven males and three females, with six from solely private clinics and four from NHS clinics, which may also treat self-funded patients.

All medical directors were interviewed by OI: nine via telephone and one in person. The interviews ranged from 12 to 45 min, being on average 28 min. The recordings and transcribed interviews were saved as documents with titles that excluded the participant's name to preserve their anonymity. The interviews were semi-structured, consisting of 14 guiding questions that targeted key topics. These included: what add-ons were offered; opinions on specific add-ons; understanding how, why and when the add-ons were used; what information was provided to patients; opinions on the traffic light system and IVF add-ons consensus document; what the ideal study type to evaluate add-ons should be and what their overall personal opinions on add-ons were. At times the questions were used flexibly, either being adapted or omitted entirely to avoid repetition. This promoted a more fluid dialogue, allowing the participant to fully express their views.

Interviews were analysed using the inductive thematic analysis process as described by *Braun and Clarke (2006)*. First, the data were transcribed verbatim, read and then re-read to enable immersion in the text. Second, meaningful and repeated units of text were identified, which were assigned codes, allowing more data to be identified and categorized into these codes. Third, the data were reviewed again by two others to ensure all codes had been identified and exhausted. Finally, the codes were grouped into four key themes on the rationale for the use of add-ons. We aimed to analyse the data in a non-biased way and included different viewpoints on each of the key themes. If multiple quotes in one theme are from the same director, this has been noted.

RESULTS

Four themes were identified from the thematic analysis of the interviews: clinical decision-making and the patient–doctor relationship; regulations and the add-on traffic light system; research and evidence; and commercialization and financialization of the IVF sector.

Clinical decision-making and the patient–doctor relationship

When speaking about the dilemmas they face in relation to add-on technologies, medical directors provided insight into the negotiations between patient and doctor in clinical decision-making.

Who ultimately chooses the course of treatment? Who bears responsibility for those choices? What is the role of the doctor's advice in a world in which patients may receive information from many other sources? What role do (not-) for-profit health systems of assisted reproduction play in navigating these questions? In this way, the add-on discussion can function as a lens onto the changing doctor–patient relationship in the fertility sector.

Most medical directors emphasized that it was the patients who initiated and requested the inclusion of add-on technologies in their cycle. They spoke against the suggestion that they would promote add-ons themselves, but highlighted that patients can be assertive in stating that they would like to include add-on technologies. In other words, medical directors position the patient request at the heart of the add-on conundrum:

> So, I think patients are assertive and that is a main driver for add-ons rather than any wish for doctors to get rich. You've got to remember, [...] the vast majority of doctors who work in IVF in the United Kingdom are on salaries. (P)

> [T]here is a lot of pressure from patients themselves requesting that we give them these things. This is despite us counselling the patients and saying there is no evidence that this works. (P)

In these characterizations of patient requests for add-ons, the medical directors highlighted a shift in the doctor–patient relationship towards a more consumerist model. Some compared the request for add-ons to explicitly commercial settings, such as supermarkets and restaurants. For example, one director responded as follows to a scenario in which patients request add-on technologies:

> If you are coming with a list, you go to Waitrose or Sainsbury's. Here, if I don't have a professional input, I am letting you down! I'm letting myself down! I'm letting the profession down! I only offer you responsibly what adds value. If it doesn't add value, it should not add to the bill. (M)

This director clearly rejects the idea that patients should make clinical decisions in a consumerist way. Instead, these decisions require professional input to ensure treatments 'add value'. According to them, taking responsibility for a 'fair and square' treatment offer is at the heart of what it means to be a fertility professional.

Another medical director similarly referenced concern about patients coming in with a 'shopping list' as if they are in a supermarket:

> Because the United Kingdom has chosen not to fund IVF and pushed it into patients having to pay for it themselves, they see themselves much more as clients rather than patients and feel they should be able to come in with a shopping list and do what they want. Much time is spent, by people like me, telling people why they shouldn't do that. (P)

Beyond a question of professionalism, this medical director illustrates how the add-on conundrum also points to a wider shift in assisted reproduction towards a private model of healthcare provision, which impacts the doctor–patient relationship. This director suggested that out-of-pocket payment encourages more consumerist behaviour among patients and requires medical professionals to spend more time adjusting expectations and clinical decision-making. In this way, the add-on discussion could become a proxy for a rejection of a more consumerist model of reproductive healthcare. Medical directors highlighted it was important to maintain professional input and decision-making power in order to assure that patients received efficacious treatment and avoided technologies and expenses without added value. This tells the story of maintaining standards of professionalism in the face of a consumerist model in which patients have more decision-making power, but are also more vulnerable to choosing to have treatments that are not necessarily in their best interest:

> If you're not actually going to provide them with something that's going to give them a chance, giving them something that's going to make them feel better, it is not appropriate. [...] It comes back to this thing about integrity. (M)

> For some people, they argue giving the patient what they want. Why? Because they have to have a say, which I can accept, but they have a say in what they know. If they don't, then we are just misleading them. (M)

Another medical director similarly referred to supermarkets when talking about their patients, but drew favourable parallels to the consumerist decision-making model these shops represent:

> Bottom line, patients are adults. I think this is where the HFEA is approaching patients and approaching doctors like patients aren't adults. We have a product and if the HFEA have such strong views, I'd say let them ban things if they think they shouldn't be on the market. (P)

> It's the same as a government going to the shop and saying why are you selling cigarettes to those gentlemen over there? That's because you have licenced it. If you ban all cigarette smoking in the UK, then end of the problem. (P)

Whereas the earlier group of doctors use the supermarket comparator to criticize consumer decision-making in assisted reproduction, this medical director compared their clinic to a shop to emphasize the legitimacy of offering consumers a choice of legal services. They suggest it should be up to the regulator to take undesirable add-ons off the market, but while they are legally available, it should be up to individual doctors and patients to navigate the add-on landscape within legal limits.

They also make a point that was often heard: the doctor's refusal to offer add-ons would not prevent the patient from accessing them, but would simply result in patients going to another clinic. The add-on issue thus reveals the contrasting interpretations of the roles and responsibilities of patients and doctors that medical directors may have.

Mitigating between these two positions of only offering treatments that have added value and offering patients a consumer choice for any add-on treatments were considerations of harmfulness and informed consent. One group of medical directors argued that patients could choose to include add-ons as long as they were not harmful:

> Giving the patient what they want is easy if it's about aspirin or progester-

> one and it's not harmful. If it's about invasive, expensive, potentially harmful procedure, then they can't be allowed to have what they want. (M)

> So then, most of the time they say: does it cause any harm? We say we don't have any evidence to show it causes harm and they say fine I will go ahead with it. (P)

These medical directors circumscribe the scope of patient choice by pointing to the limits of harm. Patients are free to request and choose add-ons, as long as they do not conflict with a doctor's prerogative to not do harm. Yet the nature of what constitutes harm is contested. Does harm refer only to medical conditions or does it also include financial harm?

> It is with the doctor at the end of the day to ensure their patients are fully informed and not being harmed. I just think not only is that harm medical but financial as well. You have to ask are you financially harming that patient? Because if you are that is really wrong. (P)

> What about the people who have the resources? You are telling them no don't do this. But they have the resources. Why are you scaring them? [...] There are some add-ons which are completely safe. There is a difference between it being safe and it being effective. (P)

The differing opinion on the duty of care beyond avoiding harm reflects core ideas about what medicine is, and whether it requires offering safe care, or exclusively effective care:

> If I'm harming patients, if I'm prescribing something of harm, that's the role of the GMC. If I'm prescribing things that are of low benefit and patients know they're of low benefit, then so what? As long as patients know. That's what medicine is. (P)

> You need to think about the evidence, and you need to deal with your patients with integrity. It's not that you can just put up a list of things and say you choose and pay for whatever you want, and we'll do it for you. That's not how medicine works. (M)

Alongside harm limitation, medical directors also emphasized 'being informed' as a key condition for meeting patient requests for add-ons:

> If you tell patients this has not been proven to be of any benefit, but it's not harmful, a patient might say well yeah okay but I'd still like it doing. In which case, I think that's okay! Provided the patient is informed. (P)

> So, as long as I'm documenting that the patient has been advised we shouldn't do this, that we don't advise this, what more can I do? These patients aren't children, they're over 18. (P)

> Number one – first do no harm. We are not here to harm patients. Secondly, patients need to be fully informed. Whenever a doctor offers a treatment they need to be informed about the risks and then the benefits and then it is up to them to make a decision. (P)

There is a widespread sense that patients being informed is key for add-on decision-making, from which at least two issues arise. First, there are divergent understandings of the relationship between physician responsibility and patient's informed consent in treatment decision-making. The medical directors expressed different views about their responsibility towards the patient; are they responsible for ensuring that the patient gets the best, least harmful, most efficacious treatment or is the patient ultimately responsible for their own treatment choices, provided that they are well informed by their physicians?

Second, the nature of the sources of information required to become informed is contested. Different interpretations on how best to inform patients emerge in relation to competing authoritative sources of information about add-ons, including the HFEA traffic light system, the treating physician's advice, marketing websites of manufacturers or scientific evidence. In addition, questions were raised about how to ensure a patient is accurately informed when external sources, such as friends and social media, are also key sites of information. Medical directors described how ensuring the patient was well informed about add-ons could be labour-intensive and 'awkward':

> They usually want them because clinic A offers them and why don't you offer them when my friend went to such and such a clinician, she was offered this, and she got pregnant. (P)

> For the patient that's very strong evidence because that's their friend, they have the proof, they have a baby there sitting in front of them. What more proof is that compared with 'we can't find any evidence to show it improves'? (P)

> If you don't offer it, they say we don't care we are willing to take this risk and if you don't offer it, we will go somewhere else. It is hard work to discourage them from using it. (P)

> Sometimes we have quite awkward conversations when they're challenging us about these sorts of things. We spend quite a lot of time talking people through why they're not relevant and what sort of evidence there is. (M)

As these reflections show, the add-on question is also one of the labour and politics of informed consent in IVF. The competing sources of information that underlie patient requests for add-ons raise new dilemmas for practitioners that may be resolved in ways that reflect underlying ideas about physician and patient responsibility in clinical decision-making. These decision-making dilemmas also exceed the patient–doctor relationship, but include external actors such as regulators, who also seek to inform patients about their treatment options. One example of this is the HFEA's above-mentioned traffic light system.

Regulations and the add-on traffic light system

The HFEA's traffic light system played a key role in the reflections of the medical directors. It was used in patient communication in various ways, provoked discussions about personalized treatment and generalized advice, and also revealed divergent views on the role of regulation in reproductive medicine.

Some participants described the traffic light system as a useful tool in patient communication:

> I've taken the liberty of copying from the HFEA websites some leaflets from there for my patients because I think they're quite nice. We just sort of print them out and have them available in house. I think it is a good system. I actually welcome these sorts of things. (P)

> We have included on the website a link to the HFEA add-on page and everywhere there is anything. We actually have slides on add-ons in our open evening slides. (P)

> If there is a particular add-on like the PGS blastocyst stage, even if it is clinically applicable we say to them: look this is a red one, do you still want to use it? and it is in the consent form and the information sheet, so that they make an informed decision. (P)

As the last quote suggests, the traffic light system was sometimes explicitly used to dissuade patients from including an add-on that they thought might help their cycle:

> It's helpful for people like me if I've got a patient demanding this and I can say well look at the traffic light. (M)

Yet, as another medical director noted, the information in the HFEA traffic lights system is not necessarily persuasive:

> We have patients saying if you don't offer it, we will go somewhere else. They don't care about what the HFEA is saying. They demand add-ons yes, but they don't seem to worry so much about whether it is red or amber. (P)

The traffic lights may also lack persuasive power to avoid including add-ons despite a red or amber classification because they only focus on the chance of increasing LBR, not on potential harm:

> You know, when people are vulnerable and desperate, they will say 'Oh, well if it's not harmful then it can't hurt'. But, if they knew that it hurt their pocket and hurt their resilience to continue with the journey, that invariably requires more than one attempt. (M)

While these medical directors referred patients to the traffic lights to discourage them from using add-ons, others found the HFEA's system unnecessarily dissuasive. This participant mentioned that the system was too simple or blunt and did not allow for personalized indications for add-ons in specific situations:

> It maybe simplifies things too much. It says green, amber, red. It oversimplifies quite complex questions. (P)

> Now, I know the HFEA have put it up because they are trying to avoid everyone just having preimplantation screening. They haven't thought about what happens for those who actually do need to have this. (P)

Implicit in these opinions is the idea that the generalized recommendation that the HFEA may not apply in specific cases, in which the inclusion of particular add-on technologies may be advised. Clinicians who do advise patients to include an add-on found the HFEA advice led to 'uncomfortable' situations and listed other reasons besides an increased LBR for including these technologies:

> The fact that it's on the HFEA website as a red, I think it's very uncomfortable now to have that conversation with patients. So, whilst I've got a practitioner who could offer it and we could offer it, we're feeling that the HFEA is almost telling us it's bad you shouldn't be doing this. Whereas two reasons patients might want it is one: to get closure and two: is to not have such a long journey to get to the final healthy embryo. So, it doesn't increase the live birth, but I think there is a place for it. (P)

As this citation suggests, the traffic light system brings up more fundamental questions about the relationship between clinicians and regulators. While some professionals welcomed the information as a patient communication tool, another felt that the HFEA took on a 'paternalistic' role with its traffic light system:

> I think it's paternalistic. [...] I'm not sure whether it's the role of a regulatory body to tell doctors what they can and cannot do. (P)

> They should be regulating clinics. [...] and to make sure clinics abide by the acts of the HFEA of 1990. Their role is to ensure that clinics don't break the law. Why do they think that they should be advising clinics what they should and shouldn't be doing I don't think that's their role. I think that's the role of the general medical council. (P)

> This big brother the HFEA is watching you. I'm telling you what's red, amber and green. Pft! A lot of us have spent a long time studying the risks and the benefits. (P)

These statements suggest a tension between a doctor's autonomy and the regulator's role in shaping treatment choices. This medical director felt like the traffic light system was too intrusive and exceeded beyond the remit of the regulator. In keeping with this, one medical director criticized the traffic light system for sending out a message of discouragement, yet not banning the use of add-ons:

> If you're going to say PGS is red, you are the governing body, why not say no one is allowed to do PGS in the country? (P)

> Why are you allowing that to be a licenced treatment in the UK? You can't criticise me for supplying a product you have licensed. (P)

This position highlights that the regulator should focus on its remit of upholding legal limits on assisted reproduction. To allow add-ons such as PGS to be used, yet present negative advice on the technology on its website, they propose, confuses the role of regulator.

It thus appears a segment of medical directors appreciate the traffic light system as a means of patient communication and as a tool to dissuade them from using add-ons. Another segment objects to this dissuasive effect of the traffic lights when they do wish to offer add-ons, whether in particular cases or more generally, and suggest it is a blunt tool that does not convey the complexities of clinical decision-making. More fundamentally, the disagreements about the traffic light system show how the current add-on debate also reflects an ongoing negotiation about the role of the regulator and regulation in the sector.

Research and evidence

The current study finds a remarkably wide variety of views among medical directors on what constitutes convincing evidence for the inclusion and introduction of add-ons. The HFEA traffic light system relies on RCT to make its recommendations, and indeed some medical directors align with this approach in their clinical practice. One participant explained what ought to be the basis for add-on inclusion:

> A proper randomized control trial. Preferably, multi centre. Preferably, by credible people. Preferably, from a place where research governance is ev-

> ident and can be verified, rather than just dreaming up results and making them up as it happened. (M)

They position RCT as one element of good, reliable research practice and suggest that this is not a given where studies on add-ons are concerned. They convey a sense that published evidence in the field is not necessarily reliable, but is sometimes the result of 'just dreaming up results'. They similarly note concerns about the lack of reliability of published evidence (the quote above and both quotes below are from the same director):

> The other issue also is that if you talk about evidence, it is a very loose word nowadays. If you don't find evidence for any intervention, you have not googled it hard enough. That is because in the literature, anybody will publish anything. (M)

> It is an extremely difficult issue because even when people do trials and they find that it doesn't make any difference, they twist things in the discussion and the conclusion, and they always milk it! They just can't surrender when they do a trial that shows this intervention is a waste of time. They just can't. They have to twist it. (M)

These citations express concern with the published evidence for add-on technologies because researchers can convey a biased message by 'twist[ing]' and 'milk[ing]' their results or not including all relevant research data in their publications. Likewise, the editorial practice of medical journals was not considered to be stringent enough, thereby enabling clinicians to find apparently supportive published evidence for treatments that have not been proven to work in high-quality RCT. What is at stake in this unreliable evidence is the patient's protection against conflict of interest:

> I do think that there is a need for patients to be protected against unscrupulous practice and therefore the HFEA can have an important role in making the evidence base that is available to doctors also available to patients. Possibly, even requiring doctors to discuss it with the patients. (P)

> They should be designed by the HFEA. There should be evidence collected by the HFEA and then published by the HFEA. A body without any bias in all of these things. (P)

In these views, the scientific evidence base can provide a foundation to protect patients against 'unscrupulous practice'. Yet, at the same time, these medical directors suggest the evidence base itself may reflect unscrupulous practice and requires the HFEA to take on the role of researcher and publisher to protect against bias.

Interestingly, while this participant proposes the HFEA could improve the evidence base and decrease concerns about bias and unscrupulous practice, others argue the opposite and raise concerns about the 'limitations of the evidence base that they're using at the moment':

> I think it's a very good initiative and I applaud it. My concern with it is the way in which evidence is assessed and the nature of evidence that is accepted. [...] if we are to only accept randomized controlled trials as acceptable sources of evidence, we are going to be in this difficult situation for an awful long time. (P)

> So, the two criticisms I've had about it are its restriction to RCTs. [and] the way in which the evidence base is assessed within the HFEA. At the moment it's done by a single epidemiologist [...] who's charged with reviewing the evidence and then advising the scientific committee what position they should be taking. [...] I'm rather concerned that this is a rather unrepresentative way of doing it. You really should have some input from people who are also caring for patients and can understand how this data should be interpreted in a more complex situation, than simply an RCT either doesn't exist and therefore you're not allowed to use the treatment. (P)

> I think it is madness to need to have an RCT. Absolute madness. If we said that, if we rolled that out to contemporary 21st century medicine, then the world would be a much less healthy place. (P)

While one group of practitioners highlight that RCT provide a means of strengthening the evidence base and good clinical practice, another suggests that too much reliance on RCT is problematic because it does not take the specific complexities of clinical decision-making into account and because an over-reliance on an RCT would stifle innovation in reproductive medicine:

> My concern at the moment is that the way in which the evidence is being assessed or generated is unhelpful to both clinicians and patients. I'm very concerned that unless we change this in ten years' time everything will be red. That's no use to anyone at all because it means the field has not advanced one iota. (P)

What is at stake in these contrasting views is not only an epistemological or methodological difference, but a set of ideas about what an RCT represents and what the nature of the relationship between clinical and research practice should be. Whereas one group of medical directors emphasized the need for high-quality RCT as a prerequisite for evidence-based clinical practice that benefits patients by protecting them from investing in unproven treatments, another group framed the reliance on RCT as limiting innovation and hindering patients from accessing potentially useful treatments.

Yet the interviews also highlighted that an often polarized debate reflects a complex set of concerns that is not black and white but follows from the negotiation of the relationship between clinical and research practice:

> There will always be a sort of pragmatism that needs to be there between what the doctor knows the evidence base to be and what they perceive their individual patient's requirements to be. (P)

> What you have to do is to consider the individual patient. Use all the resources that you've got available to you, randomized trials – brilliant – case reports, epidemiological studies, cohort studies, observational studies, databases, use it all. Then come to the conclusion that you have for the individual sitting in front of you. (P)

> Whilst accepting RCTs may be the gold standard in many ways [...] they don't address all the questions that clinicians need answering or patients. (P)

The 'pragmatism' required from the clinician that is highlighted in these

quotes, which entails both a responsibility and a degree of interpretation, is at the heart of the add-on debate. The particular ways in which clinicians resolve the uncertainties resulting from the above-mentioned potential bias and plurality of the evidence base pertains not only to the inclusion or exclusion of add-ons, but to the heart of what is perceived to be one's professional identity:

> Doctors have to use the evidence base in reality. [...] That might often involve the use of treatments that don't have a strong evidence base. In fact, IVF doesn't have a strong evidence base. So, that's what clinical medicine is. It's using the evidence base to guide the management but not dictate it. If it was dictating it then there would be no use for doctors. (P)

> Just to sit there and say there are no RCTs which show that anything works, is not medicine. You've got to say well look, there isn't evidence across the population that what I'm proposing would help everyone, but because of a, b, c and d and your history this is what I'm advising you to do, and because of a, b, c and d and your history I would advise you not to do that. That's essentially what medicine is. (P)

Beyond a discussion of efficacy, for these medical directors, the add-on question thus touches on the very heart of what it means for them to practise medicine. It highlights how the particular relation to and interpretation of an evidence base is key to the work, but is understood to require 'pragmatism' rather than being an exact science.

This pragmatic approach allows for a plurality of approaches to evidence to exist under the banner of 'best practice' or 'best treatment'. For example, beyond the question of RCT, the medical directors describe several approaches to generating and interpreting their own clinical experiences in relation to a broader evidence base:

> So, you know my view on that one [endometrial scratching] is that's the risks, they're the benefits, that's the theory, if you want it, fine! It's a bit like [...] when I was a little boy and we were watching the television and it went on the blink, my dad would come in and look at it and then give it a kick. The television nine times out of ten would come back on again. Now, there's no evidence whatsoever that kicking the television is going to make it improve, but it's just a sort of phenomenon that we do. (P)

Alongside this trial-and-error approach, some medical directors draw on their clinical experiences to suggest that certain treatments may only work for a subsection of patients and may therefore be beneficial even if their efficacy is not clear in studies drawing on larger populations:

> So, I think the treatment is probably quite close to being correct, but we're not picking up the right people, we're picking up far too many people and it's just a tiny proportion where there is really an immunological issue. (P)

By contrast, others propose working with big data and large databases to attain more clinically grounded evidence for their practice:

> Then over time with the size of that database which would be hundreds and hundreds of thousands over a few years, we would be able to see what the predictors are. [...] That to me will provide a much more clinically useful database than randomized controlled trials done in very controlled settings on patients that we hardly ever see in the clinics, and then drawing conclusions from those as if they are gospel. (P)

What is at stake here is not so much whether these views are correct, but rather that they document that there is a wide variety of interpretations of what constitutes good evidence and how this evidence relates to good clinical practice. It demonstrates how the practice of reproductive medicine is a highly interpretative and subjective practice. It shows how medical directors navigate various sources and interpretations of evidence, including their own clinical experiences:

> One of the reasons we're not changing it [embryo glue] is because we've got such good results and it's been used for four years we just thought, well why take it out? We're paying for it and not charging the patients and it's working very nicely for us. (P)

The add-ons debate thus touches on the heart of what it means to practise reproductive medicine and the responsibility, vulnerability, power and uncertainty that medical professionals hold in the clinical encounter. Yet as this final quote illustrates, what is at stake is not a plurality as such, but the potential for bias, conflict of interest and business incentives to affect this complex and interpretative work. What does it mean when complicated work of translating scientific evidence to clinical practice is joined by pressures and incentives for improved outcomes and increased revenue? Do these core negotiations change in nature when doctors also become business owners, or lose their authority and autonomy to a new managerial class in fertility practice?

Commercialization and financialization of the IVF sector

Several participants raised concerns about add-ons reflecting a profit motive in assisted reproduction:

> Some of those add-ons [...] have become introduced into the commercial market, with a drive to say actually you know we can introduce that, and people will pay for it. There is a market value to it. (M)

This profit motive and commercial pressure was associated with specific clinics, rather than experienced across the board:

> I think we work in a slightly different environment than some of those centres in London where there is a huge amount of competition going on. [There are] commercial pressures there that we don't see. Start introducing unproven things or doing things to people and start charging them for it – that's not okay. I'm not suggesting they're like that, but you have to be careful and you have to do things properly. As licenced doctors it is our duty to do that and the commercial side shouldn't have a part in it. (M)

As this quote highlights, the effect of these commercial pressures on add-on practices may be ascribed to both clinics and clinicians. In other words, participants who object to profit motives in IVF highlight both structural factors that contribute to this phenomenon and individual decisions by clinicians who may have different motivations or professional ethics:

> Now, there is no doubt that there are unscrupulous doctors who will exploit

> that, and they are here in X there is no doubt about that. My experience having worked in X and different parts of the NHS and now in X, is that that represents a tiny minority of doctors, and I'm glad it does, because doctors go into medicine to help people, not to get rich and if they wanted to get rich they'd go and do something else. (P)

In contrast to an emphasis on high standards of professionalism ('our duty') and the limitation of the problem to only a 'tiny minority of doctors', other participants did not limit their concern to particular individuals, but rather raised structural concerns about the sector more broadly. Several participants reflected on the history of the fertility sector and the move towards a more privatized model:

> There was such a public out-cry about babies being born in the NHS in test tubes and it's outrageous and the doctors got sacked. So, it all went underground, and it all grew up in the private sector. So that's why we've got this problem we have now: because the NHS rejected IVF. And IVF in 1978 was the ultimate add-on. (P)

This participant suggests that the contentious nature of IVF itself facilitated the move towards a privatized fertility sector within a national context that has a strong public health system. The effects of the 'reject[ion]' of IVF by the NHS favoured a more commercial model of healthcare within which add-on treatments can thrive. Along similar lines, another participant draws the connection between the lack of NHS support for IVF and the commercialization of the sector:

> And it has always saddened me that most of reproductive medicine is in the private sector because many of these private centres started up as charitable organisations because there was no NHS funding. They've now become big commercial ventures funded by hedge fund things. People are putting money in to get a return, so there's a drive to make money out of it. It's become a business. (M)

This description highlights the structural elements that have shifted with this move towards commercialization, including clinic consolidation into larger centres, and financialization, or the external investment by parties such as private equity in fertility clinics. This participant describes their unease with these structural shifts and hopes that individual clinicians within the 'industry' can make an effort to 'act appropriately', thereby indirectly suggesting that these shifts facilitate people doing the opposite:

> People often talk about it as an industry and I hate that. I'm not in industry, I'm a doctor working with patients. I struggle to know how that's going to be reversed and I struggle with it greatly that that's the case. But I call on my fellow doctors and clinicians and practitioners to act appropriately. (M)

> I think that the IVF industry has now got completely out of control. 80% of IVF cycles or more are being conducted by centres that belong to around 10 large companies, mostly equity based, where the person who is funding that company is out of touch completely with the face to face contact with the patient and has no understanding of what they are doing to patients. I am absolutely horrified. I am one of the last few small independent IVF units still standing, and proud to be so. [...] That is very rare. [...] When you turn a medical science into a commercial practice where finances determine how you conduct yourself, you are distancing the medical practitioner who signed a Hippocratic oath from the actual reality of what you're offering. And people in these clinic chains that we have got now all over the UK are just churning out cycle after cycle. [...] It's financially driven. Therefore, they have driven the whole add-on market because they have said how can we get more out of each patient and more out of each cycle. (P)

This participant notes that, in their experience, the move towards a more commercial and financialized model of IVF also entailed a form of disempowerment of medical practitioners. They argue that the model by which the medic runs the clinic is being replaced by one in which business people take on leadership roles and financial logics drive the ways in which fertility treatments are offered. As a result, this participant states, financial interests encourage trends towards more cycles and more add-ons in order to get 'more out of each patient and more out of each cycle'.

Similar frustration with this move towards commercialization was also expressed in relation to the patient's interpretation of the add-on offer:

> It frustrates me that people come along and still say to me 'Oh, you're just an NHS clinic. I can have that done in the private sector', but if we were doing it private, we still wouldn't be doing it. So, there a few things like that, but there are none that I'm in a great hurry to introduce. If we did, we'd have to put it through the trust and make a case for it, but we wouldn't be banned from doing it if they were worth doing. (M)

While this clinician was frustrated that their assessment of certain add-on technologies as not 'worth doing' was interpreted as an inferior offer of care compared with the private sector and indeed, some practitioners in the private sector feel similarly to the patients:

> Yes, it needs to be about customised treatment. We have the luxury of being in private. I know that in the NHS it's busy. There are lots of patients and it's very difficult [to] make it personalised for patients in the NHS. In the private sector, we do try and do that because we do have the time and the patients have the resources. (P)

In this opposition between public and private reproductive healthcare, add-ons do not represent a financial drive for more revenue, but a means of personalizing treatment and offering more individualized time and care.

While the add-on question provoked the articulation and dismissal of concerns about commercialization, another medical director gave the broadly shared view that the debate surrounding add-ons was polarizing the professional fertility community and eroded trust (all three quotes below are from the same person):

> At the moment its far too polarized into doctors are bad if they use unproven techniques because they're trying to get rich. Without doubt there are some like that, as there are in branches of every profession, but the majority of doctors are doing their best with a limited evidence base to provide the best care for their patients. (P)

> If we can acknowledge that on all sides of the discussion, then I think there is room to move forward with this

> debate. As long as we don't do that it's going to be a shouting match and no one's going to get anywhere. The only people who are going to suffer from that is patients. (P)
>
> The trouble with the literature in it at the moment [...] is it's very polemic and almost emotional. Very extreme positions are being taken at the moment which does concern me a little bit. [...] (P)

Medical directors thus express their unease with the current terms of the debate. Suggestions for improvement of the dialogue among professionals highlight how the add-on debate functions as a proxy for broader issues, including those raised in this paper: an acknowledgement of the professional integrity of doctors, the nature of scientific evidence in a rapidly changing field, and the negotiation of power relations between doctors, investors, patients and regulators within the sector.

DISCUSSION

Q2 Add-on technologies are among the most passionately debated topics in IVF today. The interviews presented here revealed considerable variation in the views of medical directors towards add-ons, and served to elaborate these diverse perspectives. Four key themes were identified in the data: clinical decision-making and the patient–doctor relationship; regulations and the add-on traffic light system; research and evidence; and commercialization and financialization of the IVF sector.

Most participants suggested that requests for add-ons were initiated by patients, who may have read about them online or heard about them from friends. This contrasts with the results of a large survey of patients in Australia, which reported that patients typically first heard about add-ons at the IVF clinic, and that the possibility of using them was raised by clinicians, although these data are subject to the limitations of reporting on the basis of recall (*Lensen et al., 2021b*). While there was broad agreement on the fact that demand originated from patients, there were differences in opinion as to how clinicians should respond. Some participants saw it as their role to dissuade patients from using unproven add-ons, while others suggested that patient autonomy should be paramount. One perspective was that a potentially ineffective add-on could be provided if the patient gave informed consent and there was no evidence that it caused harm. This prompts further questions about what constitutes harm and where the burden of proof for (lack of) harm lies. There was frequently an implicit assumption that, where efficacy of an add-on had not been proven, that the 'worst case scenario' would be that it had no effect; the possibility of an add-on reducing the chance of live birth was not considered, although this might be construed as a harmful effect. There being 'no evidence of harm' for an add-on might be a very low bar for use, because this criterion is satisfied for any therapy that has not been rigorously evaluated. Some directors emphasized that it was acceptable to respect the patient request for an add-on, provided that they were sufficiently well informed of the risks and (lack of) evidence. We suggest that the role direct-to-consumer advertising plays in shaping patient views, and the implications for informed consent, are relevant considerations here (*Lensen et al., 2021a*; *van de Wiel et al., 2020)*.

Responses to the traffic light system presented by the UK regulator were mixed, with some participants seeing this as a useful aid in informing patients and others viewing it as paternalistic. One view was that the system lacked nuance, as some participants felt that it was appropriate to use add-ons for particular subgroups of patients and some stated that they used them for reasons unrelated to live birth, such as preventing patient regret. Other examples provided were using add-ons to prevent miscarriage, or to reduce the time to live birth. The first concern, that add-ons may be beneficial for specific subgroups, may actually already be covered by the traffic light system, because a red rating indicates that there is no high-quality evidence that the add-on works in anyone. Where an effect was demonstrated in a particular subgroup, this would be incorporated into the traffic light information provided by the regulator.

Views also differed on what constituted convincing evidence, with some participants believing that randomized trials were necessary for the evaluation of treatments, and others emphasizing the value, perhaps perceived superiority, of alternative approaches. A clear divide was evident, with some participants seeing the requirement for RCT prior to regulatory endorsement as protecting patients against ineffective or harmful treatments, and others seeing it as stifling innovation, reflecting ongoing debates on this topic (*Evers, 2017*; *Macklon et al., 2019*; *Perrotta and Geampana, 2020*; *Wilkinson et al., 2019a*, *2019b*). One implication of these different interpretations of evidence is that the information presented to patients, and hence the basis for informed consent, is likely to differ between clinics. It is unclear whether patients generally feel like they have access to clear, impartial information about the evidence for treatments, or to the reasoning behind the allocation of traffic light ratings. Indeed, the interviews suggest that some medical directors may feel similarly. Greater elaboration of the traffic light process might therefore contribute to standardization of informed consent processes in the UK. In other countries, where no such resource is available to patients, there may be considerable variation in how evidence is interpreted and presented to patients.

Views on the perceived financialization and commercialization of fertility treatment were similarly varied. Some directors expressed discomfort about these commercial trends, suggesting that there was a tension between for-profit IVF and patient-centred care. By contrast, others presented their commercial model as actually being conducive to patient-centred care, as it allowed patients to select and purchase a 'personalized' suite of care. The ability to offer a menu of add-ons was seen by some as differentiating their service from publicly funded clinics, and this view was reported to be echoed by patients, who saw the availability of extras as representing innovative, tailored care. Representatives of some publicly funded clinics were bothered by the fact that, by declining to offer add-ons, their care was sometimes viewed as inferior. Some stressed that they would not offer unproven add-ons even if they were in a private setting, in effect because the impression of luxury was an illusion. There was agreement that many patients find the prospect of customized care attractive. The debate is whether the availability of customization options is actually beneficial if the options may not improve outcomes, or could be

confusing for patients (*Armstrong et al., 2019*; *Wilkinson et al., 2019b*). This is emphasized by recent qualitative work suggesting that many patients attempt to identify which combination of the many options offered will 'work for them' (*Perrotta and Hamper, 2021*).

In the study country (UK), new guidance has been issued to remind clinics of their legal obligations in relation to consumer law, which prescribes including clinical evidence and information about risks associated with add-on treatments (*Competition and Markets Authority, 2021*). It remains to be seen whether and how this will influence how add-ons are marketed and used. Guidelines issued in Australia to tackle concerns relating to presentation of success rates on fertility clinic websites led to high levels of compliance, without leading to improvements that would allay the concerns of critics, for example (*Goodman et al., 2020*). These data suggest that variation in how patients are consented and treated is likely to remain the status quo for the foreseeable future.

Only 10 doctors participated in this study, and they did represent 35 clinics, but a much greater number would be needed to provide a comprehensive analysis of clinical views on add-ons. While a diversity of views were captured, it remains possible that some sub-themes were not identified. Additionally, the senior author of this paper is an advisor to the HFEA SCAAC, who has published multiple papers on add-ons. Occasionally, interviewees strayed from the interview format to indirectly express their views to the senior author, with some becoming impassioned and others guarded. Only OI was aware which interview belonged to which particular interviewee.

Add-on technologies are among the most widely and passionately debated topics in IVF today. This paper reveals that what is at stake in the add-ons discussion is more than disagreements about the efficacy of the different technologies; rather, it touches on fundamental aspects of what it means to be an IVF professional and to practise medicine in a sector that is rapidly changing. It is proposed that the add-ons discussion functions as a proxy for a wider set of issues, tensions and changes within the IVF sector. These include the responsibility for clinical decision-making in changing patient–doctor relationships within private and public contexts, the question of autonomy in the relationship between clinics and regulators, the politics of knowledge production in the evidence base for add-on technologies and the shifts towards further commercialization, consolidation and financialization of the sector. Each of these issues are condensed in the add-on discussions, which become an expression of core ideas about what it means to practise medicine today.

OI carried out the interviews, transcribed the interviews, anonymized the transcripts and performed the primary analysis. OI is a medical student who is impartial about the use of IVF add-ons. JH is a member of the HFEA Science and Clinical Advances Advisory Committee. JH and JW have published extensively on the need for evidence-based medicine to be used for the implementation of add-ons. LvdW has no formal conflict of interest. This article aimed to analyse the data in a non-biased way and to include various points of view on the topic.

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