Evaluating the efficacy, safety, and clinical effectiveness of IVF add-ons: methodological challenges and future solutions.

The AFFINITY study group

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Abstract

Assisted reproductive technology (ART) has expanded rapidly into a complex, highly regulated, and innovative field, with in vitro fertilisation (IVF) now accounting for millions of treatment cycles globally each year. Alongside these advances, numerous supplementary interventions, commonly referred to as “IVF add-ons,” have been introduced into routine clinical practice with the aim of improving pregnancy or live birth rates, reducing miscarriage risk, or shortening time to conception. Despite their widespread adoption and substantial additional costs to patients, most IVF add-ons lack robust evidence of safety, efficacy, and cost-effectiveness. Regulatory and policy efforts to guide their use are constrained by significant methodological weaknesses in the existing evidence base, including heterogeneous definitions, suboptimal trial design, inconsistent outcome reporting, and limited translation of research findings into clinical practice. This article explores the principal methodological challenges that currently impede rigorous health technology assessment of IVF add-ons. These challenges include the absence of a clear, validated taxonomy to define and classify add-ons; lack of consensus on appropriate comparators and clinically meaningful outcomes; and failure to establish agreed thresholds for clinical utility and futility that incorporate economic considerations and patient perspectives. A major limitation arises from reliance on conventional parallel-group randomised controlled trials, which are often poorly suited to evaluating complex, multi-stage ART interventions in heterogeneous populations. We discuss the potential value of innovative trial designs—such as platform, basket, sequential multiple assignment randomised trials, hybrid pragmatic–explanatory approaches, and decentralised digital trials—to strengthen evidence generation. Collectively, these methods may enhance efficiency, improve interpretability, and better align research with real-world reproductive care.

Introduction:

The field of reproductive medicine has seen major developments over the last five decades, transforming into a fast-growing multi-disciplinary and highly regulated medical field. The introduction of Assisted Reproductive Technology (ART) treatment in the 1970s enabled millions of couples to start their family life with more than 2.5 million In-vitro fertilisation (IVF) cycles worldwide annually(De Geyter et al., 2020).

The progressive and innovative nature of ART, combined with the high motivation of both patients and fertility specialists to maximise chances of pregnancy, fuelled the rapid adoption of novel supplementary or additional fertility treatments, commonly called ‘’IVF add-ons’’(Macklon et al., 2019). Since the early 2000s, the list of IVF add-ons has rapidly expanded to include many tests, drugs, equipment, complementary therapies, laboratory procedures, and surgical interventions all sharing a common aim to enhance pregnancy or live birth rates, mitigate the risk of miscarriage, or expedite the time to achieving pregnancy(ESHRE Add-ons working group et al., 2023).

The terminology "IVF add-ons" (alternatively referred to as "adjuvant treatments" or "supplementary procedures") became formally recognised in reproductive medicine discourse during the mid-2010s, as fertility clinics increasingly incorporated optional, often expensive, adjunct interventions into conventional in vitro fertilisation (IVF) protocols(Harper et al., 2017).

Unfortunately, many of these add-ons are routinely offered to couples with infertility off-licence at an additional cost, without sufficient proof of safety, clinical and cost-effectiveness(Zemyarska, 2019). Several health regulators have attempted to control the use of IVF add-ons in practice(The Human Fertilisation and Embryology Authority, 2019), however, the quality of available evidence often hinders meaningful guideline development to inform clinical practice(Macklon et al., 2019).

A recent consensus statement by nine health regulators, professional societies, and patient advocacy groups in the UK expressed concern about the exponential use of IVF add-ons without sufficient proof of safety and efficacy(The Human Fertilisation and Embryology Authority, 2019). Many expressed concerns about the risk of exposing vulnerable patients to profiteering practice across IVF clinics in the UK due to the over or mis-selling of IVF add-ons(Zemyarska, 2019). A survey of UK IVF clinics (n=87) showed that very few clinics reported on the possibility of adverse effects of using add-ons on their websites and most claims of efficacy were based on upstream outcomes (e.g. implantation, pregnancy) with substantial pricing variations(Van De Wiel et al., 2020). The majority of IVF patients in the UK (74%) have reported using at least one IVF add-on(The Human Fertilisation and Embryology Authority, 2018), which usually incurred an additional cost and more than half (66%) expressed regret regarding using IVF add-ons(Lensen et al., 2021). Vulnerable infertile couples, who are desperate to become pregnant, often rely on anecdotal evidence and informal online sources when considering the use of IVF add-ons(Armstrong et al., 2023). Patients’ acceptability, treatment preferences, and representation remains poorly featured across studies evaluating various add-ons which further limits the generalisability of available evidence(Jack Wilkinson et al., 2019). The European Society of Human Reproduction and Embryology (ESHRE) Ethics and Law special interest group recommended evaluating IVF add-ons that are prioritised by patients for their efficacy, safety, procedural reliability, acceptability, and cost(Provoost et al., 2014).

A recent Cochrane special issue on IVF add-ons evaluated 13 different treatments (12 reviews, 170 Randomised Clinical Trials (RCTs)), and showed no clear evidence of benefit for the majority of these add-ons(the Cochrane Gynaecology and Fertility Group, n.d.). The

quality of included RCTs was generally low to very low due to poor trial methodology, varied reporting, and inadequate statistical analysis(the Cochrane Gynaecology and Fertility Group, n.d.). The recent update of the ESHRE guideline provided 42 recommendations on the use of 27 different IVF add-ons(ESHRE Add-ons working group et al., 2023). The vast majority (95%) of the recommendations were supported by low-quality trials, observational data, or consensus of the development group(ESHRE Add-ons working group et al., 2023).

The nature of ART treatments as complex multi-stage health intervention and the varied response across patient subgroups, often complicates the conduct of adequately powered RCTs(Wilkinson et al., 2016). Furthermore, variation across trial settings, heterogeneity, and poor reporting often limits comprehensive evidence synthesis using published aggregate data. Therefore, innovative research methodology with a deep understanding of ART specific challenges is required to produce high quality RCTs that could efficiently evaluate various add-ons of interest in controlled settings(J Wilkinson et al., 2019b).

Here we outline current methodological challenges that are limiting robust health technology assessment of IVF add-ons and propose solutions to inform future research.

1- Taxonomy consensus

To date several terminologies and definitions have been used to describe the additional treatments being used to optimise the reproductive outcome of couples undergoing ART treatments. The list is extensive (Appendix 1) and often used to suggest a positive perceived effect.

A key limitation across all these terminologies is the lack of a structured taxonomy that qualify a new intervention as an IVF add-on against clear criteria. That is, a taxonomy needs to include a clear definition of its purpose, breakdown of its classification criteria, and validation among key stakeholders. Establishing a clear taxonomy, anchored by the perceived mechanistic pathway of relevant interventions, is imperative to inform the clinical use of IVF add-ons, future research, and regulatory oversight (O'Cathain et al., 2019).

We propose a taxonomy process that provides categorical description of qualified IVF add-ons that depicts a clear and direct mechanistic effect during a single ART treatment cycle. In this process, a potential IVF add-on is described for its potential effect on the key elements of an ART cycle: ovarian stimulation and egg harvesting, gamete selection and fertilisation, embryo culture and selection, embryo transfer and implantation (Table 1).

In this taxonomy, interventions that are introduced before ovarian stimulation, or after embryo transfer, may not qualify as IVF add-ons, but rather adjunct therapies (e.g. natural killer cells testing in a previous cycle).

Similarly, interventions that do not demonstrate clear mechanistic evidence linked to one of the key ART treatment stages (Figure 1) and only rely on posited physiological and ad-hoc justification (e.g. acupuncture or bed rest post embryo transfer) may not qualify as an IVF add-on, though still require robust evaluation to warrant their use in clinical practice.

Several additional categories can also help to further refine the description and use of an IVF add-on. The cost implications to patients are key to describing add-ons in that, those

interventions that become industry standard and are offered at no additional cost to the patient could be considered part of routine practice. For example, most IVF units in the UK now offer time-lapse embryoscopes as part of routine practice, at no additional cost, even though there is no evidence of benefit with its use(ESHRE Working group on Time-lapse technology et al., 2020). Similarly, the use of ultrasound guidance during embryo transfer and soft embryo transfer catheters is standard practice at no additional cost to patient, and therefore, no longer qualify as an add-on, rather, an industry standard(Tyler et al., 2022). Interventions proposed for a specific subgroup of patients (e.g. women with history of recurrent pregnancy loss) could also be highlighted as conditional add-ons that should not apply to the wider IVF population in the absence of supportive mechanistic proof of benefit. Additionally, the risk and safety profile of each add-on could also feature in this taxonomy, whereby add-ons that could pose additional risks to the patient, gametes, or embryos, would be classed as high risk to aid patients making an informed decision (Table 1).

Consequently, a refined definition of IVF add-ons could be ‘’additional interventions that are introduced within an ART treatment cycle to improve chances of pregnancy with a posited mechanistic effect on one of the key elements of an ART cycle (ovarian stimulation and egg harvesting, gamete and embryo selection, fertilisation and embryo culture, embryo transfer and implantation) typically attracting additional costs to patient, and applied to specific population groups.

2- Choice of standard comparison and outcome of interest

Efficient evidence synthesis relies on comparing several treatments effects compared to a standardised treatment (or placebo) across a common outcome of interest using common study conditions (e.g. population characteristics)(Mathes et al., 2017).

A common challenge to meta-analysing data across randomised trials of IVF add-ons is the lack of an agreed standardised common comparator. This is particularly challenging when considering that ART treatments are not a single homogeneous intervention, but rather a series of interlinked interventions with key decision points designed to maximise the chances of conception for each couple. Similarly, the profile of couples seeking ART treatment is heterogenous. As such, it is impossible to standardise all aspects of an ART cycle (e.g. dose of ovarian stimulation, duration of stimulation, time of ovulation trigger) and a degree of pragmatism is needed to deliver on the ethical obligations towards research participants(Appleby, 2021).

Considering the current evidence-base and agreed practice guidelines, it is possible to drive consensus on the key aspects of routine care in ART treatment divided into four standardised elements: 1- Ovarian stimulation and egg collection: which includes downregulation of the female partner natural reproductive hormones (using any suitable agent), stimulation of the ovaries safely to harvest the maximum number of mature oocytes (using any suitable gonadotropin agent), triggering oocyte maturation and retrieval (using any suitable agent); 2-Gamete selection and fertilisation which include the use of any suitable method to select best quality gametes and fertilisation using either IVF or ICSI in the presence of male factor infertility; 3-Embryo culture and selection: which includes culturing embryos in a suitable media, grading and selection using a standardised scheme; 4-Embryo transfer and implantation: which includes the transfer of the best quality embryo using a soft catheter under ultrasound guidance, offering luteal phase support (using any suitable agent) until a pregnancy test confirming the outcome of the ART cycle (Figure 1).

Standardised reporting of key outcomes of interest is another important challenge to efficient evidence synthesis of IVF trials. While an established core outcome set exists(Duffy et al., 2020), its uptake in published trials remains limited(Li et al., 2025). To date, the majority of trials and their meta-analyses are underpowered to detect a true effect estimate for clinical pregnancy and live birth(Wilkinson et al., 2016). Only 2% of meta-analyses achieved 80% power to detect an improvement of 5 percentage points in live birth rate due to inadequate trial design(J Wilkinson et al., 2019b).

Furthermore, restricting the reporting in trials to the minimum established core outcome set can also limit the evaluation of perceived mechanistic effect for specific add-ons. For example, reporting on the number of mature oocytes would enable true evaluation of the efficacy for growth hormone when used as a stimulation add-on, and if proven non-efficacious, then further evaluation of its effectiveness to improve live birth is not warranted. This mechanistic gateway approach could help to significantly shorten the duration and cost of required trials to evaluate novel therapies to their posited mechanistic effect, before engaging in pragmatic large-scale trials that are powered to detect difference in live birth. Standardising reporting for key mechanistic outcomes of interest when evaluating IVF add-ons will also enable large scale prospective individual level patient data meta-analyses, offering additional power to detect interactions across key covariates such as age, BMI, and endometrial thickness at time of transfer(Seidler et al., 2019).

Therefore, clear justification for outcome selection is required at the start of a trial beyond simple reporting on the agreed minimum core outcome sets.

3- Consensus on utility and futility of add-ons:

Adoption of novel health technology into routine clinical practice is commonly anchored around an agreed utility criteria for their evaluated clinical and cost-effectiveness. For example, the National Institute of Clinical Excellence (NICE) commonly assess new technologies against clear criteria set around offering an improvement in one quality-adjusted-life-year (QALY) at a cost lower than £25,000-£35,000(Dakin et al., 2015).

Such criteria, however, remain absent when considering IVF add-ons with no clear consensus on an optimal utility/futility margin. This is particularly relevant when interpreting the results of meta-analyses reporting on statistical significance using risk or odds ratios of improvement over routine practice without considering the true clinical and cost implications of such add-ons. For example, a recent meta-analysis evaluated the use of hyaluronic acid (embryoglue) within embryo culture media and suggested an added benefit of 7 percentage points in chances of live birth compared to standard practice in IVF(Heymann et al., 2022). Considering the relatively low cost of embryo glue and the perceived added clinical value, it could offer high-cost utility. Conversely, more expensive interventions (e.g. pre-implantation genetic testing) may offer much lower cost-utility if offered to the wider population limiting their applicability in routine clinical practice.

Therefore, there is a need for regulators and key stakeholders to agree on a set utility/futility criterion anchored by incremental monetary benefit to facilitate the governance and adoption of new technologies into clinical practice.

Such tapered approach will enable judicious adoption of cost-effective IVF guidelines into clinical practice, with a clear guidance on target patient group, and estimated added value.

This is particularly relevant when counselling patients on the incremental benefit versus cost of each IVF add-on. To date, patient and lay representatives' input into IVF research remains limited, particularly from under-served communities where health inequality is more prevalent. Patients' acceptability, willingness and ability to pay for evaluated IVF add-ons should be incorporated into regulatory decision making for including or excluding certain add-ons into clinical practice.

4- Improved health technology assessment methodology

The conventional assessment of health technologies in assisted reproductive technology (ART) has predominantly relied on parallel design randomised controlled trials (RCTs) to facilitate direct comparisons between novel interventions and established standard techniques(J Wilkinson et al., 2019a). Although RCTs are widely regarded as the gold standard for generating high-quality evidence, they present several notable constraints. Specifically, such trials require substantial resources, over prolonged durations, attract significant financial costs including human capital, infrastructure, and also regulatory compliance(Wilkinson and Stocking, 2021). Some have suggested abandoning randomised trials in favour of relying on large observational studies(Macklon et al., 2019), this however, raises additional concerns on offering biased conclusions with no adequate standardised comparisons(J Wilkinson et al., 2019b). Given the fast pace at which new add-ons are introduced, there is a need to consider using alternative more efficient health technology assessment methodology.

Platform and basket trial designs have emerged as innovative options to enable rapid evaluation of new medical technologies. Unlike traditional parallel-group trials, platform trials (often called multi-arm multi-stage trial) employ a master protocol that allows for contemporaneous evaluation of multiple interventions against a shared control group across a shared homogeneous population (Figure 2), with an option to adapt allocation to interventions groups based on interim analyses(Woodcock and LaVange, 2017). By enabling real-time modifications based on interim outcomes, this design can enhance clinical relevance and statistical efficiency to evaluate several interventions, while maintaining rigorous causal inference.

Basket trials, on the other hand, assess the efficacy of a single intervention across multiple patient subgroups or conditions based on biomarkers or disease characteristics (e.g. predicted poor responders vs normo-responders)(Redman and Allegra, 2015). These designs enhance efficiency by reducing redundancy, optimising resource utilisation, and permitting faster decision-making regarding therapeutic efficacy. By incorporating adaptive elements, such as early stopping rules and dynamic patient allocation, platform and basket trials can shorten development timelines while maintaining robust evidence standards(Park et al., 2019). An example of adaptive trial design could be the evaluation of all available add-ons to improve the outcomes of women with diminished ovarian reserve undergoing ART treatment compared to standard treatment. Contrastly, basket trial design may enable evaluation of a common intervention like health supplements, applied to various subgroups with different causes of infertility undergoing ART treatments.

Most IVF add-ons are added as salvage treatments in addition to standard care, often using an additive process depending on the patient response. The use of Sequential, Multiple Assignment, Randomised Trials (SMARTs) incorporate multiple stages of randomisation, allowing investigators to evaluate dynamic treatment strategies, where therapeutic decisions

are adapted based on individual patient responses (Almirall et al., 2012; Nahum-Shani et al., 2012). Unlike traditional RCTs, which assess static treatment regimens, SMART trial design can enable precise evaluation of treatment protocols that factors in information gathered during the ART treatment cycle and maximise translation to clinical practice. However, their complexity demands careful planning, including predefined decision rules and robust statistical methods to account for repeated randomisations(Kidwell, 2014). For example, such trial design can be extremely helpful to evaluate different ovulation trigger agents factoring in patients' response during the ART treatment cycle to reduce the risk of ovarian hyperstimulation syndrome.

Hybrid (Pragmatic-Explanatory) trials are another emerging design that is focused on bridging the gap between mechanistic and applied clinical research. In this design, an intervention is evaluated to confirm its efficacy to improve key mechanistic outcomes (e.g. increase number of mature eggs), and if proven, the intervention is then evaluated for its effectiveness to improve key clinical outcomes (e.g. live birth). This design enables high internal validity, establishing controlled settings to examine posited mechanistic effects, whilst at the same shortening the time to assess the intervention effectiveness in hands-on, day-to-day clinical practice(Ford and Norrie, 2016). This is particularly relevant in the field of ART as novel interventions or repurposed ones, can be evaluated for their mechanistic impact first, before investing in more expensive full scale effectiveness trials.

Furthermore, such trial design can expedite intervention evaluation for key elements such as dose-finding, interaction assessments, and short term safety outcomes(Tunis et al., 2003) by incorporating randomisation and blinding alongside broader eligibility criteria and standardised outcomes assessment(Thorpe et al., 2009).

The move to digitalise clinical practice across fertility clinics also opens up an opportunity to move towards decentralised digital clinical trials. Adopting digital outcome reporting and clinical data curation can significantly speed up the process of randomised trials conduct while maintaining high internal validity. With many digital platforms entering clinical practice such as telemedicine, wearable devices, eConsent, and Virtual Wards Health technology, there is immense potential to improves participant recruitment and retention in trials while minimising physical site visits and expanding inclusivity through enhanced geographic and demographic participation(Vayena et al., 2023). This is particularly advantageous when evaluating specific subgroups in the field of reproductive medicine that are traditionally challenging to include in randomised trials such as recurrent pregnancy loss, poor responders, and others with rare medical conditions(Dorsey et al., 2020). The prospect of harvesting harmonised outcomes, using seamless digital platforms across multiple sites could significantly enable more efficient evidence synthesis using prospectively planned individual patient level data meta-analyses of trials conducted across different settings and countries.

However, several challenges still limit the conduct of such decentralised trials such as variation in available digital research infrastructure, regulatory heterogeneity across regions, and limited digital literacy among participants. As the demand for real-world evidence grows, decentralised trials are poised to become a cornerstone of modern clinical research, offering scalable and patient-friendly alternatives to traditional paradigms(Sinha et al., 2024).

Conclusion:

Adopting novel methodology could help to eliminate current inefficiencies in clinical trial conduct in reproductive medicine. The proposed framework could help to expedite and standardise the evaluation of IVF add-ons and inform their safe evidence-based adoption into clinical practice.

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