Stakeholders Summary Report

Introduction:

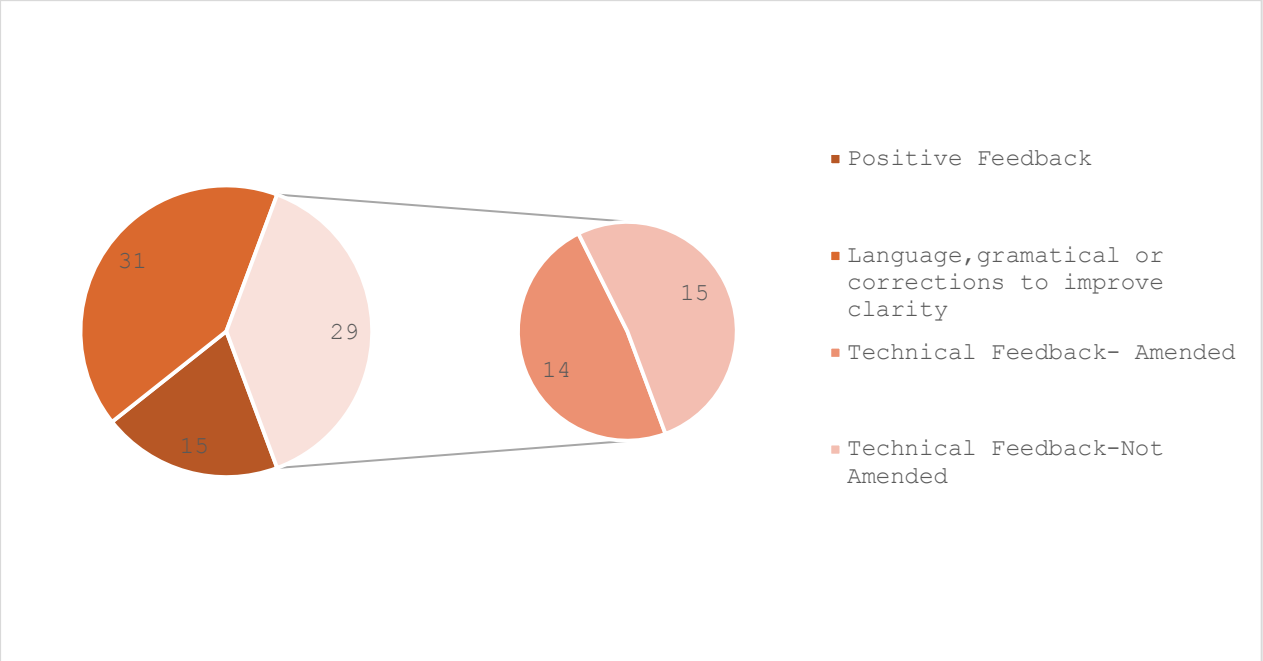
The Indian Fertility Society (IFS) guideline for poor ovarian response was opened for stakeholder review between 27 February 2024 and 7 May 2024. Over this period, the stakeholders were invited to review the document through social media campaigns and direct emails. The draft document was displayed on the IFS website. Comments, suggestions, and feedback were collected through the online portal and email.

Results:

A total of 28 reviewers across 10 countries provided feedback. Nine reviewers represented specific groups or were affiliated to national or international organizations. All comments provided were reviewed and discussed by the members of the Guideline Development Group (GDG). The summary of actions taken is as follows:

- 15 comments provided positive feedback and did not require further action.
- 31 comments were suggestions for grammatical changes or revisions to enhance clarity.
- 29 comments were considered technical feedback aimed at evidence summaries or recommendations provided. Of these, the GDG accepted suggestions from 14 questions and made suitable amendments. The GDG formulated responses for the remaining 15 questions, which are provided in the report below.

Summary of Feedback and Suggestions:



Reviewer	Organizations/Groups

Ameet Patki	President, Indian Society of Assisted Reproduction (ISAR)
Gedis Grudzinskas	Past Editor (Clinical), Reproductive BioMedicine Online
Gitanjali Bhasin	Non-governmental organization/Patient representative
Hrishikesh Pai	Immediate past president, Federation of Obstetric and Gynecological Societies of India (FOGSI); The International Federation of Gynecology and Obstetrics (FIGO) Representative
Jane Stewart	Deputy Director Education, International Federation of Fertility Societies; Past Chair, British Fertility Society
Linda Giudice	Immediate Past President, International Federation of Fertility Societies (IFFS), Past President, American Society for Reproductive Medicine (ASRM)
Nandita Palsheker	Past President, FOGSI
Raj Mathur	Past Chair, British Fertility Society
Ying Cheong	Coordinator SIG Reproductive Endocrinology, European Society of Human Reproduction and Embryology (ESHRE)

Reviewer	Country
Abha Maheshwari	Scotland
Alberto Vaiarelli	Italy
Baris Ata	Turkey
Carlos Calhaz-Jorge	Netherlands
Aanchal Garg	India
Animesh Agrawal	India
Bindu Bajaj	India
Shalini Raman	India
Monica Verma	India
Ethiraj Balaji Prasath	Singapore
Michael Grynberg	France
Jayant Mehta	UK
Neelam Potdar	United Kingdom
Ratna Chattopadhyay	India
Shalini Chawla Khanna	India
Siladitya Bhattacharya	UK
Soumya Ranjan Panda	India
Sujoy Dasgupta	India
Yoni Cohen	Israel

List of Comments

Sno	Reviewer	Chapter/Section	Page number	line number	Feedback/suggestions	GDG Response
1	Soumya Ranjan Panda	13.1. Does Intraovarian Platelet Rich Plasma (PRP) Improve Efficacy or Safety in Poor Responders?	100	29	From the discussion, it has been evident that there is lack of high quality studies involving Platelet Rich Plasma (PRP) in poor responders. There are two systematic reviews by Xualing Li et al., 2023 and Soumya R et al., 2020. Although both studies found an improvement of ovarian reserve parameters, both are limited by two major drawbacks i.e the included studies were of low quality and and the study end points were not live birth rate. In fact in current literature pool there is no high quality RCTs involving live birth rate as the study end point. In such a scenario, although advocating Platelet Rich Plasma (PRP) for poor responders is equivocal, it will be unfair to not recommend PRP in a situation where other therapies also do not work. Hence the recommendation (strong) that- "Intraovarian platelet rich plasma therapy is not recommended in poor responders" should be changed to "the recommendation for Intraovarian platelet rich plasma therapy is equivocal for poor responders". we should wait till more number of high quality studies come up, to give a strong recommendation "for" or "against" PRP for poor responders.	Intraovarian administration of PRP is currently an experimental therapeutic intervention. Existing literature primarily comprises a limited number of observational studies, constituting the principal basis of knowledge on this subject. The absence of data from RCTs impedes assessment of efficacy. Moreover, we still do not have a comprehensive understanding of efficacy, optimal preparation techniques, ideal dosage, and safety profile. Considering the available evidence, the routine implementation of such therapy cannot be deemed "equivocal," and is therefore, not recommended.
2	Soumya Ranjan Panda	1.3 Scope	9 to 10	1 to 36	the "strength of recommendation" and quality of recommendations are not defined.	The strength and quality of the recommendations have been clearly defined in the document.
3	GRYNBERG Michael	NA	NA	NA	Congratulation for these guidelines, very clear, with a good methodology. The manuscript looks overall perfect. No additionnal comment from my side.	Thank you.
4	Jayant Mehta	Generalized	NA	NA	Two questions that the group may want to consider and elaborate on are: a) What is the Quality of Oocytes in POR. It is a well known fact that stimulation regimes last longer and the concentration of drugs used is much higher in POR patients. My experience has demonstrated a poor Nuclear and Cytoplasmic synchronisation, leading to poor fertilsation, cleavage and	We wish to clarify that the clinical guidelines have been developed to address specific key questions with parameters, including population, intervention, comparator, and outcomes (PICO framework). While we acknowledge the importance of understanding the quality of oocytes in patients with POR and

					Blastulation rates. As a consequence, pregnancy rates, in FER cycles of POR patients, are significantly lower in the same aged group of non-POR patients.. b) Are there any benefits of IVM in POR. Evidence exists that a larger cohort of follicles 12-14 mm are observed, all of them don't progress to develop to mature Oocytes.	the potential benefits of IVM, these aspects do not fit within the defined framework of our guideline. The guideline addresses the role of IVM in poor responders through the key question: "Does In-Vitro Oocyte Maturation Improve Efficacy or Safety in Poor Responders?" This question focuses on evaluating the efficacy and safety of IVM specifically in the context of POR. We aim to provide evidence-based recommendations to guide clinical practice and improve patient outcomes in this specific population.
5	Jayant Mehta	1.1 Legal disclaimer	5	16, 17	Remove "These guidelines should not be construed as professional advice. They do not represent the advice of all clinicians associated with IFS. The information contained herein is subject to change without notice."	The language used maintains the clarity and legal integrity with respect to the guideline.
6	Raj Mathur	5.2. Is mild ovarian stimulation protocol superior to conventional protocols (GnRH-antagonist or long GnRH agonist protocol) in patients with poor ovarian response?	46	7	The ISMAAR definition of mild stimulaiton is recognized to be vague. It would be better to give clinicians a better understanding by using the ESHRE guideline pramatic definition, which is the use of no more than 150 iu FSH daily dose	We have included the ESHRE definition of the gonadotropin dose up to 150 IU/day. Additionally, the GDG has included the ISMAAR definition to address the role of oral ovulation stimulation agents. Studies using more than 150 IU/day were excluded.
7	Raj Mathur	5.4. Is DUOSTIM superior to Antagonist/Mild stimulation or Two Conventional (BISTIM) in patients with poor ovarian response?	53	4	Dusotim provides more oocytes than ONE cycle of conventional stimulation. This is not clear from the opening sentence of the rationale.	The text will be revised accordingly to enhance clarity.
8	Raj Mathur	4.3. Is There a Value of Genetic Polymorphism Testing in Predicting Poor Ovarian Response?	31	10	An important part of the rationale for not doing genetic polymorphism testing is that there is no evidence-based intervention that can be carried out based on the results of testing. This should be mentioned.	The rationale has been modified as per this feedback
9	Raj Mathur	4.5. Does Estradiol Pre-Treatment (Priming) Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?	33	24	It should say 'embryo transfer' instead of 'oocyte transfer'	Accepted and amended accordingly.
10	Raj Mathur	5.2. Is mild ovarian stimulation protocol superior to conventional protocols (GnRH-	47	13, 17	I feel a 'Strong' recommendation is not warranted. perhaps 'Conditional' is more reasonable. importantly, in the rationale, it should be discussed that there may be, within the poor	Based on the evidence available, we have equally recommended both protocols for women with poor response. The justification

		antagonist or long GnRH agonist protocol) in patients with poor ovarian response?			responder group, some women with a better prognosis and these may have a better cumulative live birth rate with conventional stimulation. I quote from the Montoya-Boetro meta-analysis, which says 'our research cannot exclude a potentially beneficial effect of COS over MOS in women with a better prognosis. Patients of intermediate prognosis (Polyzos and Sunkara, 2015; Alviggi et al., 2016) may experience better outcomes since previous reports have shown that not only age but also the number of oocytes plays a crucial role in CLBRs in this group (Li et al., 2019). Thus, it would be of great interest to evaluate whether COS could improve reproductive outcomes (especially CLBR) in better prognosis women (i.e. the general population), mainly if we take into account evidence supporting that the number of oocytes retrieved is associated with the number of euploid embryos (La Marca et al. 2017) and CLBRs (Sunkara et al. 2011; Drakopoulos et al. 2016; Devesa et al. 2018; Polyzos et al. 2018b)'	for the same has been provided in the "Rationale for recommendation" section. Future research must be directed to identify the subgroup of poor responders who may benefit from conventional stimulation over mild stimulation.
11	Raj Mathur	5.6.Is Progesterone Primed Ovarian Stimulation (PPOS) protocol superior to GnRH antagonist protocol in patients with poor ovarian response?	58	6,7	Surely, the important thing is that PPOS mandates a freeze-all approach. This should be stated, at presently it is only implied by saying it requires more resources for freezing.	The text has been amended. The statement "Additionally, the procedure requires additional resources for freezing and frozen embryo transfer." has been revised to "The protocol mandates embryo freezing which requires additional resources and frozen embryo transfer."
12	Raj Mathur	7.2.Is the addition of Testosterone as an Adjuvant superior to no Adjuvant inPoor Responders?	76	12	The T-Transport study (transdermal testosterone) should be referenced here. However, I am aware it is only so far published as a Conference abstract	The results of the study have not been published. The GDG considered T-transport study; however, in the absence of related publications, it was excluded.
13	Raj Mathur	1.2 POR Guideline Development Group	7	6	I would like to extend my congratulations, and thanks to the Guideline Development Group. This is an excellent document and I am sure it will be very helpful for clinical practice internationally	Thank you.
14	Shalini Raman	1.2 POR Guideline Development Group	5	1	Good initiative	Thank you.
15	Ratna Chattopadhyay				Thanks for your kind consideration, it is an outstanding guidelines as per my knowledge and experience, it reflects all of your precise and dedicated analysis.	Thank you.

16	Nandita Palshetkar				The guidelines on poor ovarian reserve by the Indian Fertility Society are an invaluable resource for clinicians and patients alike. The comprehensive approach to addressing this complex issue demonstrates a deep understanding of the challenges faced by individuals dealing with poor ovarian reserve. Dr. K D Nayyar's leadership in spearheading these guidelines is commendable. His expertise and dedication to advancing fertility care have undoubtedly enriched the field and provided much-needed guidance to practitioners. His commitment to excellence sets a high standard for others to follow. The guidelines offer practical recommendations backed by current research, ensuring evidence-based care for patients. The emphasis on personalized treatment approaches underscores the importance of tailoring interventions to individual needs, promoting better outcomes and patient satisfaction.	Thank you.
17	Monica Verma				Heartiest congratulations for compiling these guidelines, a great piece of evidence based clear comprehensive recommendations. It was indeed a pleasure going through it and looking forward to more of such great academics.	Thank you.
18	Monica Verma	1.1 Legal Disclaimer	5	4	The current clinical practice guideline on POR HAS (instead of have). Congratulations to the IFS-GDG for a very comprehensive, precise, evidence based well compiled guideline.	Thank you.
19	Monica Verma	3. Tabular Summary of Recommendations	15	4.1	Any evidence for cut off values for AMH and AFC. Any evidence for FSH/ E2 values for predicting poor ovarian response in patients above 40 years.	The cut-offs for AMH and AFC levels have been described in the POISEDON criteria.
20	Monica Verma	6.1 What is the safety and efficacy of recombinant FSH versus urinary gonadotropin in Patients with Poor Ovarion Response?	19	6.1	Should urinary gonadotropins be specified as highly purified?	This comment is accepted, “urinary gonadotropin” has been revised to “highly-purified” at one instance.
21	Monica Verma	1.3 Scope	9	11	Can something be added regarding unexpected poor ovarian response?	The scope was defined prior to analysis and therefore cannot be changed.
22	Animesh Agrawal	12.2. Does Routine Intracytoplasmic Sperm Injection (ICSI) Improve Efficacy or Safety in Poor	92	8	More evidence is needed to support the ICSI efficacy in poor responders.	The recommendation is in line with the feedback provided.

		Responders?				
23	Shalini Chawla Khanna	2.2 What is poor ovarion response?	14	4 to 15	The POSEIDON classification can be represented in a table format instead of describing it the word format to give a clear idea about the classification.	The POISEDON criteria were defined according to the table.
24	Ethiraj Balaji Prasath	12.2. Does Routine Intracytoplasmic Sperm Injection (ICSI) Improve Efficacy or Safety in Poor Responders?	92	25 to 28	Although lack of evidence is in favor of not recommending ICSI for efficacy of poor responders, it may enhance chances of Fertilization and having an embryo transfer. An advisory in favor of ICSI for poor responders may be given.	Considering the available evidence, the GDG cannot recommend the use of ICSI over IVF in all patients with POR.
25	Ethiraj Balaji Prasath	5.4.Is DUOSTIM superior to Antagonist/Mild stimulation or Two Conventional (BISTIM) in patients with poor ovarian response?	54	3 to 9	DUOSTIM may be advised to increase number of oocytes collected and thereby increase number of embryos available.	The "Rationale for recommendation" for freezing has been modified to indicate that- "*Duostim yields additional retrieved oocytes and more viable embryos for transfer besides reducing the dropouts compared to conventional stimulation protocol. However, it does not improve the OPR or LBR when compared to conventional stimulation. Data on cost-effectiveness for increased cost of gonadotropins in the same cycle and freezing and thawing of embryos is unavailable. Further data on safety and long-term outcome of neonates has not been reported*."
26	Sujoy Dasgupta	2.2 What is poor ovarion response?	14	4 to 15	Group 1 and group 2 are "unexpected" poor responders because prestimulation ovarian reserve parameters are normal. In contrast, group 3 and 4 are "expected poor responders" because prestimulation ovarian reserve parameters are normal	The text has been amended to improve clarity.
27	Aanchal Garg	11.1. Is Elective Freeze All Embryo Transfer Beneficial for Efficacy in Poor Responders?	88	3	Can we include the proposed Day of Embryo Transfer also in the Questions in subheading of embryo transfer ? As poor responders continue to present a challenge, with less treatment choices available, shortening the length of embryo culture has been shown to be beneficial . Transferring embryos at an early cleavage stage (day 2) may provide a protective advantage by reducing the effect of environmental stress during extended culture .Also we may not have sufficient embryos to transfer with extended culture. Thus, Day 2 transfer (instead of Day 3 or 5) has been suggested by some studies as a method to improve pregnancy rates in Poor responders.	The key question addressed the comparison between the freeze-all versus fresh-all approaches in poor responders.
28	Aanchal	3. Tabular Summary of	2	15	Can we include a question on ' Should an endometrioma be	The questions were pre-defined according

	Garg	Recommendations			surgically managed before IVF in poor reserve patients' under the heading of Evidence based recommendations on Prestimulation management as we know that the ovarian reserve and response is decreased in women with endometriomas, as compared to same aged healthy women.	to the methodology of guideline development.
29	Gitanjali Bhasin	4.9.Does Alternative Medicine-Based Therapy Improve Efficacy and Patient Related Outcomes in Patients with Poor Response?	31	1	Alternate healing options like Acupuncture can improve chances of success rate and be a motivational factor especially for women undergoing psychological stress. Overall, this is a guideline which has been well researched. It is taking care of all aspects of women showing poor response. It looks into all fields of care for a couple undergoing IVF treatment and a much needed guideline.	Thank you.
30	Jane Stewart	2.3.What is the burden of Poor Ovarian Response in Assisted Reproductive Technology Procedures like IVF/ICSI?	14	16 to 18	Also important for managing patient expectations	Accepted and amended accordingly.
31	Jane Stewart	6.1.What is the safety and efficacy of recombinant FSH versus urinary gonadotropins in Patients with Poor Ovarian Response?	59	5	You haven't mentioned biosimilars - should they be included?	We did not find studies of poor responders that compared biosimilars with recombinant FSH or urinary gonadotropins.
32	Jane Stewart	13.3. Does In-Vitro Activation of Ovarian Tissue Improve Safety and Efficacy in Poor Responders?	101	21	Ovarian tissue autotransplant is effective when tissue taken in ovaries with normal reserve and increasingly practiced for fertility preservation pending significant ovarian damage eg chemotherapy. Tissue has been stored for some DOR patients but outcomes likely to be poor as described here. It is perhaps worth clarifying the distinction.	The scope of the key question covers intervention of invitro activation and not autotransplantation
33	Jane Stewart	2.3.What is the burden of Poor Ovarian Response in Assisted Reproductive Technology Procedures like IVF/ICSI?	14	24	26% of cycles OR of cancelled cycles?	The statement indicates POR to be an issue in 26% of all cycles.
34	Jane Stewart	5.4.Is DUOSTIM superior to Antagonist/Mild stimulation or Two Conventional (BISTIM) in patients with poor ovarian response?	51	10	"With successful.....dual stimulation" is not a proper sentence - needs clarifying	Accepted and amended accordingly.
35	Bindu Bajaj	5.6.Is Progesterone Primed Ovarian Stimulation (PPOS) protocol superior to GnRH	57	39	the evidence summary says in favour however, recommendation is against	Thank you for this comment. The GDG discussed this question at length. The PPOS protocol is not favored over GnRH antagonist protocol despite promising cycle

		antagonist protocol in patients with poor ovarian response?			control, but the quality of evidence was very low. Moreover, there is no additional advantage in terms of oocyte number, viable embryos, or LBR and involves mandatory cryofreezing. This adds to the cost, time to pregnancy, and required technical support.
36	Alberto Vaiarelli	5.4.Is DUOSTIM superior to Antagonist/Mild stimulation or Two Conventional (BISTIM) in patients with poor ovarian response?	51	I think the recommendations regarding the use of DuoStim are not in line with recent publications. In fact, in patients defined as poor prognosis due to advanced maternal age and reduced ovarian reserve, this type of approach has the primary benefit of reducing drop-out and shortening the time to obtaining a healthy embryo compared with conventional strategies. In addition, the protocol that is used must be correct otherwise we do not have the benefits. DuoStim reduces time to pregnancy, minimizes treatment discontinuation, and is potentially cost-effective. 1) Garcia-Velasco JA, Cimadomo D, Cerrillo M, Vaiarelli A, Ubaldi FM. Hum Reprod. 2023 Aug 1;38(8):1643-1644. 2)Low-quality evidence from a randomized controlled trial due to an inappropriate IVF setting to challenge Dual Stimulation strategy. Ubaldi FM, Vaiarelli A, Cimadomo D, Cerrillo M, Rienzi L, Garcia-Velasco JA. Hum Reprod. 2023 Aug 1;38(8):1645-1647. doi: 10.1093/humrep/dead108. First,, the authors of Bistim study Published by MASSIN are not only comparing two ovarian stimulation strategies but also two completely different settings such as fresh oocyte insemination versus oocyte accumulation via vitrification and fresh versus vitrified-warmed first embryo transfer strategy. Moreover, the study, limited in its sample size, is multicentric and the oocyte vitrification performance (cryo-survival rate: 81.6%) is below the benchmark value at reference centers. This is already a matter of concern; if the oocyte vitrification protocol per se is underper- formed, it becomes subject to poorer outcomes after warming. Indeed, differences were reported by Massin et al. (2023) only in the dual stimulation arm between the two paired cohorts of oocytes, the first cohort being vitrified warmed (e.g. fertilization rate: 66.1%) and the second cohort being fresh (e.g. fertilization rate: 79.7%). Even more	Thank you for sharing your insights and referencing recent publications regarding the use of DuoStim in patients with poor prognosis. It is essential to consider the evidence landscape when evaluating the suitability and efficacy of DuoStim. The points raised by the GDG, following the review of RCTs comparing DuoStim with conventional antagonist protocols, underscore the need for robust evidence to support clinical decisions. Despite limitations in some studies, RCTs remain valuable in informing practice guidelines. The RCTs indicated similar clinical outcomes on number of embryos retrieved and the number of euploid embryos. Studies that did indicate benefits were not RCTs by design and had a risk of bias. Furthermore, the GDG's assessment of the available evidence suggested a lack of convincing data establishing DuoStim as superior to conventional protocols in terms of clinical pregnancy or live birth outcomes. The observed heterogeneity in practice across studies, specific expertise required, and limited data on long-term safety and neonatal outcomes following DuoStim further emphasize the need for cautious interpretation and ongoing research in this area. DuoStim protocols also necessitate use of additional resources and cost for freezing.

concerning, the implantation, cumulative positive heartbeat and live birth rates were all lower after dual stimulation (see Supplementary Figure S2 in Massin et al. (2023)), most probably because oocyte vitrification was performed exclusively in this study arm. Nevertheless, this impact was not statistically significant perhaps due to a limited sample size and the absence of data on the blastulation rates.

Second, Massin et al. conducted their sample size calculation by setting 1.5 § 2 additional oocytes in the dual stimulation arm versus the control as the difference to be captured with enough statistical power. This is irrespective of the literature on this topic; in fact, most of the studies published to date reported 0.5- to 1-oocyte larger cohorts with dual stimulation (Glujovsky et al., 2020). Furthermore, our concern here is that the main advantage of dual stimulation is a higher cumulative live birth rate due to lower treatment discontinuation, rather than a slightly higher overall number of oocytes collected. Perhaps, setting those out- comes as the main endpoints would have been more reasonable, especially in the context of poor prognosis and poor responders. In fact, in this population, those outcomes might be assessed in a relatively short timeframe.

Third, the patients recruited by Massin et al. are mostly young while dual stimulation expresses its true potential in women who are, mostly, older than 40 years (i.e. subject to significantly lower blastulation rates and significantly higher aneuploidy rates at the blastocyst stage). The unexpectedly good response reported here by many patients is indeed proof of a faulty definition of 'poor prognosis'. Moreover, excluding good responders from the study only for the assessment of secondary outcomes further biases the comparison in our view, by interfering with the true overall conclusions of the study, especially since the rate of women excluded was substantial and uneven among the two randomized arms (61.4% in the control versus 34.1% in the dual stimulation arm, respectively; P 1⁄4 0.0184).

Fourth, the dual stimulation protocol used by Massin et al. is very different from previous studies in terms of the type of gona-dotropins (HMG rather than rec-FSH), trigger of

final oocyte mat-uration (hCG rather than GnRH agonist), days between the first and second stimulations (1 rather than 5), and strategies to avoid LH surge in the second stimulation (vaginal progesterone rather than GnRH antagonist). In particular, hCG instead of GnRH agonist trigger may affect the anovulatory wave due to diverse half- life and intracellular signals. GnRH agonist trigger can in fact elicit a flare-up effect and down-regulate AMH expression in the follicles recruited in the anovulatory wave. Moreover, natural progesterone (instead of GnRH antagonist) as used by Massin et al. only in the second stimulation of the dual stimulation proto- col, along with bypassing the 5-day post-hCG trigger washout period (critical to attain luteolysis), are further relevant deviations from the ideal workflow. Both these deviations may have affected per se both the monitoring and the management of this unconventional stimulation protocol, especially for clinicians inexperienced with this administration.
In addition, another RCT was published in March 2023 (Cerrillo et al., 2023) in a more appropriate patient population and with a more appropriate dual stimulation protocol. Cerrillo et al. showed similar efficacy with two conventional stimulations ver- sus dual stimulation but shorter time to euploid blastocyst with the latter strategy.
In conclusion, although Massin et al. is a registered RCT, we think that it failed to provide first class evidence to assess the suitability of dual stimulation. Dual stimulation is an unconventional stimulation strategy aimed at minimizing the risk of treatment discontinuation in very poor prognosis patients that truly benefit from a second stimulation being conducted in the shortest possible timeframe. To be fairly evaluated, this unconventional stimulation strategy should be framed in a suitable scenario. Young women undergoing IVF in a setting subject to treatment reimbursement policies and who arbitrarily vitrified oocytes for the sole purpose of proving unnecessary a strategy not applying to them in the first place certainly are not the proper population to challenge dual stimulation effectiveness. Dual stimulation certainly does not apply to an ART regulatory context where embryo vitrification is not allowed, and multiple cycles of IVF are reimbursed. Moreover, dual stimulation requires

					large expertise with vitrification protocols and with the management of a second stimulation in the same ovarian cycles to be legitimately questioned. The results presented in Massin et al. are therefore not surprising and largely misleading. We can at least agree with the authors on one statement, though, 'Duostim appears to be safe for women, and the quality of embryos obtained with Duostim seems unimpaired'. Perhaps this represents the bottom line and the main take-home message of their RCT. please take in consideration this reference in order to summurize the benefit of duostim protocol in correct patients population defined poor prognosis patients (AMA and POR) Second stimulation in the same ovarian cycle: an option to fully-personalize the treatment in poor prognosis patients undergoing PGT-A. Vaiarelli A, Cimadomo D, Gennarelli G, Guido M, Alviggi C, Conforti A, Livi C, Revelli A, Colamaria S, Argento C, Giuliani M, De Angelis C, Matteo M, Canosa S, D'Alfonso A, Cimadomo V, Rienzi L, Ubaldi FM. J Assist Reprod Genet. 2022 Mar;39(3):663-673. doi: 10.1007/s10815-022-02409-z. Epub 2022 Feb 7.	
37	Linda Giudice				I have read through the document – it is quite comprehensive and providing practitioners with strength of the evidence for all the different key outcomes is highly valuable. I have no further substantive comments. Congratulations and ty for the opportunity to review this guideline for an increasingly prevalent clinical condition.	Thank you
38	Yoni Cohen	No Suggestion	1	1	Dear Dr. Nayar and members of the Indian Fertility Society, I would like to express my gratitude for the opportunity to review these important practice guidelines. The draft was kindly provided to me by prof. Igal Wolman. As a Reproductive Endocrinology and Infertility specialist, I completed my fellowship at the McGill Reproductive Center in Montreal, Canada. Currently, I am affiliated with	Thank you

					the Tel Aviv Sourasky Medical Center, home to one of the largest fertility clinics in Israel. Additionally, I serve as a senior lecturer at the Faculty of Medicine, Tel Aviv University.	
39	Yoni Cohen	2.2 What is poor ovarian response?	13	11	I believe it's crucial to elaborate on the distinctions between POR (Poor Ovarian Reserve Response), DOR (Diminished Ovarian Reserve), and POI (Primary Ovarian Insufficiency). These terms represent distinct etiological entities in certain cases and clarifying their differences would enhance understanding	Accepted and amended
40	Yoni Cohen	2.2 What is poor ovarian response?	13	22	Regarding the Bologna criteria, it's noted that the first feature includes, aside from age, 'any other risk factor for POR.	Accepted and amended
41	Yoni Cohen	2.2 What is poor ovarian response?	13	23	The second feature of the Bologna criteria should be corrected to specify the retrieval of 3 or fewer oocytes (or <4 oocytes). Additionally, it's important to add that ovarian stimulation should involve at least 150 IU of FSH per day. Furthermore, I think that it's essential to specify that the Bologna criteria were developed based on the consideration of ovarian reserve markers such as AMH or AFC as a post hoc test after a trial of ovarian stimulation.	Accepted and amended
42	Yoni Cohen	4.1 Is There a Value of Hormone Testing at Baseline in Predicting Poor Ovarian Response?	27	06 to 08	AMH correlates with the response to stimulation. However, it's important to exercise caution in specifying its predictive value for pregnancy outcomes, because it was not proven.	Accepted and amended
43	Yoni Cohen	4.1 Is There a Value of Hormone Testing at Baseline in Predicting Poor Ovarian Response?	27	21	The effect of hormonal contraception on AMH levels was evaluated in a recent study by Nelson et al. (2023). I recommend adding this important data to the guidelines. (Nelson SM, Ewing BJ, Gromski PS, Briggs SF. Contraceptive-specific antimüllerian hormone values in reproductive-age women: a population study of 42,684 women. Fertil Steril. 2023 Jun;119(6):1069-1077. doi: 10.1016/j.fertnstert.2023.02.019. Epub 2023 Feb 18. PMID: 36801456.)	The stated study did not address the specific population and outcomes of interest.
44	Yoni Cohen	4.4 Is There a Value of Immunological Testing at Baseline in Predicting Poor Ovarian Response?	32	4 to 6	Anti ovarian antibodies testing was suggested for POI and not for POR	We agree with the reviewer that anti-ovarian antibodies may play a role in the development of premature ovarian insufficiency. However, poor ovarian response represents a mild form of the same spectrum of disease and may eventually lead to POI in some patients.

						Hence some researchers have proposed a similar causative hypothesis for POR and hence we attempted to identify any published literature on a possible association between anti-ovarian antibodies and POR.
45	Yoni Cohen	4.5 Does Estradiol Pre-Treatment (Priming) Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?	33	19 to 24	Many women with POR are undergoing oocyte cryopreservation. I suggest adding data on the differences in the number of oocytes collected, as this would be valuable information for clinicians. This addition could also be relevant in other sections of the guidelines, such as page 35, lines #34-40	Added the data: "The number of mature oocytes retrieved per cycle (1.133, 95% CI 0.099–2.167) and number of zygotes per cycle (0.804, 95% CI 0.037–1.571) were not significantly improved in patients treated with an LE protocol"
46	Yoni Cohen	4.5 Does Estradiol Pre-Treatment (Priming) Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?	33	24	oocyte transfer should be corrected to embryo transfer	Accepted and amended accordingly.
47	Yoni Cohen	4.6 Does OCP Pre-Treatment Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?	36	6	In the evidence summary of this section, it's mentioned that according to the Cochrane review, there was no difference in the gonadotropin dose (as noted on page 35, line #30). However, in the rationale for recommendations, it is stated that OCP may lead to an increased total gonadotropin dose. I recommend either providing a reference for this statement or correcting the sentence for consistency.	Thank you for your comment. The reference study has now been cited in the guideline document.
48	Yoni Cohen	5.1 Is GnRH-antagonist protocol superior to GnRH-agonist protocols in patients with poor ovarian response?	44	3	The sentence 'There was a significant difference between...' lacks clarity. It's unclear what the significant difference refers to. Further clarification is needed to improve understanding.	The statement "The study found that the number of oocytes retrieved was significantly higher with long GnRH agonist compared with the short agonist regimen (4.42 ± 3.06 vs. 2.71 ± 1.60), while there was no significant difference between long agonist and antagonist regimens (4.42 ± 3.06 vs. 3.30 ± 2.91). " referred to oocytes retrieved across the three protocols.
49	Yoni Cohen	5.1 Is GnRH-antagonist protocol superior to GnRH-agonist protocols in patients with poor ovarian response?	44	6	I suggest adding the RCT by Merviel et al. (2015) to the references of this section. In this study, they compared the short agonist to GnRH antagonist protocol, providing relevant insights. (Merviel P. Comparative prospective study of 2 ovarian stimulation protocols in poor responders: effect on implantation rate and ongoing pregnancy. Reprod Health. 2015 May 30;12:52. doi: 10.1186/s12978-015-0039-2. PMID: 26025412; PMCID:	Since the meta-analysis by Papamentzelopoulou et al. discussed in this section already included the study by Merviel et al. (2015), the latter was not mentioned separately.

					PMC4460718).	
50	Yoni Cohen	9.1 Should IVF/ICSI cycles be converted to IUI or cancelled if there is Poor Response to Ovarian Stimulation?	83	29	It appears that the recommendations contradict each other, particularly the second one discussing conversion to IUI. This recommendation doesn't seem to be supported by the studies discussed earlier. Clarification or adjustment may be needed for consistency.	Accepted and amended accordingly.
51	Yoni Cohen	13.3 Does In-Vitro Activation of Ovarian Tissue Improve Safety and Efficacy in Poor Responders?	101	1	In vitro ovarian tissue activation was suggested for POI but not for POR. This highlights a clear distinction in treatment approaches for these conditions	The scope of the guideline is limited to patients with POR. Therefore, analysis of evidence was restricted to studies of patients with POR.
52	Yoni Cohen	3. Tabular Summary of Recommendations	17	1	1. Higher gonadotropin doses above 300 IU (e.g., 450 and 600 IU) were analyzed by a Cochrane meta-analysis in 2017, which did not find a higher number of oocytes retrieved or an improved ongoing pregnancy rate. Therefore, I recommend adding a recommendation such as: 'A gonadotropin dose higher than 300 IU is not recommended in POR' to the guidelines 2. In a randomized controlled trial, the modified natural cycle was compared with a microdose GnRH agonist flare protocol (Morgia 2004), with no observed difference. Therefore, I recommend adding a recommendation such as: 'Modified natural cycle is not recommended over the conventional protocol' to the guidelines 3. I suggest categorizing In Vitro Maturation, Platelet Rich Plasma Infusion, Stem Cell Therapy, and In Vitro Ovarian Tissue Activation under the subcategory of 'experimental treatments' within the guidelines. These interventions may require further research and validation before being considered for routine clinical use	Subsections addressing comments 1 and 2 have been included in the document.
53	Siladitya Bhattacharya				Thank you very much for the invitation to review this IFS guideline. Unfortunately, I am not able to take this on due to other competing deadlines. I wish you every success in publishing and implementing the guideline.	Thank you.
54	Carlos Calhaz-Jorge	5.4 Is DUOSTIM superior to Antagonist/Mild stimulation or Two Conventional (BISTIM) in patients with poor ovarian response?			1 - some conditional recommendations use the word "probably", which makes sense to me. However, many other conditional recommendations are totally affirmative. Is it intended? Maybe you can consider my remark. 2 - Recommendation 5.4 (DUOSTIM) compares duostim vs GnRH antagonist. In the Duostim protocols antagonist	Accepted and amended accordingly.

					is also used. So, maybe it is better to say "Duostim protocol is not recommended over GnRH antagonist conventional protocol..." Just a suggestion, of course.	
55	Neelam Potdar	4.1 Is There a Value of Hormone Testing at Baseline in Predicting Poor Ovarian Response?	27	21	AMH can be tested any 'time' during the cycle 'change the word period'	Accepted and amended accordingly.
56	Neelam Potdar	4.5. Does Estradiol Pre-Treatment (Priming) Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?	33	24	Do you mean 'embryo transfer' instead of 'oocyte transfer'	Accepted and amended accordingly.
57	Neelam Potdar	7.3 Is the addition of DHEA as an Adjuvant superior to no Adjuvant in Poor Responders?	76	25	Consider being clear in the recommendation 'DHEA as an adjuvant in ovarian stimulation is not recommended in poor responders as there is lack of evidence for improvement in pregnancy and live birth rates'	Justifications are provided in the "Rationale for recommendation" section.
58	Neelam Potdar	7.5 Is the addition of Glucocorticoids as an Adjuvant superior to no Adjuvant in Poor Responders?	80	26	Consider re-phrasing recommendation – There is no evidence for the use of glucocorticoids as an adjuvant in poor responders and therefore these should not be used.	Accepted and amended accordingly.
59	Neelam Potdar	9.1 Should IVF/ICSI cycles be converted to IUI or cancelled if there is Poor Response to Ovarian Stimulation?	83	29	Recommendation 2: It is difficult to expect a woman who has undergone IVF to have established tubal patency. It maybe that Semen parameters are slightly low; in these cases a pragmatic approach is required and IUI seems reasonable without increasing risk of harm. In my opinion recommendation 2 of GPP is not needed. First recommendation is sufficient.	Accepted and amended accordingly.
60	Neelam Potdar		7	2	Many thanks for inviting me to review the guideline. It is an excellent comprehensive guideline and will be extremely useful to standardise clinical practice.	Thank you.
61	Ying Cheong				I have gone through this and is by and large in line with the ESHRE guidelines and other international guidance. So well done. I do not have further specific comments.	Thank you.
62	Baris Ata	2.2.What is poor ovarian response?	13	7 to 8	"..lower live birth rate per stimulation than age matched normal responders." No evidence suggest that these women have worse quality oocytes, so the distinction shoudl be made that they have lower live birth rate per stimulation cycle.	Accepted and amended accordingly.
63	Baris Ata	4.1. Is There a Value of Hormone Testing at Baseline in Predicting Poor	25		Evidence summary; what were the definitions for POR in the original studies are not mentioned	

		Ovarian Response?				
64	Baris Ata	4.2. Is there a value of Ultrasound Imaging at Baseline in Predicting Poor Ovarian Response?	28	32 to 35	How is the study by Sanverdi et al. Relevant. It seems as a matter of synchrony at the start of stimulation which may have affected the decision to trigger regardless of follicle count.	For the same AFC, the variance affects ovarian response. An AFC of 12 with huge variance depicts asynchronous follicles, which would affect oocyte yield. As there is no further evidence on this parameter, we could not include this aspect in the recommendations.
65	Baris Ata	4.5. Does Estradiol Pre-Treatment (Priming) Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?	35		Why is the recommendaton against estradiol priming "conditional" while RCTs fail to show a benefit?	Accepted and amended accordingly.
66	Baris Ata	5.2.Is mild ovarian stimulation protocol superior to conventional protocols (GnRH-antagonist or long GnRH agonist protocol) in patients with poor ovarian response?	47		The definition of mild stimulation is missing. The term has evolved over the years from being defined by the number of oocytes aimed to collect (which is not relevant for poor responders) to one defined by a maximal gonadotropin dosage, which is already considered a high dose in Europe, UK and Australia. The whole section hangs in the air without the description of mild stimulation.	The GDG members have adopted the ISMAAR definition of mild stimulation. A detailed definition has now been included for clarity.
67	Baris Ata	5.3.Is GnRH-agonist flare protocol superior to long GnRH-agonist protocols in patients with poor ovarian response?		34 to 35	A convincing reference is required to claim that progesterone exposure impairs follicle recruitment. It does not seem to be the case in the luteal phase or PPOS or I fail to see a rationale.	Accepted and amended accordingly.
68	Baris Ata	5.4.Is DUOSTIM superior to Antagonist/Mild stimulation or Two Conventional (BISTIM) in patients with poor ovarian response?	53,54		Would you consider expanding recommendations about Duostim? Perhaps making it clear that you would not recommend an otherwise possible fresh ET for the sole purpose of DUOSTIM may help. Otherwise, why you advise against duostim in comparison to consecutive stimulation. In women with POR each and every follicle counts and you cannot predict when you will be able to gather a larger cohort to stimulate, i.e., in the follicular phase or the luteal phase. Indeed, available data hints that luteal phase may be better in terms of oocyte yield, perhaps due to better synchronization or else. In the absence of an intent for a fresh ET luteal phase stimulation should not be ruled out. I would like to take the opportunity to make a point about the neitre guideline, in the same line of thought, it reads	There is limited evidence available to further expand on the indications for DuoStim.

					as if the sole purpose is to stimulate, collect and transfer in the same cycle. Which may not apply to women undergoing oocyte cryopreservation or embryo cryopreservation for medical or non-medical indications. It may be appropriate to highlight this fact or modifying some of the recommendations for different scenarios.	
69	Baris Ata	5.5.Is Luteal Phase Stimulation superior to Follicular Phase Stimulation in patients with poor ovarian response?	56	10 to 13	The sentence here kind of contradicts the former recommendation about duostim. As mentioned above, it is understandable that luteal stimulation may enhance oocyte yield, but where is the evidence and mechanism for improving oocyte quality, by what metric? I have the same concerns as above for the recommendation strongly against luteal stimulation.	Accepted and amended accordingly.
70	Baris Ata	5.6.Is Progesterone Primed Ovarian Stimulation (PPOS) protocol superior to GnRH antagonist protocol in patients with poor ovarian response?	58		Recommendation against PPOS reads contradictory to the evidence presented. Again, the guideline seems to address only cycles with an intent for a fresh embryo transfer. In that case this needs to be made very clear throughout the guideline. The most comprehensive references seem to be missing from this section. Our systematic reviews.	The GDG group discussed and acknowledged the efficacy of PPOS in controlling LH surge. At best, the evidence was in favor of a similar outcome. The PICO question was regarding a recommendation based on whether PPOS is superior to the antagonist protocol. However, owing to the poor quality and scarcity of available data for poor responders, a recommendation could not be made regarding preference of PPOS over the GnRH antagonist protocol. The excellent comprehensive review mentioned by Ata et al. (2021) was not included as the methodology clearly mentions the mix of all types of populations (good, normal, and donors). No separate analysis was available for poor responders. Individual studies mentioned in the meta-analysis were considered. Sensitivity analyses, including only RCTs, only women with high ovarian reserve (donors and patients with PCOS), and only women with diminished ovarian reserve yielded similar results for all of the four outcomes.
71	Baris Ata	8.1.Does the Addition of Hormonal Assessment (Oestradiol/Progesterone/L	84		Despite the absence of evidence, some recommendations can be given as good practice points or guideline development group opinion if you wish to do	Thank you for the suggestion.

		H) To Ultrasound Monitoring Improve Monitoring Efficacy and Safety In Poor Responders?		so. Women with POR are probably the ones that would benefit the most from endocrine monitoring, e.g., the activity of a follicle as reflected by estradiol levels, imminent ovulation by increasing LH or Progesterone levels etc. The deliberations and conclusions of the GDG could be mentioned if there is an agreement.	
72	Abha Maheshwari	1.3 Scope	21	rather than fresh – live birth rate per embryo transfer	Accepted and amended accordingly.
73	Abha Maheshwari	3. Tabular Summary of Recommendations		4.10- does this include weight/ BMI as well? I think lifestyle chapter should say – diet / types of diet.	Accepted and amended accordingly.
74	Abha Maheshwari	4.9 Does Alternative Medicine-Based Therapy Improve Efficacy and Patient Related Outcomes in Patients with Poor Response?		you may wish to mention that we have no knowledge / data as to how they can react with stimulation regimens	Accepted and amended accordingly.
75	Abha Maheshwari	6.1.What is the safety and efficacy of recombinant FSH versus urinary gonadotropins in Patients with Poor Ovarian Response?		I am struggling to find evidence for The addition of hMG midcycle in patients who are hyporesponsive to recombinant FSH is probably recommended	Studies supporting the recommendation were not mentioned. Therefore, we have added the relevant information under the “Rationale for recommendation” section in the attached document on pages 63 and 64 and marked it in yellow. Based on the evidence, we found it necessary to add the phrase "in long agonist cycles."
76	Hrishikesh Pai			I have gone through the attachments and the draft for guidelines looks excellent.	Thank you.
77	Ameet Patki			I read with great interest about the POR and I must congratulate you and the team for a fantastic review. I am sure this in depth and exhaustive literature will help and enable scores of fertility specialists in diagnosis and management of this rather tricky subject.	Thank you.