April 2023

ESHRE Working Group recurrent implantation failure

ESHRE good practice recommendations on recurrent implantation failure

European Society of Human Reproduction and Embryology

REVIEW REPORT

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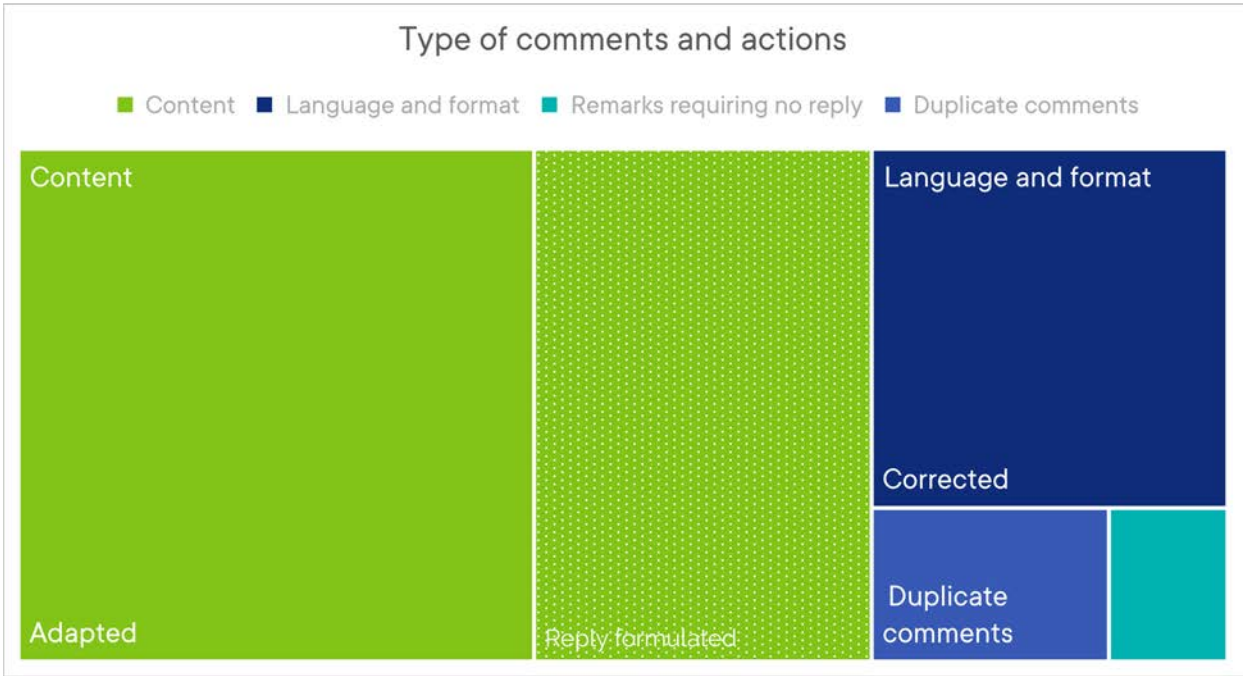
The draft of the paper “ESHRE good practice recommendations on recurrent implantation failure” was published for public review for 4 weeks, between 1 November and 1 December 2022.

This report summarizes all reviewers, their comments and the reply of the working group and is published on the ESHRE website as supporting documentation to the paper.

During the stakeholder review, a total of 204 comments (including 12 duplicates) were received from 35 reviewers.

The comments were focussed on the content of the guideline (137 comments), language and format (42 comments), or were remarks that did not require a reply (6 comments). All comments to the language and format were checked and corrected where relevant.

The comments to the content of the paper (n= 144) were assessed by the working group and where relevant, adaptations were made in the paper (n= 87; 60.4 %). Adaptations included revisions and/or clarifications of the text, and amendments to the recommendations. For a number of comments, the working group considered them outside the scope of the paper or not appropriate/relevant (n= 57; 39.6 %)



Experts that participated in the stakeholder review

The list of representatives of professional organization, and of individual experts that provided comments to the guideline are summarized below.

Representatives of professional organisations

Organisation	Country	Representative
Montgomery Fertility Center	USA	Oluyemisi Famuyiwa
SSC for women's health (ISTH) SISET (Italian Society for the study of Thrombosis and Haemostasis).	Italy	Elvira Grandone
Gedeon Richter	Switzerland	Julian Jenkins
Vitrolife Sweden AB (Vitrolife Group)	Sweden	Mark Larman
IVI-RMA Global	Spain, Portugal, Italy, UK	Antonio Requena Vanessa Vergara Nicolás Prados
IGENOMIX (Vitrolife Group)	Spain	Carmen Rubio
Next Fertility Prof. Zech	Austria	Dietmar Spitzer Maximilian Murtinger Maximilian Schuff
Nadezhda Women's Health Hospital, Sofia Nadezhda IVF group	Bulgaria	Georgi Stamenov
Hungarian Human Reproduction Society Versys Clinics Human Reproduction Institute	Hungary	Attila Vereczkey

Individual experts

Reviewer	Country
Baris Ata	United Arab Emirates
Carlos Calhaz-Jorge	Portugal
Jean Calleja-Agius	Malta
Enver Kerem Dirican	
Tarek El-Toukhy	UK
Aboubakr Mohamed Elnashar	Egypt
Ahmed Fawzy Galal	Egypt
Timur Gürgan Antonios S. Makrigiannakis	Turkey
Mitranovici Melinda Ildiko	Romania

Katarzyna Jankowska	Poland
Rukhsana Karim	Pakistan
Elena Kostova	The Netherlands
Tansu Kucuk	Turkey
Fang Ma	China
Cristina Magli	Italy
Massoud Massoud	UK
Genia Rozen	Australia
Anastasia Salame	United Arab Emirates
Marco Sbracia	Hungary
Michael Scholtes	Germany
Linda Stevens Brentjens	The Netherlands
Luis Ferreira Vicente	Portugal
Yezhou Yang XiaoYong Qiao	China
Elena Yanushpolsky	USA
Chi Chiu Wang	Hong Kong
Xingbang Zheng	China

Reviewer comments and replies

NR	Reviewer	Page	Line	Comment	Action / Reply
INTRODUCTION					
165	Carlos Calhaz-Jorge	1	28-29	"RIF as the failure to achieve a clinical pregnancy after two to three IVF cycles with one to four good quality embryos". This sentence is not clear: - I guess the word "cycles" means transfers - it seems the authors are accepting that up to four embryos can be transferred in one transfer.	We have revised the definition and phrasing.
32	Marco Sbracia	1	19/ rec 1	In the paper reported (Zegers-Hochschild 2017) there is not definition about implantation failure and eventually it is diagnosed by a negative beta-hCG test and no by ultrasound, such as subsequently reported in line 81 of page 2. The paper should be consistent in each part in order to no generate confusion in a such debated matter	We have amended the definition of achievement of an early pregnancy, referring now only to detection of beta hCG in serum or urine.
33	Marco Sbracia	1	32/ rec. 2	Syndrome or disease are not synonyms. Syndrome is a clinical picture with several symptoms that may show several causes (such as RIF?) Be consistent	The sentence the reviewer refers to reads "the concept of RIF as a syndrome or disease that can be diagnosed and treated is open to challenge." This sentence does not suggest syndrome and disease are synonyms, and as the word "syndrome" is not used elsewhere in the text in relation to RIF, no changes were made
METHODS					
104	Chi Chiu Wang			A flow chart as page 22 Figure 5 with evidence for recommendation is prefer	We have added an annex with a detailed overview of the different elements substantiating the individual recommendations.
72	Baris Ata	2	68	...draft of the paper which was published ...	This was adjusted in the text.
166	Carlos Calhaz-Jorge	2	81	Closing parentheses should be after "urine", not in the following line	The working group considers both hCG detection and US visualisation to be considered "achievement of a pregnancy". Assuming the confusion stems from the word

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					"positive pregnancy test" we have removed this.
193	Cristina Magli	/	/	In line 45, it is stated that the GPR provides recommendations for terminology, investigations and treatment. Is the recommendation for terminology the one reported in lines 96-98 and 173-178? I think that it should be made more clear, also because this is the proposal of a “focus group” receiving an online survey. Please define the “focus group” giving at least the number of professionals forming the group.	We have amended the methods section to clarify the process for determining the terminology and the threshold
194	Cristina Magli	/	/	A series of recommendations are listed. I do not understand how the majority of them are rated. For example, what is the evidence supporting the recommendation of lifestyle factors, page 9, to be green? Maybe the survey? Same question for the recommendations in page 10. The first is yellow irrespective of the results of the survey and of some control studies. The second is green, but no supporting citation is reported, besides being actually valid also for non-RIF couples.	We have clarified in the methods section that we have considered published data, complemented with the survey, biological rationale and expert opinion to reach the recommendations. We have also added an annex with a detailed overview of the different elements substantiating the individual recommendations.
195	Cristina Magli	/	/	Which was the weight of the survey results in determining the given recommendations, considering the scarcity of studies?	We have added further information to the methods section to address this comment, and we have added a detailed overview of the factors and evidence considered for each recommendation
196	Cristina Magli	/	/	In general, I have the impression that irrespective of the good intention to clarify a condition affecting a notable proportion of patients, the evidence is so scarce to provide clear indications, also in the attempt to avoid uncontrolled use of add-ons.	We agree with this comment and hope that further well-executed studies on the topic will help to improve the future clinical management of RIF
179	Carlos Calhaz-Jorge	22	Fig 5	Neither of the 3 recommended interventions are discussed in this section	We have added a paragraph in the section on "treatments based on diagnostic findings" summarizing the treatments discussed linked to the respective investigations, and referring to the section where these were discussed
34	Marco Sbracia	2	81/rec3	The ultrasound diagnosis of pregnancy cannot be associated with implantation anyway, since from the beta-hCG test (10-12 days after transfer) at the visualization of a gestational sac with or without heart beat at least passes three weeks. Be careful in the definition.	We have considered this comment thoroughly and to avoid ambiguity, we have removed US visualisation restricting the

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					definition to confirmation of an early pregnancy through a beta hCG test.
8	Tansu Kucuk			Best graded (A) evidence is gathered from published systematic reviews. A recommendation which is supported by evidence is ideal. But that evidence should be evaluated by experts of the field whose opinions are valued as the bottom grade! No further diagnostic or therapeutic, evidence supported option is given in the GPR for a patient to whom all is done but still not pregnant. Expert opinion is strongly needed although least valued in the evidence grading.	We have added further information to the methods section to address this comment.
59	Rukhsana Karim			Indeed this topic is the need of the day. 1- The document is very lengthy and the recommendations should be summarized at the end so as to make it more reader friendly. 2- The target audience is not clearly defined. 3- The definition of RIF is not very clear. if it's not a 'one size fits all' criterion then instead of recurrent implantation failure (RIF), use implantation failure. 4- The recommendations and evidence should be graded and classed 5- The date of expiry/next update should be clearly written	We have added some information to the methods section and have added an annex to the document, but would like to stress that the current document is a good practice recommendation rather than an evidence-based guideline.
80	Elvira Grandone			In the introduction, authors acknowledge the high heterogeneity of definitions of the studies so far published. It is conceivable that this heterogeneity has affected findings and interpretation of the different studies. Therefore, I fully agree that this is one of the most relevant limitations of the available evidence and does not give enough robustness to all recommendations/suggestions that experts give. However, the present document will inform a good clinical practice, as these recommendations should ensure an appropriate use of evidence. For these reasons, authors should declare in the methods which type of studies (randomized controlled trial, prospective study, retrospective study etc) is guiding mostly their recommendation and why some studies are better than others. Furthermore, when the initial criteria are not followed, they should clearly explain why in a certain case a small and/or an observational study is better that a RCT (small sample size, no clear definition of outcomes, etc.). Ideally, for each issue, authors should give a "gradient" of relevance in terms of robustness of findings. This should be declared in the methodology, so that readers can better understand why in some cases recommendations/ suggestions "in favor/against procedure" are given, apparently in the presence of similar evidence. To do an example: at the end of the paragraph of preimplantation genetic testing for aneuploidy (PGT-A), this procedure is suggested in	We have clarified in the methods section that we have considered published data, complemented with the survey, biological rationale and expert opinion to reach the recommendations. We have also added an annex with a detailed overview of the different elements considered for each recommendation, including the quality of the data where available.

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				spite of a meta-analysis of RCTs that failed to show an improvement in both clinical pregnancy and RIF (random effects model: RR 1.07; 95% CI 0.36 to 3.15; 820 p=0.90; I^2=89% and RR 0.98; 95% CI 0.32 to 2.94; p=0.97; I^2=87%) in women who underwent PGT-A. It is likely that authors suggest to perform PGT-A in relation to two retrospective studies where embryo testing was conducted by either array CGH or NGS approaches on blastocyst biopsies, showing that PGT-A could be considered a good strategy for women with RIF. On the other hand, in the paragraph regarding the use of low-molecular weight heparins (LMWH), authors recommend not to use them based on the systematic review by Busnelli et al. (Scientific Reports 2021) and on two observational studies (Berker 2011, Busnelli 2021). Indeed, in their paper in Scientific Reports, Busnelli et al. state that they downgraded evidence of RCT by two levels for risk of bias and by one level for imprecision. Also, they downgraded the level of the evidence provided by Berker et al. (observational study) by one level for risk of bias. In the same manuscript, for similar reasons, Busnelli et al. show that pooling of results of observational studies did not show a beneficial effect of PGT-A on both pregnancy (random effects model, OR 1.58; 95% CI 0.35–7.12; p = 0.55; I2= 86%) and live birth chances (random effects model, OR 0.83; 95% CI 0.33–2.07; p = 0.69; I2= 44%) and in the discussion they state : "…Meta-analysis of studies investigating the possible impact of intrauterine G-CSF infusion, LMWH, hysteroscopy, blastocyst-stage ET, ZIFT, PGT-A and AH failed to observe an impact on IVF outcome" Busnelli et al. declare why they downgraded RCTs, but other authors (Akhtar MA, et al. Heparin for assisted reproduction. Cochrane Database Syst Rev. 2013 Aug 17;(8):CD009452) did not downgrade the same RCTs, thus reaching different conclusions. In this Cochrane, the same RCTs (involving 386 women) were included. Peri-implantation LMWH administration during assisted reproduction was associated with a significant improvement in live birth rate compared with placebo or no LMWH (odds ratio (OR) 1.77, 95% confidence interval (CI) 1.07 to 2.90, three studies, 386 women, I(2) = 51%, very low quality evidence with high heterogeneity)	
112	Carmen Rubio			We would appreciate the inclusion of a more detailed description of the criteria employed for the classification. Similar criteria should apply for all the tests and interventions, and these criteria must be clear, published, objective and measurable.	We have clarified in the methods section that we have considered published data, complemented with the survey, biological rationale and expert opinion to reach the recommendations. We have also added an

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					annex with a detailed overview of the different elements for each specific recommendation.
SECTION - DEFINING RIF					
9	Tansu Kucuk	3	92	Is the first statement of the paragraph refer to RIF in ART only or include the natural pregnancy attempts as well? And contradicts with the sentence on page 30, line 924, which is referring only ART cycles defining RIF.	We have clarified in the text that RIF can only be suspected in ART patients, and therefore should not consider natural pregnancy attempts
142	Ahmed Fawzy Galal	3	99	Would like to replace phenomenon by A special scenario confined to ICSI/IVF patients	We have used the term "a distinct scenario" as suggested by the reviewer.
10	Tansu Kucuk	3	110	Who are those couples undergoing ART and can be foretold that they will fail regardless of the treatment? Why ART then?	To date, other than extreme clinical situations such as a severe untreatable Asherman, few predictors of RIF exist and those that do are not considered powerful enough to preclude a patient from treatment. We have not amended the text.
11	Tansu Kucuk	3	111	What is meant by saying “specific pathology”?	We have amended 'specific pathology to "an identified pathology "
86	Aboubakr Mohamed Elnashar	4	122	AMH is not standard (routine) for every infertile female	AMH or other ovarian reserve testing is included in other guidelines and recommendations referred to and hence included in the list. The discussion on AMH as part of the fertility work-up is outside the scope of the current paper on RIF.
76	Fang Ma	4	124	the big part only discusses the ART….	RIF is considered an observation linked to ART. It was clarified in the text that RIF can be suspected in ART patients after embryo transfer, but not with natural pregnancy attempts
169	Carlos Calhaz-Jorge	6	161	Nice figure! What’s the meaning of “IVF attempt”? Embryo transfer? A new IVF cycle?	We have addressed the suggestions in the figure

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				In the table of the second half of the figure, I guess the first “maternal age” row should be “<35” instead of “<34”	
74	Baris Ata	5	163	While I understand that selection of a threshold to define RIF is somewhat arbitrary in nature, and clinically there is a few simple additional investigations that may be required once the threshold is met, it may be OK to call RIF when estimated chance of implantation reaches 60%. However, in the research setting, I strongly believe a higher threshold should be used to recruit a study population, who is much more likely to have other biological mechanisms than randomly occurring embryo aneuploidy to ensure a high signal to noise ratio in the data. Otherwise, we will be doomed with a lot of random findings as has been the case for decades, which is also reflected in the papers you have reviewed in the therapeutic section of this guideline.	We have added se definition and more stringent threshold to be used in the research setting.
12	Tansu Kucuk	5	165	A negative result is a bad luck when the odds is 50/50. For 51/49 and over, it is a failure.	The statement refers to the threshold aiming to discriminate a non-implantation event by chance from an non-implantation event likely indicative of a problem. We have slightly amended the sentence to clarify it.
168	Carlos Calhaz-Jorge	5	171	The text is repetitive. I suggest remove “was considered” after 60%	This was adapted in the text
13	Tansu Kucuk	5	175	There is no “treatment option” recommended in the GPR…	There are 3 suggested treatment options provided, as well as treatments based on investigations performed, such as reviewing estradiol treatment. We have therefore not amended the sentence
197	Cristina Magli	8	185	“date” should be “data”	This was adjusted in the text.
113	Carmen Rubio	5	168-175	The considered threshold of 60% should not be global, it must change according to different individual characteristics, such as age, clinical history, ultrasound, hormones, etc. Another approximation could be an odds ratio to calculate this probability.	We have added a sentence on ‘individualised’ chances to clarify and ensure correct interpretation
167	Carlos Calhaz-Jorge	3	92-93	“RIF as a secondary phenomenon of infertility or ART as it can only be observed in couples undergoing ART.” If RIF can only be observed after ART, it is not consistent to say that can be secondary to infertility or ART	We agree with the comment and have amended the text to clarify that RIF can only be observed in couples undergoing ART. We have removed "infertility" from the sentence.
103	Chi Chiu Wang	4	Fig 1	Endometrium evaluation by ultrasound, HSG and histology missing	Endometrium evaluation by ultrasound, HSG and histology is not included in other

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					guidelines and recommendations referred to and hence included in the list. The discussion on Endometrium evaluation by ultrasound, HSG and histology as part of the fertility work-up is outside the scope of the current paper on RIF.
78	Fang Ma	6	Fig 2	Need a space in the title.	This was adjusted in the text.
114	Carmen Rubio	6	Fig 2	There is a mistake in the chance of pregnancy per IVF attempt (it is not 25%, it should be 27.6%).	We have corrected the figure
108	Tarek El-Toukhy		Fig 2	In the section of setting a threshold for the cumulative chance of successful implantation to signal action, the document uses the references of Wynes C, et al, 2021 and Reig A, et al, 2020 to provide an example of how clinics data can be used to guide establish an RIF threshold for starting interventions. There are 2 major concerns with the use of this example: 1- The table provided gives the false impression that pregnancy rates are significantly improved when using PGT-A at all age groups, which is not true as evidenced by the two existing RCTs (Blockeel et al, 2008 and Rubio et al, 2013), and the results of the systematic review of Busnelli A et al, 2021. 2- The two studies are massively different in their design, analysis and remit and should never have been combined into one table (one study, Wynes C, et al, 2021 used EIM data in 2017 reported from 1382 clinics offering ART services in 39 countries with different methods of data collection and variable levels of reporting (as the study itself admitted), whilst the other study (Reig A et al, 2020) is a report from a single centre of a highly selected group of patients who had single embryo transfer after PGT-A). Any suggestion that those two studies are comparable and their data could be combined in one table is potentially misleading. Please either remove this table or add a clear statement that the 2 sets of data are not comparable and should not be seen as such, and that there is no robust evidence to show a more favourable outcome after PGT-A in RIF patients.	We acknowledge the limitations of the respective studies used for the crude estimation example. It was clarified in the figure that clinics can implement the threshold for their patient population rather than for each specific patient, by making a crude estimation table for certain patient groups. The proposed studies where only used to provide some example numbers for the table, but these should be changed to the data from the respective clinic to become an appropriate tool for the clinics.
105	Chi Chiu Wang	7	Fig 3	Embryo transfer failed to results in pregnancy should be more than 2 at least. If only more than 1, it is more than just by chances	By definition more than 1 failed embryo transfer (being at least 2) could be considered "recurrent". We have changed

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					the text "more than 1 ET" to "at least 2 ETs" to improve clarity
37	Marco Sbracia	5	173/rec 6	The choice of a threshold at 60% is not substantiated, since the model reported are mathematical extrapolation of old data of poor quality or just math calculations without any validation of clinical data. Furthermore, is a generic value that no take in account woman's age, previous transfer of blastocyst or cleavage-stage embryos It seems that this threshold is an arbitrary decision based on literature data that are of poor quality. The threshold choose should be determined by robust data taking in consideration most of possible variables instead that an arbitrary decision. Since there is a lack of data on this issue the authors should clearly state that this threshold is obtained by a weighted arbitrary decision instead than from robust clinical data. Furthermore, the authors may give this threshold as a probability fork oscillating between 60-70% such as showed from applied example in page 6 and the crude estimation at page 6	We have discussed the comment of the reviewer, but consider we have provided sufficient information on the basis of arriving at 60% and we think this is consistent with the suggestion of the referee. We have therefore not amended the text.
38	Marco Sbracia	7	201/rec 7	How the authors recognized in the previous sentence about the limitations and the quality of data available on RIF, and the very low number of RCT, for each recommendation and statement of the study group should be reported the quality of data on which the authors have formulated their recommendations, in order to make aware the readers about the quality of the guideline statement.	We have clarified in the methods section that we have considered published data, complemented with the survey, biological rationale and expert opinion to reach the recommendations. We have also added an annex with a detailed overview of the different elements considered for each recommendation, including the quality of the data where available.
35	Marco Sbracia	3	96/rec 4	In describing the "scenario" should be added the term repeated transfer of embryos presumably viable, in order to be consistent with the topic of guideline.	The sentence was not changed, since the wording “sufficiently often” already implies more than once, e.g. repeated.
36	Marco Sbracia	3	99/rec 5	RIF more than a secondary phenomenon should be considered an iatrogenic event.	We have discussed this comment, but considering RIF as an iatrogenic event would imply that failure is never due to an inherent embryo or maternal factor which is not the case. Therefore, we have not changed the text

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163	Carlos Calhaz-Jorge		Methods	Use “positive pregnancy test” as reflecting successful implantation seems to be questionable. What is a positive pregnancy test? Beta-HCG >20 mIU/mL? This criterion is so vague that may contribute to the weakness of many assumptions. I’m sure the authors’ option is based in a good reasoning. However, I suggest some sentence of caution is added about this issue.	Much consideration has been given to this issue and definitions selected that can be applied in the varied clinical settings in which the document would be applied. However, a caveat has been added as suggested.
62	Rukhsana Karim			Role of antioxidants in management of RIF : For Reference: Sofoklis Stavros1,2, Antonios Koutras2 , Thomas Ntounis2 , Konstantinos Koukoubanis2 , Theodoros Papalios2 , Despoina Mavrogianni1 , Peter Drakakis1. Failure of Implantation in IVF due to oxidative stress. HJOG 2021, 20 (2), 45-52 | doi: 10.33574/hjog.0045..... Failure of implantation in IVF due to oxidative stress is a challenging and complex problem for both clinicians and researchers, because it does not enquire a holistic and standardized approach. Maybe the best option is personalized medicine depending on both the etiology and the special characteristics of each patient, due to the fact that it plays a key role in several biological and molecular mechanisms on patients undergoing IVF. Not only do reactive oxygen species provide a field for treatment options, but also a preliminary evaluation of every individual couple. Tesarik, J. Towards Personalized Antioxidant Use in Female Infertility: Need for More Molecular and Clinical Studies. Biomedicines 2021, 9, 1933. https:// doi.org/10.3390/biomedicines9121933.....studied the role of deferent antioxidants especially, Co enzyme Q10, Melatonin and resveratrol	While we agree with the reviewer that in RIF an standardised approach may not be appropriate, the value of personalised medicine delivered through antioxidants remains to be more convincingly demonstrated before they can be actively recommended for clinical practice.
94	Michael Scholtes	4		Prevention of RIF has not been adequately addressed. Pre-treatment work up should be performed by an experienced fertility specialist, not just as a supervisor of doctors in training, physician assistants and nurse practitioners. Designing the right COH protocol will provide the best number of oocytes/embryos of good quality.	Based on the suggestion of the reviewer we have added a sentence to the text on the quality of the ART procedures. However, it is outside the scope of the paper to provides details on who should carry out the work up or what stimulation protocol should be applied.
77	Fang Ma	5		The threshold is confused, why,maybe more proper and convincing statistical interpretation.	We have added more specific information on the threshold to clarify and ensure correct interpretation

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30	Genia Rozen	3-6		Pages 3-6 discuss our 'theoretical cumulative implantation rate' concept and study without reference to our paper, published in Human Reproduction in 2021. We were the first to propose this approach. Furthermore, our paper was published before that of Ata B et al, 2021. We are unsure how to explain this oversight and lack of citation, especially given publication in Human Reproduction, 18 months ago. Rozen, G., et al. (2021). "An algorithm to personalise the diagnosis of recurrent implantation failure based on theoretical cumulative implantation rate." Hum Reprod.	Thank you for informing us on this error. We have reintroduced the reference to the paper by Rozen 2021.
7	Tansu Kucuk			The term "recurrent implantation failure" implies that we, "ART specialists", have done everything correct and perfect, but the embryo failed to implant. Is it the case really? Even after employing the cutting edge technology of genetic screening using sequencing, we cannot guarantee the normality of a given embryo. A competent embryo can invade any tissue in women's abdominal cavity (see varieties of ectopic pregnancy). What is failing may not necessarily be the implantation only but the whole IVF treatment itself. So, I will dare to offer "recurrent IVF failure" instead.	The IVF treatment may indeed fail at several procedural steps, for example the step of fertilization, the step of blastocyst formation in-vitro, the process of implantation or the process of pregnancy continuation. We therefore suggest to remain with the commonly used and well introduced term alluding specifically to the distinct temporal phase of the IVF treatment, which is between ET and hCG test.
56	Linda Stevens Brentjens			Although the proposed definition of RIF allows a more individualized approach that could benefit the patient, one must also recognize that the novel definition can be challenging when conducting scientific research. Compared to a generic definition of RIF based on e.g. a fixed number of embryo's transferred, the novel definition allows a wider interpretation which can lead to increased heterogeneity in the patient group. Although changing the definition would not fully eliminate this problem, one must be mindful that a specific treatment could turn out to be ineffective if studied in a (too) heterogeneous group of patients with implantation failure, whereas it could be effective if applied more specifically.	We argue that a generic definition, applied across, for example, different age groups, renders an even more heterogenous group of patients labelled with RIF. We believe the proposed individualised RIF definition can be readily applied in research setting and will generate data of greater clinical utility if applied. In the text, we have added a sentence on the use of the definition in a research setting.
57	Linda Stevens Brentjens			By not taking into account that the likelihood of implantation decreases with every non-successful embryo transfer, it should be acknowledged that the given formula can lead to an overestimation.	The text already addressed the issue of reducing complexity for practicality reasons and state that this is a heuristic approximation. Therefore no amendments were made.

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75	Fang Ma			1. The overview of this talks about RIF, however mainly focuses on the RIF among the ART population, so , the title, or the organization of the sections might be more better.	As we have sought to make clear, RIF can only be identified after ART as this is the only context in which there is certainly that an embryo with potential to implant has been present in the uterus. We have slightly amended the title and text to make this more clear.
144	Georgi Stamenov			A definition involving the calculation of individual criteria (sufficiently often) for which we do not have a calculation model, or everyone would use their own model, which will include different characteristics with different degrees of influence on the calculated probability, cannot be accepted. If we ought to use the proposed definition, it would require a unified method of calculating this "sufficient number of attempts" to be applied by all because, if everyone applies a different calculation model involving different criteria, we would again face the problem of lack of generalisability of findings as different investigations and treatments are applied to different patient groups. In addition, in the criteria for calculating success it would be appropriate to include only indicators for which there is sufficient evidence available by reviews and meta-analyses and which have a direct biological significance on the embryo implantation process.	The point made is well taken but introduces the concept of being the recognition of RIF for which further investigation is considered indicated on the patient context. While one method to calculate this is provided, the referee is correct that many others might be applied. Moreover, we would agree that for research and other purposes a more straightforward and unified definition is provided. This was amended in the text. To facilitate clinical practice, we have included a summary table indicating the number of embryo transfers that should have taken place in different age groups with or without known euploid transfer.
146	Georgi Stamenov			The proposed probability calculation models cannot adequately cover the individual case because uniform factors are used, and as suggested in the same guideline, each case is individual, and the specific features of the case must be considered. If the necessary investigations (inflammation and structural abnormalities of the endometrium) are not done, the case cannot be examined and assessed thoroughly and individually. According to the proposal in this document, necessary investigations and subsequent treatments should be done only after reaching the next unsuccessful attempt, for which the predicted success chance is more than 60%, according to the predictive analysis carried out. This analysis, however, would not be accurate without the additional proposed investigations of the patients (hysteroscopy, embryo competence, endometrial	The reviewer indicates that the threshold can only be considered to have been reached if information is already available regarding the outcome of a range of endometrial investigations, and they make a cogent case for doing this after once failed cycle. The working Group has taken a different view, seeking to provide guidance as to the stage in the treatment pathway when such investigations might be considered. We would concur with the points made, and

NR	Reviewer	Page	Line	Comment	Action / Reply
				functionality) that need to be done before the individual "by chance" IVF attempts expire. Furthermore, an additional consideration when proposing such a model is that, particularly in older patients, time is of the essence, and keeping them waiting for a conclusive diagnosis before intervening is unethical, as their reproductive function declines significantly with age. In addition, there are various proposed approaches to determine the chance of conceiving, and the selection of one such model, as highlighted on page 4, line 134, is impossible because there is no such standardized exact model. The proposed IVF predict tool returns varying results (page 5, line 156) and uses very general input data to calculate success (age, number of attempts, donor or own eggs). The only specific factor in this calculator is the cause of infertility, which we know can be different – from damaged tubes, irregular ovulation, endometriosis, cervical, and low sperm count. Using only these general parameters to determine the chance of success is precisely the opposite of respecting the individual clinical context. The introduction of such a calculator and/or table would encourage a one-size-fits-all approach rather than offer an individualized strategy we seek as clinicians. As emphasized in line 125, each case is unique and the only way to carry out an individualized approach is by conducting referral tests (incl. Immune profile and endometrial dating). According to the strategy proposed in this text on line 144, such a model can be derived by using published data, the European IVF monitoring data collection, and data of the ART clinic itself, which, in our opinion, can include not only the age, euploidy rate, and number of embryos transferred, as stated in line 146, but also the individual's hysteroscopy findings and lack of pathology. That is why we propose these should also be considered, not only if there are numerous unsuccessful implantation cycles, but even after the first unsuccessful IVF attempt. The next proposed crude estimation in figure 2 is the example table of individual clinical data. Such a table could include additional studies (conducted after the first unsuccessful IVF attempt) to expand our knowledge of the patient, give us a more precise definition of the possibility of success, and guide action. However, even such an approach would require unification of the investigation methods, which is impossible at this stage.	ultimately each clinic may be in a position to determine this based on a number of additional variables including local performance of the clinic. However since most clinics do not yet have access to such analytics, the working Group has taken the view to provide a more simple and readily applicable approach and to aid the use of consistent criteria, provided a Table with a simple criteria based only on age and knowledge of euploid state that both addresses the recognition that 'one size does not all' and the need for a simple and readily adopted definition.

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147	Georgi Stamenov			It would be appropriate in the clinical practice to start looking for the causes of failure (through as many investigations as necessary) and ways to treat them after each failure because each subsequent attempt (and failure) is costly in both economic and emotional terms for the patients. Therefore, we suggest to act after each failure instead of using a model to calculate a sufficient number of attempts. It is crucial that action be taken to improve the success rate as early as possible in the couple's attempts to conceive. If we use the example case and data in figure 2, that patient must make 4 attempts, during which they will inevitably lose oocytes, suffer emotional distress, and bear an increased financial burden, which may discourage them from continuing, or indeed reduce their chances of success. In this case, if the necessary tests are applied straight after the first unsuccessful attempt and an approach is taken with immunological treatment or personalized embryo transfer, the chances for successful implantation can improve. We all agree that this phenomenon of more than 2-3 times implantation failure exists, and we are all aware that adequate actions must be taken to prevent these failures from happening again and again. For this to happen, it is necessary to find the underlying cause for each of these unexplained cases, and of course, this can only be done individually for each couple. This process is most easily accomplished by conducting individual investigations on the well-known possible indicators of an embryo implantation problem – gross anatomy and molecular/histological features (which are not recommended in this guideline) indicative of non-functional endometrium, incompetent embryo or unsynchronized interaction between them. Furthermore, without investigations, the patients will not be able to comprehend why these failures continue to occur, and they will eventually change the clinic. The new clinic would then start the individual "by chance" cycles all over again. We agree that the honest discussion with the patient/couple is of high importance, and during this discussion, we as clinicians, are obliged to expose our hypothesis for the implantation failures and to explain why there should be a following cycle with or without treatment.	The arguments of the reviewer are well made and acknowledged by the presumption made that all women have been previously subject to a full fertility work up. The reviewer proposes performing endometrial receptivity tests following each implantation failure but to date there is insufficient evidence to support this approach. Indeed, the proposed approach is aimed at avoiding unnecessary tests and treatments. However after consideration of this comments from the reviewers indicating possible value we have added that assessment of specific aspects of endometrial function by testing can be considered.
149	Georgi Stamenov			Investigation of the uterine cavity, embryo competence, and endometrial functionality may vary in methodology, as well as reference values vary from clinic to clinic. By conducting routine examinations of patients, sufficient data is accumulated, by which internal reference values can be derived, and on the other hand, by their active sharing	The working group recommends to consider hysteroscopy, but indeed does not recommend embryo grading, or endometrial functionality assessment. If the reviewer

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				in the form of publications and discussion in global and regional forums, they can be gradually optimised, so that overall optimisation of the investigation/treatment process is gradually reached. The diagnostic approaches themselves (hysteroscopy, embryo grading, and tests for endometrial functionality) are observational and, apart from taking samples from the patients, cannot do any harm to the patient. On the contrary, they would give the clinician important additional insigt that will be indispensable in making an adequate decision about the subsequent treatment. For this reason, we cannot agree with this guideline's lack of recommendation for hysteroscopy, embryo grading, and endometrial functionality assessment. These methods provide essential information about the patients' condition and should be incorporated in their work-up plan to accumulate data for their or other patients' future treatment. Regarding the recommended lifestyle factors investigations (BMI, stress, coffee intake), for which the data are very few, general, and non-standardized, a major issue is the distant and not entirely clear biological relationship between them and the implantation process . For example: page 9, line 236 says obesity affects receptivity by displacing the window of implantation. Changes in lifestyle factors could indeed have a positive effect on implantation success, but only after defining the actual cause of the implantation failure (endometrial, embryological, or both). We propose not to give up the hysteroscopic findings, embryo quality, and endometrial receptivity assessment, but to include them in the "recommended" section.	considered these methods provide essential information about the patients' condition, they could be performed, but unfortunately the studies do not support these tests to be recommended for clinical practice.
SECTION - INVESTIGATIONS IN RIF					
2	Elena Yanushpolsky	9	239	Given that vit D levels seem to be associated with everything from depression to hypertension to uterine fibroids and (?) infertility, but none of the placebo controlled RCTs showed any benefits of re-supplementation/ over-supplementation (not even for bone issues)- why recommend Vitamin D evaluation/supplementation? All patients should be taking prenatal vitamins that contain recommended daily amounts, plus adequate dietary intake – should be sufficient.	We have considered this and other comments to the recommendations on vitamin D measurement and supplementation. In line with our statement that the role of vitamin D supplementation in ART remains controversial, the recommendation was reformulated as "'There is insufficient data to recommend the routine measurement and treatment of Vitamin D levels."

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27	Jean Calleja-Agius	9	239	Discuss safe dose of Vitamin D to be administered, which serum levels are optimal	We have amended the recommendation to state that there is insufficient data to recommend the routine measurement and treatment of Vitamin D levels. As such, further information on optimal serum levels and doses was not added
91	Dietmar Spitzer Maximilian Murtinger Maximilian Schuff		239	As the it is stated in the draft, vitamin D assessment and supplementation in ART remains controversial. While there are some correlations found in regard to miscarriage and dysregulated vitamin D levels (Chen et al, 2022; Tamblyn et al, 2022) as well as lower live birth rates in women with insufficient vitamin D status, the association between (recurrent) implantation failure and dysregulated Vitamin D level is rather of theoretical nature than supported by robust studies.	We have considered this and other comments to the recommendations on vitamin D measurement and supplementation. In line with out statement that the role of vitamin D in ART remains controversial, the recommendation was reformulated as "'There is insufficient data to recommend the routine measurement and treatment of Vitamin D levels.''
25	Jean Calleja-Agius	9	246	Dosage, ideal serum levels	We have amended the recommendation to state that there is insufficient data to recommend the routine measurement and treatment of Vitamin D levels. As such, further information on optimal serum levels and doses was not added
24	Attila Vereczkey	/	/	Multivitamin supplementation issue would suggested to include as well as dietary or diet suggestions, like high protein diet, etc.	We consider diet suggestions to be included as "optimalisation of lifestyle factors". As to our knowledge, apart from some evidence to support the benefit of components of the Mediterranean diet in general, there is no evidence to support the prescription of a specific diet after RIF. For these reasons, we have not elaborated on this in the text.
116	Carmen Rubio	9	236 - 238	Lifestyle review is recommended in RIF cases, and one of these factors is BMI. One of the reasons given to review BMI is a potential WOI displacement (Bellver et al., 2021b), which is assessed by Endometrial Receptivity Testing, but then this kind of receptivity evaluation is not recommended according to this same paper. So, in this section it is	We have considered the reviewers' comment and have removed the sentence on the window of implantation (WOI).

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				acknowledged the existence of WOI displacements, but the tool for detecting it is not recommended...this is incongruent.	
40	Marco Sbracia	9	239 / rec 9	It is not clear how the study group decided that vitamin D deficiency should be assessed. There are not evidences at all that Vit.D deficiency or Vit.D supplementation may be useful in IVF and in RIF. Also, a recent metanalysis (Cozzolino et al 2020) showed no effect of Vit.D on IVF. The only reason alleged by authors is that it is "widely applied in clinical practice". If this is the role of ESHRE GUIDELINE, TO APPROVE WHAT OTHERS DO IN CLINICAL PRACTICE, they are completely unnecessary, and we can save time and money to do and review these guidelines. So please state that there not data available on the utility of Vit.D level investigation or supplementation, and any evaluation on their utility is postponed when more data will be available.	We have considered this and other comments to the recommendations on vitamin D measurement and supplementation. In line with out statement that the role of vitamin D in ART remains controversial, the recommendation was reformulated as "'There is insufficient data to recommend the routine measurement and treatment of Vitamin D levels."
97	Antonio Requena Vanessa Vergara Nicolás Prados			The authors state that there are no evidence of association of VD with RIF or benefit with the treatment. Instead of not recommending it (red), it can be considered base only in a single paper (Cimadomo 2021) where it is only recommended without proof. In our opinion vit D should be in the red (insufficient data group)	We have considered this and other comments to the recommendations on vitamin D measurement and supplementation. In line with out statement that the role of vitamin D in ART remains controversial, the recommendation was reformulated as "'There is insufficient data to recommend the routine measurement and treatment of Vitamin D levels."
26	Jean Calleja-Agius	10	266	Comment on it's role or lack of role	We consider that we have sufficiently covered the relevance and role of genetics in RIF and have not further expanded the section.
28	Jean Calleja-Agius	10	266	Emphasis on the lack of additional benefit obtained by doing pre-implantation genetic screening on all embryos (can also be mentioned in line 828 page 27)	We consider that we have sufficiently covered the relevance and role of genetics in RIF and have not further expanded the section.
100	Yezhou Yang XiaoYong Qiao	10	275	In the assessment of the uterine cavity, abnormal uterine contraction and uterine peristalsis at the time of embryo transfer may also be one of the causes of RIF. Therefore, this evaluation is necessary in patients who have not found other definitive causes of RIF. As mentioned in the recommendations, 3D transvaginal ultrasound has been proposed as an alternative non-invasive procedure for diagnosis of uterine anomalies,	We have considered the comment of the reviewer regarding abnormal uterine contraction and uterine peristalsis at the time of embryo transfer. To the best of our knowledge, abnormal uterine contraction

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				the assessment of abnormal uterine contraction can be completed at the same time, while 4D ultrasound can be used as a method to assess uterine peristalsis.	and uterine peristalsis have not been linked to RIF and it has not assessed outside research settings. While it may also be one of the causes of RIF, to date no intervention has been shown to alter outcomes so its impact on implantation remains uncertain.
87	Aboubakr Mohamed Elnashar	10	282	3 D ultrasound can be considered , but if not available saline sonohysterography not HSG	We have added a sentence on sonohysterography in the text.
65	Baris Ata	11	292	Moffett and Shreeve 2015 seems like an irrelevant reference here.	We have removed the reference as suggested
198	Cristina Magli	11	292	Level of evidence?	We have clarified in the methods section that we have considered published data, complemented with the survey, biological rationale and expert opinion to reach the recommendations. We have also added an annex with a detailed overview of the different elements considered for each recommendation, including the quality of the data where available.
49	Mitranovici Melinda Ildiko	11	294	Salpingectomy cannot be done by hysteroscopy, I think you are referring to laparoscopy	The sentence on salpingectomy refers to other uterine cavity anomalies and respective treatments and is not linked to hysteroscopy. We have changed the sentence to avoid misreading.
88	Aboubakr Mohamed Elnashar	11	298	Hysteroscopy or 3 D ultrasonography is preferred?	The recommendation states that the Hysteroscopy can be considered, especially when there is a suspicion for a uterine anomaly visualised on transvaginal ultrasound. We recommend 3D ultrasound followed up with hysteroscopy only in case of a uterine anomaly visualised on transvaginal ultrasound

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50	Mitranovici Melinda Ildiko	11	299	You brought up hysterosalpingography, but you did not specified hysterosonography at all if it is relevant	We have added a sentence on sonohysterography in the text.
16	Tansu Kucuk	32	988	HSG is not only for tubal patency but is also for synechia and other endometrial pathologies…	We have added "and other endometrial pathologies" to the table
117	Carmen Rubio	10	272-274	59% of clinicians consider the WOI displacement to be relevant and 47% consider the endometrial microbiome to be relevant. Why are these tests not recommended? What threshold is applied to decide if the test should be recommended or not, according to the clinician's practice?	We have moved the information on the uptake of the different tests to the respective sections, where also the studies are listed. The reasoning of the working group is additionally documented in annex 2.
170	Carlos Calhaz-Jorge	11	293 - 294	Salpingectomy is not a "uterine cavity anomaly"	We have removed salpingectomy from the list of interventions for uterine cavity anomalies
64	Baris Ata	4 & 10	267 – 274 (Fig 1)	Studies on the effect of hydrosalpinges did not exclusively involve women who had ultrasound visible hydrosalpinges. Women with HSG diagnosed hydrosalpinges were also included in some studies. Hence, it may be reasonable to assume that hydrosalpinges not detectable by transvaginal ultrasound but only visible by HSG or other contrast imaging (e.g., HyCoSy) may also be interfering with implantation. Would you consider recommending a test of tubal patency in addition to ultrasound assessment of uterine anatomy. Particularly if the period between initial investigation of tubal patency and diagnosis of RIF has been long.	We did not include a tubal patency test for all RIF patients, but we have added a sentence stating that " HSG of other means of imaging of the fallopian tubes can be considered if there is a doubt on hydrosalpinges after ultrasound."
41	Marco Sbracia	10	267/ rec 10	The guideline should highlight the possible role in RIF of adenomyosis, endometriosis, and sub-mucosal fibroids, in the association with RIF. Eventually also the 3 tesla MRI may be suggested in particular cases. And again, hysteroscopy is a second level diagnostic test that has to be requested in particular cases, and no just because its "widely used" it is right (see the previous rec9).	We have added a sentence stating that "Assessment of the presence of adenomyosis, endometriosis and submucosal fibroids should be carried our prior to IVF. However, of there is renewed suspicion due to emerging clinical signs or ultrasound features noted after RIF, then further investigations including MRI or diagnostic laparoscopy should be considered. " With regards to hysteroscopy, it is explained that this can be considered (not is recommended), especially when there is a suspicion for a uterine

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					anomaly visualised on transvaginal ultrasound.
85	Aboubakr Mohamed Elnashar			An evaluation of the pelvic anatomy for detection of hydrosalpinges using TV US.	We had already included that if 3D ultrasound has not been performed at fertility workup, it can be considered in patients with RIF. We consider tubal patency testing is also performed during the fertility work-up, and have now added a sentence stating that " HSG of other means of imaging of the fallopian tubes can be considered if there is a doubt on hydrosalpinges after ultrasound." .
145	Georgi Stamenov			We believe performing a hysteroscopy should be routine practice before commencing other diagnostic and therapeutic approaches. It could help identify various endometrial pathological conditions directly responsible for subsequent implantation failures, such as endometritis, adenomyosis, polyps, micropolyps, endometrial hyperplasia, and metaplasia. Should there be no indication for further investigation of an endometrial problem, then embryo causes should be considered. There should be standardized criteria for evaluation of the quality and competence of the embryo – morphological and/or kinetic characteristics.	We consider there is no evidence base to support this view. Ruling out small anatomical abnormalities does not exclude functional endometrial defects. Providing recommendations on standardising embryo assessment is out of the scope of the current document. This topic is addressed by the Istanbul consensus document, which is currently under revision.
143	Georgi Stamenov			As clinicians, we must search for an underlying cause for the lack of success. The management of patients with repeated implantation failure should include investigating the key players –endometrium functionality, embryo competence, and/or timely and synchronized interaction of the two. Without looking into any of those three components, it is incredibly difficult to convince patients to just keep trying.	We fully agree with the underlying premise of this point. The OPTIMUM trial - in which RIF patients were treated based on diagnostic findings - suggests that using diagnostics to assess the cause of RIF is likely to improve the efficacy of interventions which would then be applied with more rationale than at present. At present, however, few validated tests of value in the context of RIF are available.
66	Baris Ata	11	300	Would you consider mentioning the following paper here as well? Cozzolino M, Diaz-Gimeno P, Pellicer A, Garrido N. Use of the endometrial receptivity array test to guide	We have added the suggested recent study to the paper

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				personalized embryo transfer after a failed transfer attempt was associated with a lower cumulative and per-transfer live birth rate during donor and autologous cycles. Fertil Steril 2022;118: 724–36.	
171	Carlos Calhaz-Jorge		301	I suggest to remove the word “principal” in “The principal mechanisms underlying …”. It implies that we know the non-principal mechanisms, which is not true.	This was corrected in the text
67	Baris Ata	12	325	The Simon et al. 2020 study reported that p_ET would be beneficial “only” in the per protocol analysis, not “particularly”. Though English is not my first language, but feels like a difference exists between the two.	This was corrected in the text
118	Carmen Rubio	11	301-303	It is mentioned that Receptivity is a very complex process and that it is unlikely that just one test could provide sufficient insight for clinical use. However, Endometrial Receptivity tests are not intended to assess the entire receptivity process, but instead determines WOI displacements, hence addressing one process related with Receptivity and Implantation., This does not imply that other tests, evaluating other factors (miRNA, metabolic, microbiome…etc) could complete the endometrial evaluation.	We have added a sentence reading "It cannot be excluded that in future a more comprehensive assessment of endometrial receptivity through a combination of tests may show to be of benefit in the context of RIF {Hernández-Vargas, 2020 #563}". We have added that assessment of specific aspects of endometrial function by testing can be considered.
119	Carmen Rubio	11	317-320	Conclusions extracted from Liu et al., 2022 publication are wrong. In the text it is mentioned that “In this patient population, comparable ongoing pregnancy rate (OPR)/LBR was found between patients undergoing personalised embryo transfer (p-ET) with endometrial receptivity testing and those with routine ET (40.7% vs. 49.6%; OR 0.94; 95% CI 0.70 to 1.26; 6 studies; n=2552) (Liu, et al., 2022)”. However, this is not what the paper from Liu states. The Liu meta-analysis compared clinical outcome with pET in patients that had Non-receptive results and with pET in patients that had Receptive results. This suggests that in both groups ERA was performed, but in one of them it was necessary to adjust progesterone exposure duration and in the other it was not necessary because the patients were already Receptive. Thus, this is not standard ET, since standard ET would be to transfer without knowing if the endometrium is Receptive or not. Moreover, the other conclusion from this study was not mentioned, which is that the RIF population using ERA achieved similar outcomes compared to good prognosis patients (especially, those good prognosis patients that used ERA, being superior to those non-ERA patients, although not significant) which is not commonly expected, as RIF patients generally have poorer outcome rates than good prognosis patients.	We have double-checked and amended the results for the Liu paper

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120	Carmen Rubio	11-12	321-325	Two papers were mentioned that did not study specifically the RIF population, which is the topic of these guidelines and the target population for Endometrial Receptivity tests (as a proportion of relevant WOI displacement is larger in the RIF population). Thus, not finding a benefit in a non-RIF population, should not be an argument to not recommend these tests to the RIF population.	In the absence of specific studies in RIF patients (whatever was the previous definition of RIF, that we claimed here as being biased), the benefit on the prediction of implantation in general was considered as the main outcome. We have added a sentence in the methods section to clarify this.
121	Carmen Rubio	12	326 - 328	It is mentioned that there is not enough evidence supporting Endometrial Receptivity testing, however there are only three papers referenced in this section (two of which were performed in good prognosis patients). With that said, there are more than 30 papers demonstrating the benefit of testing Endometrial Receptivity in different populations. Indeed, there are two recent publications specifically studying the RIF population: Jia et al 2022 compared RIF patients with and without endometrial receptivity testing, finding that the former significantly increased the reproductive outcome. In addition, Rose 2022, demonstrated how patients with several implantation failures, get pregnant at higher rates, and with increased LBR when adjusting the progesterone timing according to Endometrial Receptivity evaluation. Here are some of the publications demonstrating how RIF patients have obtained good clinical outcome rates after personalising the embryo transfer based on Endometrial Receptivity evaluation: The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. Ruiz-Alonso M, Blesa D, Díaz-Gimeno P, Gómez E, Fernández-Sánchez M, Carranza F, Carrera J, Vilella F, Pellicer A, Simón C. Fertil Steril. 2013 Sep;100(3):818-24. What a difference two days make: "personalized" embryo transfer (pET) paradigm: a case report and pilot study. Ruiz-Alonso M, Galindo N, Pellicer A, Simón C. Hum Reprod. 2014 Jun;29(6):1244-7. Endometrial receptivity array: Clinical application. Mahajan N. J Hum Reprod Sci. 2015 Jul-Sep;8(3):121-9. Efficacy of the endometrial receptivity array for repeated implantation failure in Japan: A retrospective, two-centers study. Hashimoto T, Koizumi M, Doshida M, Toya M, Sagara E, Oka N, Nakajo Y, Aono N, Igarashi H, Kyono K. Reprod Med Biol. 2017 Jun 27;16(3):290-	Based on the comment from this reviewer and others indicating a possible value we have added that assessment of specific aspects of endometrial function by testing can be considered.

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				296. Personalized Embryo Transfer Helps in Improving In vitro Fertilization/ICSI Outcomes in Patients with Recurrent Implantation Failure. Patel JA, Patel AJ, Banker JM, Shah SI, Banker MR. J Hum Reprod Sci. 2019; 12(1):59-66. Why results of endometrial receptivity assay testing should not be discounted in recurrent implantation failure? Simrandeep K., Padmaja N. The Onco Fertility Journal. 2019; 2(1): 46-49. The Reproductive Outcomes for the Infertile Patients with Recurrent Implantation failures May be improved by Endometrial Receptivity Array Test. Ota, T., Funabiki, M., Tada, Y., Karita, M., Hayashi, T., Maeda, K. et al. Journal of Medical Cases. 2019; 10(5), 138-140. Does personalized embryo transfer based on ERA improve the outcomes in patients with thin endometrium and RIF in Self Versus Donor Programme? Selvaraj P, Selvaraj K, Sivakumar M, Chandrasekar H, Srinivasan V. Journal of Gynecological Research and Obsterics, 6(3), 076-080. Evaluation of Pregnancy Outcomes of Vitrified-Warmed Blastocyst Transfer before and after Endometrial Receptivity Analysis in Identical Patients with Recurrent Implantation Failure. Kasahara Y, Hashimoto T, Yokomizo R, Takeshige Y, Yoshinaga K, Toya M. et al Fertility & Reproduction. 2020; 3(2):35-41. Role of endometrial receptivity array in current implantation failure. Samadhiya R, Swarnkar G, Singh A, Chittawar P. Fertility Science and Research, 8(2), 180. Comparison of the Effectiveness of Endometrial Receptivity Analysis (ERA) to Guide Personalized Embryo Transfer with Conventional Frozen Embryo Transfer in 281 Chinese Women with Recurrent Implantation Failure. Jia Y, Sha Y, Qiu Z, Guo Y, Tan A, Huang Y. et al. Med Sci Monit. 2022;28:e935634. Identifying women with a narrow window of embryo implantation using the endometrial receptivity assay. Rose B. International Journal of Clinical Obstetrics and Gynaecology 2022; 6(3): 52-54.	
158	Georgi Stamenov	11		Endometrial receptivity : There are many options to determine the implantation window (histological and transcriptomic strategies) in order to personalize embryo transfer according to the exact moment of the window, according to literature. A number of studies have shown the importance of endometrial dating for implantation success, such as:	Based on the comment from this reviewer and others indicating a possible value we have added that assessment of specific aspects of endometrial function by testing can be considered.

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				• RCT showing a significant improvement in pregnancy rates at the first and cumulative rates up to 12 months, and implantation rates at the first attempt after using ERA test to diagnose the endometrial factor in the work-up of the infertile couple - Simón C, Gómez C, Cabanillas S, Vladimirov I, Castillón G, Giles J, Boynukalin K, Findikli N, Bahçeci M, Ortega I, Vidal C, Funabiki M, Izquierdo A, López L, Portela S, Frantz N, Kulmann M, Taguchi S, Labarta E, Colucci F, Mackens S, Santamaría X, Muñoz E, Barrera S, García-Velasco JA, Fernández M, Ferrando M, Ruiz M, Mol BW, Valbuena D; ERA-RCT Study Consortium Group. A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. Reprod Biomed Online. 2020 Sep;41(3):402-415. doi: 10.1016/j.rbmo.2020.06.002. Epub 2020 Jun 15. PMID: 32723696. • Meta-analysis showing no significant improvement in IVF outcomes except in the LBR for patients undergoing the first IVF cycle - Huy Phuong Tran, Thuy Thi-Thanh Tran, Ly Thi Le, Bao The Pham, Sang Ngoc-Thanh Vu, Loc Thai Ly, Tuyet Thi-Diem Hoang, The impact of an endometrial receptivity array on personalizing embryo transfer for patients with infertility: a meta-analysis, F&S Reviews, Volume 3, Issue 3, 2022, Pages 157-173, ISSN 2666-5719, https://doi.org/10.1016/j.xfnr.2022.06.002. • Meta-analysis showing that non-receptive patients with RIF of endometrial origin could benefit from pET after ERA test - Liu Z, Liu X, Wang M, Zhao H, He S, Lai S, Qu Q, Wang X, Zhao D, Bao H. The Clinical Efficacy of Personalized Embryo Transfer Guided by the Endometrial Receptivity Array/Analysis on IVF/ICSI Outcomes: A Systematic Review and Meta-Analysis. Front Physiol. 2022 Apr 27;13:841437. doi: 10.3389/fphys.2022.841437. PMID: 35574479; PMCID: PMC9092494. • Study on ER Map for the identification of cases of WOI displacement and personalised embryo transfer scheduling is an effective strategy for improving ART outcomes - Enciso, M., Aizpurua, J., Rodríguez-Estrada, B. et al. The precise determination of the window of implantation significantly improves ART outcomes. Sci Rep 11, 13420 (2021). https://doi.org/10.1038/s41598-021-92955-w • Study on increased percentage in WOI displacement in RIF patients compared with good-prognosis patients and proposing pFET as a treatment strategy - Li Y, Li XF, Liao JN, Fan XX, Hu YB, Gan R, Lu G, Lin G, Gong F. Clinical value of histologic endometrial dating for personalized frozen-thawed embryo transfer in patients with repeated implantation failure in natural cycles. BMC Pregnancy Childbirth. 2020 Sep 11;20(1):527. doi: 10.1186/s12884-020-03217-y. PMID: 32917168; PMCID: PMC7488450.	

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				• Study showing significantly improved pregnancy outcomes in patients with RIF - He, A., Zou, Y., Wan, C. et al. The role of transcriptomic biomarkers of endometrial receptivity in personalized embryo transfer for patients with repeated implantation failure. J Transl Med 19, 176 (2021). https://doi.org/10.1186/s12967-021-02837-y • Study showing that pET guided by ERA in patients of RIF with displaced WOI improves IRs and OPRs - Patel JA, Patel AJ, Banker JM, Shah SI, Banker MR. Personalized Embryo Transfer Helps in Improving In vitro Fertilization/ICSI Outcomes in Patients with Recurrent Implantation Failure. J Hum Reprod Sci. 2019 Jan-Mar;12(1):59-66. doi: 10.4103/jhrs.JHRS_74_18. PMID: 31007469; PMCID: PMC6472200. • Study showing that the histologic endometrial dating of RIF patients in natural cycles may be a biomarker for a receptive endometrium in diagnosing WOI displacement. - Li, Y., Li, X.f., Liao, J.n. et al. Clinical value of histologic endometrial dating for personalized frozen-thawed embryo transfer in patients with repeated implantation failure in natural cycles. BMC Pregnancy Childbirth 20, 527 (2020). https://doi.org/10.1186/s12884-020-03217-y • Study showing that each woman has her own individual maturation rate to reach the receptive window of implantation, and this stage should be matched with timing of embryo transfers. - Alfer J, Fattahi A, Bleisinger N, Krieg J, Behrens R, Dittrich R, Beckmann MW, Hartmann A, Classen-Linke I, Popovici RM. Endometrial Dating Method Detects Individual Maturation Sequences During the Secretory Phase. In Vivo. 2020 Jul-Aug;34(4):1951-1963. doi: 10.21873/invivo.11992. Erratum in: In Vivo. 2020 Sep-Oct;34(5):3055. PMID: 32606167; PMCID: PMC7439867. In all these studies, clinical trials, reviews and meta-analyses, the bottom line is the same – we need to find an approach to dating the implantation window because women with failed implantation can benefit from it. And as it is proposed to find a model for predicting the probability of success after embryo transfer on line 144, we should take advantage of the published data, the European IVF monitoring data collection, or the ART centers' own data to use their own approach and apply own reference values to determine the exact timing of endometrial receptivity.	
122	Carmen Rubio	12		Given all the evidence above, properly referenced, it should be considered to modify the statement for Endometrial Receptivity tests to: Endometrial Receptivity testing can be considered in RIF populations.	Based on the comment from this reviewer and others indicating a possible value we have added that assessment of specific

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					aspects of endometrial function by testing can be considered.
159	Georgi Stamenov			• Study showing significantly improved pregnancy outcomes in patients with RIF - He, A., Zou, Y., Wan, C. et al. The role of transcriptomic biomarkers of endometrial receptivity in personalized embryo transfer for patients with repeated implantation failure. J Transl Med 19, 176 (2021). https://doi.org/10.1186/s12967-021-02837-y • Study showing that pET guided by ERA in patients of RIF with displaced WOI improves IRs and OPRs - Patel JA, Patel AJ, Banker JM, Shah SI, Banker MR. Personalized Embryo Transfer Helps in Improving In vitro Fertilization/ICSI Outcomes in Patients with Recurrent Implantation Failure. J Hum Reprod Sci. 2019 Jan-Mar;12(1):59-66. doi: 10.4103/jhrs.JHRS_74_18. PMID: 31007469; PMCID: PMC6472200. • Study showing that the histologic endometrial dating of RIF patients in natural cycles may be a biomarker for a receptive endometrium in diagnosing WOI displacement. - Li, Y., Li, X.f., Liao, J.n. et al. Clinical value of histologic endometrial dating for personalized frozen-thawed embryo transfer in patients with repeated implantation failure in natural cycles. BMC Pregnancy Childbirth 20, 527 (2020). https://doi.org/10.1186/s12884-020-03217-y • Study showing that each woman has her own individual maturation rate to reach the receptive window of implantation, and this stage should be matched with timing of embryo transfers. - Alfer J, Fattahi A, Bleisinger N, Krieg J, Behrens R, Dittrich R, Beckmann MW, Hartmann A, Classen-Linke I, Popovici RM. Endometrial Dating Method Detects Individual Maturation Sequences During the Secretory Phase. In Vivo. 2020 Jul-Aug;34(4):1951-1963. doi: 10.21873/invivo.11992. Erratum in: In Vivo. 2020 Sep-Oct;34(5):3055. PMID: 32606167; PMCID: PMC7439867. In all these studies, clinical trials, reviews and meta-analyses, the bottom line is the same – we need to find an approach to dating the implantation window because women with failed implantation can benefit from it. And as it is proposed to find a model for predicting the probability of success after embryo transfer on line 144, we should take advantage of the published data, the European IVF monitoring data collection, or the ART centers' own data to use their own approach and apply own reference values to determine the exact timing of endometrial receptivity.	Based on the comment from this reviewer and others indicating a possible value we have added that assessment of specific aspects of endometrial function by testing can be considered.
92	Dietmar Spitzer Maximilian		335	Investigating chronic endometritis. It is correctly stated that chronic endometritis (CE) seems to be routinely investigated in	We have added the suggested reviews on CE treatment and expanded the information on

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	Murtinger Maximilian Schuff			clinical practice, even there is a lack of standardization. First, while there were many (even contradictory) postulations how CE might influence endometrial receptivity and implantation process – the lack robust studies must not be neglected. Second, the huge variations in staining techniques and the lack of a consensus (HE, CD138; CD 38, see Margulies et al, 2021) are an important source of error. The is most probably reflected in broad variances of CE prevalence (Murtinger et al, 2022; Huang et al, 2020). The diagnostic criteria of a sole plama cell per hpf is rather questionable. It is not unequivocally clear whether few PC cells can be found in the endometrium of healthy women (Achilles et al, 2005) nor if their presence is cycle depended (Ryan et al, 2022). Interestingly, while the prevalence of CE seems to by high be histological evaluation, in the clinical practice of hysteroscopy the classical sings of CE (i.e., diffuse micropolyps, stromal edema, focal hyperemia, strawberry aspect, and endometrial hemorrhagic spots) are rare. In general, the use of plasma cells as a sole diagnostic criterion without the hysteroscopy-based for CE should at least be scrutinised. In regard to the CE therapy-it should be mentioned that there is also no consensus in application of CE (route of application, dose, duration, combination of different antibiotics) and, the huge deviation in cure rates. The citation of Vitagliano et al., 2018 for higher LBR/oPR should be countered by other critical meta-analysis which do not see a clear advantage of application of antibiotics. (Cheng et al, 2022; Kato et al, 2022). The risk of side effects of application of broad and long-term antibiotic regimens should be mentioned as well.	the diagnosis. We also included a general conclusion on that any conclusions regarding the diagnosis and treatment of endometritis are significantly hampered by the lack of standardisation, and therefore investigation and treatment of chronic endometritis can merely be considered in RIF, not recommended.
15	Tansu Kucuk	12	340	Endometritis can also be detected using methylene blue dying of endometrium during hysteroscopy (chromohysteroscopy) (Kucuk T, Safali M. Chromohysteroscopy for evaluation of endometrium in recurrent in vitro fertilization failure. J Assist Reprod Genet, 2008; 25:79-82).	We have added chromohysteroscopy to the list of diagnostic tests for endometritis.
125	Carmen Rubio	12	346	Doxycycline is not effective against all pathogens that could cause chronic inflammation (e.g. Gardnerella, Klebsiella, Enterobacter, Enterococcus, ...). The best option for treating chronic endometritis is to determine the bacterium/bacteria causing the pathology and establish a specific therapy based on antibiotics effective against the targeted bacteria. In that way, we not only decrease the probabilities of a failure with the chosen treatment, but also avoid creating new antibiotic resistances.	We have removed "doxycycline" as it was only included as an example. The topics of appropriate antibiotic selection and antibiotic resistance are outside the scope of this paper.

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123	Carmen Rubio	12	339 - 340	Not only can chronic endometritis be diagnosed by hysteroscopy, hematoxylin and eosins (H&E) staining as well as CD138-labelling, but also by performing a bacterial culture or using molecular techniques such as PCR, RT-PCR and NGS. Bacterial culture has the limitation of not being able to isolate some pathogens that are difficult to grow under standard culture conditions. Molecular techniques, on the other hand, are able to detect and identify both culturable and non-culturable microorganisms. Moreno I, Cicinelli E, Garcia-Grau I, Gonzalez-Monfort M, Bau D, Vilella F, et al. The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology. Am J Obstet Gynecol. 2018;218(6):602.e1–602.e16.	We have added bacterial culture and molecular techniques to the list of diagnostic tests for endometritis.
124	Carmen Rubio	12	342 - 344	Effectively there is a lack of standardization regarding the concentration of plasma cells but also, there are additional limitations of histology: (1) dependence on the piece of endometrial sample analyzed (2) variability of staining (3) observer experience (4) phase of the menstrual cycle in which the sample was collected Punnonen R, Lehtinen M, Teisala K, et al. The relation between serum sex steroid levels and plasma cell infiltrates in endometritis. Arch Gynecol Obstet 1989;244:185-91)	We have added a comment on the limitations of histology as a diagnostic tests for endometritis.
68	Baris Ata	12		Assessment of chronic endometritis : Would you be able to recommend criteria for the diagnosis of CE? If not how is the reader supposed to test for it?	As there is no standardised approach for CE diagnosis, it was not feasible to detail a suggested approach and advising on this was considered to be beyond the scope of this paper. We did extend the information on the diagnostic approaches used in clinical practice. On this, we want to point out that we suggest to consider investigation and treatment of chronic endometritis in RIF, but it is not recommended.
42	Marco Sbracia	12	335 / rec 11	About the role of chronic endometritis in RIF there are different point of view about it. A recent paper of Vitigliano A et al 2022 and Cheng X et al 2022, reported effects only in particular cases and no for all. Furthermore, it is not already clear how perform diagnosis and the cut off for plasma cells needed to diagnose it. So, the conclusion of Good Practice in RIF statement is quite risky, and again do not say it "seems to be routinely	We have added the suggested reviews on CE treatment and expanded the information on the diagnosis. We also included a general conclusion on that any conclusions regarding the diagnosis and treatment of

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				investigate in clinical practice" (line 341): in case it is routinely used send patients to Lourdes it justified do that? Just to know. Please report that it is a problem no well substantiated by scientific evidences and it may be considered only for study purposes.	endometritis are significantly hampered by the lack of standardisation, and therefore investigation and treatment of chronic endometritis can merely be considered in RIF, not recommended.
172	Carlos Calhaz-Jorge	12		Recommendation chronic endometritis "A standardised diagnostic procedure for…". The previous text refers only to the lack of standardization in histologic criteria. Should the recommendation state "A standardised diagnostic criteria for…" or is there anything else that I didn't get?	There is a need for standardisation in the histology tests, but there are also other tests used and reported on in the literature, so the test in clinical practice is problematic, but also making conclusions on CE (due to different tests used).
126	Carmen Rubio	12		Despite agreeing with the statement, we consider that the new molecular techniques should be taken into consideration for Chronic Endometritis diagnosis. These techniques are based on the detection of DNA and therefore, offer an objective result and are able of detect and identify culturable and non-culturable pathogens, allowing clinicians to choose the best treatment against the identified pathogen/s instead of using broad-spectrum antibiotics.	In follow up of this comments, we have made reference to the DNA based techniques, but we consider more research on those techniques is needed before they can be described as the gold standard means for CE testing in RIF
127	Carmen Rubio	12		Given all the evidence above, properly referenced, and the fact that the authors referenced that clinicians are using CE study in 85% of cases, it should be considered to modify the statement for Assessment for chronic endometritis and specific antibiotic treatment should be considered in the RIF population.	We have added a more detailed justification on why CE testing is to be considered rather than being recommended.
173	Carlos Calhaz-Jorge	13	356	I guess that EMT<7 should EMT ≤7. Please check	The study of Liao 2021 uses <7mm and >7mm (or 7-14mm). Therefore, the text is correct, even if this seems inconsistent with the sentence above
129	Carmen Rubio	13	389	In the study performed by Franasiak, et al., 2016, the samples analyzed were the tips of catheters used during the embryo transfer. This entails very small samples of endometrial fluid taken in only 33 patients tested. In the most recent study of Moreno et al., Microbiome 2022, the findings from the analysis of the endometrial liquids and biopsies taken from 342 infertile patients asymptomatic for infection and undergoing assisted reproductive treatments, indicated that the endometrial microbiota composition before embryo transfer is a useful biomarker to predict reproductive outcome, offering an opportunity to further improve diagnosis and treatment strategies.	As a relevant recent study on the topic, we have included the study by Moreno et al in the paper. We also kept the study by Franasiak, even if we understand the reviewer has some methodological concerns on this study.

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				They conclude that the presence of pathogenic bacteria such as Atopobium, Bifidobacterium, Chryseobacterium, Gardnerella, Haemophilus, Klebsiella, Neisseria, Staphylococcus and Streptococcus in the endometrium together with depletion of Lactobacillus spp. is associated with impaired reproductive function. These data indicate that the endometrial microbiome should be considered as a possible emerging cause of implantation failure and/or pregnancy loss. Moreno I, Garcia-Grau I, Perez-Villaroya D, Gonzalez-Monfort M, Bahçeci M, Barrionuevo MJ, Taguchi S, Puente E, Dimattina M, Lim MW, Meneghini G, Aubuchon M, Leondires M, Izquierdo A, Perez-Olgiati M, Chavez A, Seethram K, Bau D, Gomez C, Valbuena D, Vilella F, Simon C. Endometrial microbiota composition is associated with reproductive outcome in infertile patients. Microbiome. 2022 Jan 4;10(1):1. doi: 10.1186/s40168-021-01184-w. PMID: 34980280; PMCID: PMC8725275.	
128	Carmen Rubio	13	387 - 389	Other studies have demonstrated that, infertile patients undergoing IVF and who have transferred during the receptive stage, obtained significantly better reproductive outcomes (in terms of implantation, pregnancy, ongoing pregnancy and live birth rates) when the endometrium was Lactobacillus-dominated (defined as ≥ 90% or ≥ 80% Lactobacillus spp.), compared with those where it was not: Moreno I, Codoñer FM, Vilella F, Valbuena D, Martinez-Blanch JF, Jimenez-Almazán J, Alonso R, Alamá P, Remohí J, Pellicer A, Ramon D, Simon C. Evidence that the endometrial microbiota has an effect on implantation success or failure. Am J Obstet Gynecol. 2016 Dec;215(6):684-703. doi: 10.1016/j.ajog.2016.09.075. Epub 2016 Oct 4. PMID: 27717732. Kyono K, Hashimoto T, Kikuchi S, Nagai Y, Sakuraba Y. A pilot study and case reports on endometrial microbiota and pregnancy outcome: An analysis using 16S rRNA gene sequencing among IVF patients, and trial therapeutic intervention for dysbiotic endometrium. Reprod Med Biol. 2018 Oct 25;18(1):72-82. doi: 10.1002/rmb2.12250. PMID: 30655724; PMCID: PMC6332758.	We have evaluated the suggested references and added the relevant ones to the section
130	Carmen Rubio	13	387 - 392	Current evidence suggests that what might really interfere with fertility is the presence of pathogens in the uterine cavity, and not the requirement of a specific commensal taxon. This is supported by our results showing that the absence of bacteria (non-detectable samples) may also be found in association to good reproductive outcomes. In the study performed by Moreno, et al., 2022 the data obtain from endometrial biopsies and endometrial liquids of 341 infertile patients suggested that the absence of bacteria,	While the notion of the uterine cavity as a harbour for a microbiome is hotly debated, we have amended the text describing the evidence for dysbiotic microbiota and impaired reproductive function in line with the reviewer's comment

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				including Lactobacillus, does not impede implantation and reinforces the evidence supporting the role of pathogenic bacteria as a risk factor in reproduction. This is consistent with results reported by others such as Franasiak, et al., 2016, showing that the isolation of bacterial pathogens from the embryo transfer catheter tip is associated with poor IVF outcomes. Then, it could be hypothesized that the main role of Lactobacillus spp. in reproduction consists of avoiding the colonization of the uterine cavity by pathogenic bacteria. Moreno I, Garcia-Grau I, Perez-Villaroya D, Gonzalez-Monfort M, Bahçeci M, Barrionuevo MJ, Taguchi S, Puente E, Dimattina M, Lim MW, Meneghini G, Aubuchon M, Leondires M, Izquierdo A, Perez-Olgiati M, Chavez A, Seethram K, Bau D, Gomez C, Valbuena D, Vilella F, Simon C. Endometrial microbiota composition is associated with reproductive outcome in infertile patients. Microbiome. 2022 Jan 4;10(1):1. doi: 10.1186/s40168-021-01184-w. PMID: 34980280; PMCID: PMC8725275.	
131	Carmen Rubio	14	394 - 396	Some studies have reported the efficacy of using Microbiome profiling analysis tests. In a first of its kind study, a prospective cohort study consisting of 158 females with RIF (defined as at least three previous failed in vitro fertilization–embryo transfer (ET) attempts), wherein microbiome endometrial testing was suggested to all patients who had failed ET three or more times. The study group of 107 patients underwent the test before an additional transfer, while 51 patients with history of RIF continued with ET without these tests, to make up the control group. More than 50% of the patients studied had a dysbiotic endometrial microbiota. Personalized treatment recommendations based on the test results improved in vitro fertilization outcomes. Implantation rate, clinical pregnancy rate and ongoing pregnancy rate were significantly higher in the treated group compared with the control group. Moreover, broad-spectrum antibiotic treatments were avoided, reducing physical and economic burdens to the patients. Nanako Iwami, Miho Kawamata, Naoko Ozawa, Takahiro Yamamoto, Eri Watanabe, Masahito Mizuuchi, Osamu Moriwaka, Hirobumi Kamiya. Repro Health. 2020;6[1]:27-29. Abstract Review No: AR3	There is indeed a growing body of evidence suggesting that testing of the microbiota of the reproductive tract may be predictive of IVF treatment outcome , studies demonstrating the benefit of interventions to modulate it are still awaited. We have checked the additional references provided, but as we could not retrieve this and confirm it is a peer reviewed publication, the reference nor the study results were added to the text.
132	Carmen Rubio	14	398. .	It is important to add and to take into consideration the following: The Human Microbiome Project has highlighted the importance of microorganisms and their genomes in human health and disease and has brought to light the value of detecting dysbiotic	We have added an introductory sentence on the Human Microbiome Project

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				microbiomes to facilitate the improvement of clinical management. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 2012;486:207-14.	
69	Baris Ata	13		Microbiome profiling : Would you consider mentioning Sola-Leyva A, Andrés-León E, Molina NM, Terron-Camero LC, Plaza-Díaz J, Sáez-Lara MJ, Gonzalvo MC, Sánchez R, Ruíz S, Martínez L, Altmäe S. Mapping the entire functionally active endometrial microbiota. Hum Reprod. 2021 Mar 18;36(4):1021-1031. doi: 10.1093/humrep/deaa372. Which shows RNA seq based microbiome profile is very different from DNA based microbiome profile., and put it in context to strengthen the recommendation against microbiome profiling.	We have amended the text to include this information and the suggested reference
133	Carmen Rubio	14		Given all the evidence above, properly referenced, it should be considered to modify the statement for Microbiome profiling to: Microbiome profiling assessment should be considered in RIF population.	While we considered the reviewers suggestions for the evidence section, we remain with our conclusion that a number of questions remain to be addressed before the proper place of microbiome testing in the context of RIF can be ascertained. We have therefore not modified the recommendation. However, it may well be the case that sufficient evidence will be available to change this for the next update.
89	Aboubakr Mohamed Elnashar	14	409	Assessment of thyroid function is recommended (not to be considered)	We have added that while the Thyroid association recommends thyroid function assessment in the context of ART, it is not specifically recommended as a RIF investigation, as there is no evidence of a link between thyroid function and implantation failure.
52	Julian Jenkins	14	411-425	Recommend to separately consider “assessment of late follicular progesterone levels” and “assessment of mid-luteal progesterone levels” as these are separate issues. The former solely concerns endogenous progesterone production whereas for the latter exogenous progesterone therapy is of crucial importance providing opportunities for possibly beneficial, simple, therapeutic intervention.	We have amended the text and have split up the evidence for late follicular and mid-luteal progesterone level assessment, but we did not split the recommendation.

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53	Julian Jenkins	14	411-425	For “assessment of late follicular progesterone levels” minor modification to the current draft is proposed as below: In recent years there has been growing interest in the reported association between premature progesterone rises, measured around the time of triggering oocyte maturation and clinical outcomes after fresh embryo transfer. While still a topic of debate, there is a widespread view that this can lead to endometrial/embryo asynchrony, meriting delaying embryo transfer to a subsequent freeze thaw cycle (Bosch, et al., 2010, Venetis, et al., 2013). Deferred embryo transfer in cases of premature P4 elevation (Lawrenz, et al., 2018) have been shown to restore implantation rates in cohort studies. However, questions remain about the validity of published cut-off levels for individual centres as assays can vary. Local validation of cut-off P4 levels is recommended.	Thank you for rewriting the text for the section on progesterone to implement the split between late follicular and mid-luteal progesterone, We have redrafted the text in line with your suggestions
54	Julian Jenkins	14	411-425	For assessment of mid-luteal progesterone levels additional text to the current draft with minor modification is proposed as below: A Cochrane meta-analysis reported a higher live birth/ongoing pregnancy rate with progesterone compared to placebo/no treatment for luteal phase support (LPS) (5 RCT, OR 1.77, 95% CI 1.09-2.86, 642 women) (van der Linden, et al., 2015). Consistent with the possibility that absorption from the vagina may be variable between women, there is increasing evidence linking low blood P4 levels on the day of embryo transfer to poorer outcomes after fresh embryo transfer (Thomsen, et al., 2018) and after frozen embryo transfer (Alsbjerg, et al., 2018) (Labarta, et al., 2021, Lawrenz, et al., 2018). Individualized P4 administration for the latter scenario, has been shown to restore implantation rates in cohort studies (Álvarez, et al., 2021, Labarta, et al., 2021). However, questions remain about the validity of published cut-off levels for individual centres as assays can vary. Local validation of cut-off P4 levels is recommended.	Thank you for rewriting the text for the section on progesterone to implement the split between late follicular and mid-luteal progesterone, We have redrafted the text in line with your suggestions
134	Carmen Rubio	14	411-425	After red this section it looks like progesterone measures must be considered. All referred papers were in favors.	While the evidence may support the assessment of P4 levels, the working group considered a firm recommendations can not be made in view of the lack of standardisation and clearly defined P4 cut off levels hance the recommendation was stated as "can be considered".

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98	Antonio Requena Vanessa Vergara Nicolás Prados			Subclinical hypothyroidism is NOT related with implantation failure or miscarriage based in recent studies, but it IS related with neonatal cognitive development issues. It should be in the not recommended group.	We have added that while the Thyroid association recommends thyroid function assessment in the context of ART, it is not specifically recommended as a RIF investigation
175	Carlos Calhaz-Jorge	15	428	I guess “traction” should be “attraction”. Please check.	We have checked and corrected the language
151	Georgi Stamenov	16	466	In the paragraph for T lymphocytes, there is a sentence and a reference for CD56+ cells, which is probably in the wrong paragraph.	We have moved the sentence from the review of Woon 2022 to the section on NK cells
176	Carlos Calhaz-Jorge		456	I don’t understand the sentence “(See endometrial receptivity investigations).” Does it refer to “endometrial receptivity tests”?	We have checked and corrected this in the text
1	Katarzyna Jankowska			Sorry, but these recommendations are made without any knowledge of reproductive immunology. The recommendations set us back 20 years. Implantation disorders mainly result from immunological disorders, the consequence of which is endometritis (recurrent infections are one of the symptoms of immunodeficiency!), progesterone deficiency often coexists with Hashimoto's disease, because thyreoperoxidase (TPO) is present not only in the thyroid gland, but also in the cumulus oophorus eggs, and therefore anti-TPO antibodies, cause not only hypothyroidism, but also hypogonadism. Not to mention complement deficiencies (C2, C4) and many other immune disorders. I propose to invite a clinical immunologist to make a recommendation, then the percentage of implantation disorders will be much lower	We note the opinion expressed by the reviewer and understand that there are others who share these views. However an objective review of the published literature for the purposes of a guide to good practice does not identify robust evidence to support changing the advice at this time.
84	Luis Ferreira Vicente			In the draft about the RFI document I wonder if ,the decision of putting in red the trombophilia screening, should only be in red in cases where there is no other risk factors. As it is stated in the text, up to 74% of clinicians claim to investigate the existence of a thrombophilia. So, I wonder there aren’t so many clinicians wrong in taking that decision… In the text, it is assumed that it should be investigated in cases with risk factors (which are not listed).	We have amended the recommendation to stated that "Assessment of APA and APS is recommended in RIF women with additional risk factors for thrombophilia, and can be considered in women without such risk factors."

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				I believe it would be wise to consider keeping the Thrombophilia screening without risk factors in red, but add the same Thrombophilia screening with risk factors in yellow.	
60	Rukhsana Karim	18	531	Antiphospholipid screening should be included in the investigations of RIF. For Reference: Papadimitriou E, Boutzios G, Mathioudakis AG, Vlahos NF, Vlachoyiannopoulos P, Mastorakos G (2022) Presence of antiphospholipid antibodies is associated with increased implantation failure following in vitro fertilization technique and embryo transfer: A systematic review and meta-analysis. PLoS ONE 17(7): e0260759. https://doi.org/10.1371/journal.pone.0260759. Among 629 references that this systematic search yielded from Medline and Cochrane Library, a limited number of 17 studies, involving 4,075 women of reproductive age, were included in this systematic review and meta-analysis. All included studies involved women with at least two implantation failures in IVF-ET vs. either women with one successful IVF-ET or women with at least one successful spontaneous pregnancy or unselected healthy fertile women with no history of IVF-ET. We found, in this meta-analysis, that in women experiencing at least two implantation failures in IVF-ET, presence of either any type of anti-PL antibodies or anti-CL antibodies only or LA antibodies is associated with a significant 3.06, 5.06 and 5.81 RR for impaired implantation rate, respectively, as compared to women experiencing one successful IVF-ET. In addition, in women experiencing at least two implantation failures in IVF-ET, presence of either anti-CL or LA or anti-β2GPI or anti-PS antibodies is associated with a significant 13.92, 3.37, 15.04 and 164.58 RR for impaired implantation rate, respectively, as compared to women with at least one successful spontaneous pregnancy or unselected healthy fertile women with no history of IVF-ET.. The possible association of anti-PL antibodies with female infertility has been suggested since 1980s. Women with APS and women with anti-PL antibodies may present with impaired ovarian follicles reserve and more frequently with premature ovarian failure [29–31]. In guidelines, it is suggested to evaluate anti-PL antibodies in women suffering from recurrent miscarriages [5]. Similarly, in women presenting multiple implantation failures in IVF-ET, it could be suggested to measure these antibodies, in order to investigate causality and, eventually, suggest treatment when additional studies will be available.	We have added the recent review in the evidence section.
61	Rukhsana Karim	18:	538	5/138 (2,88%)????.....needs correction	The original publication by Vomstein includes in Table 4 "5/139 (2.88)". This seems in incorrection in the original study. We have

NR	Reviewer	Page	Line	Comment	Action / Reply
					kept only the percentage as to avoid confusion
95	Michael Scholtes	8		RIF is supposed to take place after transfer of a couple of viable embryos. Why is a detailed assessment of previous treatments omitted, the COH protocol, the documentation of the IVF report, where PKI´s may yield a relevant picture of the supposed quality of the embryo. Suboptimal application of stimulation, planning of the ovum pick up and processing of the punctate might diminish embryonic quality. Transport IVF, still being very popular in the Netherlands cannot be considered to be of interest for patients. The importance of the endometrial thickness is disproportionally stressed, the appearance also plays a role. Why is adenomyosis left out, where MRI may be helpful in diagnosing this difficult situation.	We already stated in the paper that "Focussing on couples that would be able to achieve a pregnancy through ART implies that a standardised range of investigations (the 'fertility workup') will have already been completed before the treatment process starts and that patients are deemed suitable for ART and for carrying a pregnancy. The components of the fertility workup have been previously described by ESHRE {Vlaisavljevic, 2021 #85} (Figure 1). These recommendations for good practice in RIF assume that this baseline fertility workup will already have been carried out prior to commencing ART" . We have now added that "Furthermore, focussing on couples that would be able to achieve a pregnancy through ART also implies that ART procedures are performed by fully trained and qualified personnel using state-of-the-art technology and procedures". We consider this addresses the comments of the reviewer, apart from making recommendations of an appropriate OS protocol, which is not considered feasible given the lack of supportive data for an evidence-based approach
135	Carmen Rubio	18	548 - 552	This section is focused on factors related to the embryo, however no references related to the embryo are added (line 551). We suggest including in the text the following references that refers specifically to the mitochondrial DNA content in the embryo. The reference related to the endometrium should not have been mentioned here (Eker et al,	While we have added some reference to give them credit, we consider the recent review by Podolak 2022 summarizes all relevant studies suggested by the reviewer.

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				2021). Diez-Juan A, Rubio C, Marin C, et al. Mitochondrial DNA content as a viability score in human euploid euploid embryos: less is better. Fertil Steril 2015; 104:504-41. Fragouli E, Wells D, Mitochondrial DNA assessment to determine oocyte and embryo viability. Semin Reprod Med 2015; 33:401-9. Treff NR, Zhan Y, Yao X, et al. Levels of trophectoderm mitochondrial DNA do not predict the potential of sibling embryos. Hum Reprod 2017; 32:954-62. Victor AR, Brake AJ, Tyndall JC, et al. Accurate quantitation of mitochondrial DNA reveals uniform levels in human blastocysts irrespective of ploidy, age, or implantation potential. Fertil Steril 2017; 107:34-42. Krzysztof Lukaszuk, Amira Podolak. Does Trophectoderm Mitochondrial DNA Content Affect Embryo Developmental and Implantation Potential? Int J Mol Sci. 2022 Jun; 23(11): 5976. Yi-Xuan Lee, Chi-Huang Chen, Shyr-Yeu Lin, et al. Adjusted mitochondrial DNA quantification in human embryos may not be applicable as a biomarker of implantation potential. J Assist Reprod Genet. 2019 Sep; 36(9): 1855–1865. Neelke De Munck, Alberto Liñán, Ibrahim Elkhatib, et al. mtDNA dynamics between cleavage-stage embryos and blastocysts. J Assist Reprod Genet. 2019 Sep; 36(9): 1867–1875. Amira Podolak, Izabela Woclawek-Potocka, Krzysztof Lukaszuk. The Role of Mitochondria in Human Fertility and Early Embryo Development: What Can We Learn for Clinical Application of Assessing and Improving Mitochondrial DNA? Cells. 2022 Mar; 11(5): 797. Ahmed El-Damen, Ibrahim Elkhatib, Asina Bayram, et al. Does blastocyst mitochondrial DNA content affect miscarriage rate in patients undergoing single euploid frozen embryo transfer? J Assist Reprod Genet. 2021 Mar; 38(3): 595–604. B Lledo, J A Ortiz, R Morales, et al. Comprehensive mitochondrial DNA analysis and IVF outcome. Hum Reprod Open. 2018; 2018(4): hoy023. Frank Shao-Ying Wu, Shao-Ping Weng, et al. Suboptimal trophectoderm mitochondrial DNA level is associated with delayed blastocyst development J Assist Reprod Genet. 2021 Mar; 38(3): 587–594. Licheng Ji, Tingting Liao, Juan Yang, et al. Deep sequencing shows that accumulation of potentially pathogenic mtDNA mutations rather than mtDNA copy numbers may be associated with early embryonic loss. J Assist Reprod Genet. 2020 Sep; 37(9): 2181–2188.	

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177	Carlos Calhaz-Jorge	18		Recommendation about mtDNA content : The recommendation refers only to embryo mtDNA content. However, the precedent text also refers to endometrium mtDNA. Please, consider to extend the recommendation	We have removed the information on endometrial mtDNA in the text, making the text consistent with the recommendation.
136	Carmen Rubio	19	568 - 570	We suggest including the following reference with analysis of the spent media in RIF patients. Haitao Xi, Lin Qiu, Yaxin Yao et al. Noninvasive Chromosome Screening for Evaluating the Clinical Outcomes of Patients With Recurrent Pregnancy Loss or Repeated Implantation Failure. Front Endocrinol (Lausanne) 2022; 13: 896357.	We have added this reference and a further reference on non-invasive PGT in the PGT-A section
137	Carmen Rubio	19	585 - 587	We suggest clarifying the message of the paper by Rodrigo et al., 1019, with the following modified sentence: “A retrospective case control study showed no correlation of sperm aneuploidy FISH with RIF as an independent factor, being sperm concentration the main driver of sperm aneuploidy. However, ≈24% of males with RIF having an abnormal FISH result were normozoospermic”	We have amended the text in the paper
29	Jean Calleja-Agius	20	617	This is a repetition as the need of parental karyotyping has already been discussed further up	We included this information for the male partner as well as for the female partner, but it has now been removed.
SECTION - INTERVENTIONS FOR RIF					
17	Massoud Massoud	21	645	The review concluded that endometrial injury did not increase the chances of pregnancy. This review did not consider the SCRATCH work , N E van Hoogenhuijze et al Hum Reprod . 2021 Jan 1;36(1):87-98. I think the recommendation should be amber not red	The RCT of van Hoogenhuijze et al Hum Reprod . 2021 was not included as it focussed on women with 1 previous failed IVF/ICSI treatment rather than RIF. The working group did not consider the recommendation would be changed based on the single RCT.
152	Georgi Stamenov	23	672	We found an additional meta-analysis on the G-CSF impact on the embryo implantation outcome in RIF patients that concludes that “G-CSF treatment improved the clinical pregnancy rate” in RIF patients. Hou, Z., Jiang, F., Yang, J. et al. What is the impact of granulocyte colony-stimulating factor (G-CSF) in subcutaneous injection or intrauterine infusion and during both the fresh and frozen embryo transfer cycles on recurrent implantation failure: a systematic review and meta-analysis? Reprod Biol Endocrinol 19, 125 (2021). https://doi.org/10.1186/s12958-021-00810-4	We have amended the text to include this second recent meta-analysis

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153	Georgi Stamenov	23	680	There is a systematic review showing that G-CSF seems safe and well-tolerated in cancer patients: Lapidari P, Vaz-Luis I, Di Meglio A. Side effects of using granulocyte-colony stimulating factors as prophylaxis of febrile neutropenia in cancer patients: A systematic review. Crit Rev Oncol Hematol. 2021 Jan;157:103193. doi: 10.1016/j.critrevonc.2020.103193. Epub 2020 Dec 10. PMID: 33309891.	We take note of the suggestion from the reviewer, but do not consider it would be appropriate to make a comment that G-CSF treatment is well-tolerated based on a data from a non-comparable patient population
43	Marco Sbracia	22	657 / rec 12	Figure 5 is misleading and there are several inaccuracies, in the items recommended, can be considered or not recommended. PGT-A is a screening test (such as reported by T) and no an intervention. Considering it an intervention or a treatment is false and it is possible to see a severe conflict of interests on this affirmation by several guideline extenders. So, remove PGT-A from interventions. Furthermore, chronic endometritis and antibiotics treatment for it is totally incorrect at the light of more recent data. Furthermore, again the same conflict of interest may be observed for HCG intrauterine infusion, that none reports have showed be useful in these cases. The most recent papers showed no utility at all. Figure 5 should be presented, after extensive modifications, at the end of the interventions evaluated.	While PGT-A is indeed a test, it is conducted on the embryos and may have clinical implications on the IVF treatment. After discussion, we therefore elected to consider it to be an intervention during IVF and not an investigation on the couple. We have amended the figure to reflect the final list of recommendations, and added that it is to be considered a summary with more details on the interventions discussed and the reason why they are recommended or not in the body of the paper.
44	Marco Sbracia	23	661/ rec 13	About the use of G-CSF in RIF cases: How did the authors make the affirmation about subcutaneous administration statement: they did not report any data about it, and conversely a metanalysis by Busnelli et al 2021 showed a positive effect of subcutaneous treatment. So, the authors should explain their affirmation about its role in RIF from the "good practice statement." Even though may be justified the negative evaluation of intrauterine infusion of G-CSF, as well as all intrauterine treatments including hCG instillation, since they may have a negative impact on endometrium and may be determine iatrogenic lesions, the subcutaneous G-CSF infusion at the light of published data may have a role in selected cases.	We have added more details to the evidence section, and a justification for the recommendation reading "Overall, there is conflicting evidence on whether intrauterine G-CSF administration improves LBR in patients with RIF. For subcutaneous G-CSF administration, it was considered that prior to a possible recommendation for clinical practice, the possible benefit in terms of pregnancy rates in RIF patients needs further corroboration, both in terms of follow-up to live birth and safety aspects."
180	Carlos Calhaz-Jorge	23		Recommendation about G-CSF administration : Although the administration is not recommended, all the descriptive precedent text seems to show positive results of its	We have added a justification for the recommendation reading "Overall, there is conflicting evidence on whether intrauterine

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				use. I suggest to include some additional sentence that makes clear the reasoning for "non-recommended"	G-CSF administration improves LBR in patients with RIF. For subcutaneous G-CSF administration, it was considered that prior to a possible recommendation for clinical practice, the possible benefit in terms of pregnancy rates in RIF patients needs further corroboration, both in terms of follow-up to live birth and safety aspects."
102	Yezhou Yang XiaoYong Qiao	23	685	Few RCTs evaluated the effectiveness of lipid infusions during ART in RIF patients. A systematic review and meta-analysis, including 5 RCTs totalling 843 patients, reported a higher clinical pregnancy (172/417 vs. 119/426; RR 1.55; 95% CI 1.16 to 2.07; I^2=44.2%) and LBR (132/417 vs. 73/426; RR 1.83; 95% CI 1.42 to 2.35; 687 I^2=0%) with intervention (Rimmer, et al., 2021).	we have adapted the text as was recommended
21	Anastasia Salame	23	681-696	The data presented seemed to be in favor of the intervention however the conclusion was against. The recommendation conclusion was based on what? The side effects of the intervention or something else? This needs to be clarified.	We have amended the text to be consistent with the recommendation of not recommending intravenous lipid infusion
70	Baris Ata	23		Intravenous lipid infusion : While I am not convinced in the effectiveness of iv lipid and would agree with the recommendation against it, the text cites studies suggesting benefit, and the recommendation does not sound justified by the text. Would you consider elaborating more on your justification for the recommendation against iv lipid. I worry that the same applies to recommendations on IVIG, PBMC and PRP. More detailed justification can be more convincing for the reader.	The reviewer makes a fair point and we have revised the text to avoid the possible confusion he highlights. We have amended the text to be consistent with the recommendation of not recommending intravenous lipid infusion
181	Carlos Calhaz-Jorge	23		Recommendation about Intravenous lipid infusion : Although the administration is not recommended, all the descriptive precedent text seems to show positive results of its use. I suggest to include some additional sentence that makes clear the reasoning for "non-recommended"	We have amended the text to be consistent with the recommendation of not recommending intravenous lipid infusion
22	Anastasia Salame	24	697-711	The data presented seemed to be in favor of the intervention however the conclusion was against. The recommendation conclusion was based on what? The side effects of the intervention or something else? This needs to be clarified.	The text states that the data are based on observational data only, small populations, side effects have been reported and ethical concerns raised. These factors support the decision for not recommending IVIG
182	Carlos Calhaz-Jorge	24		Recommendation about Intravenous IG : Although the administration is not recommended, all the descriptive precedent text seems to show positive results of its	The text states that the data are based on observational data only, small populations,

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				use. I suggest to include some additional sentence that makes clear the reasoning for "non-recommended"	side effects have been reported and ethical concerns raised. These factors support the decision for not recommending IVIG
191	Timur Gürgan Antonios S. Makrigiannakis	24	713	The idea of autologous HCG-primed PBMC intra-uterine administration has been previously described by Yoshioka et al, 2006. The improved reproductive outcomes were attributed to the possible immune modulation as a result of the local inflammation triggered by the PBMCs on the endometrium. Since then, several approaches have been proposed with the method being used in different versions: autologous PBMCs were inserted either primed or unprimed. In case of primed PBMCs, apart from HCG, CRH has also been used with significant results (Eur J Clin Invest. 2019 May;49(5):e13084, Eur J Clin Invest. 2015 Apr;45(4):380-4, Zygote 2019 Aug;27(4):214-218). The method has been described as effective in both fresh and frozen cycles after transfer of both cleavage embryos or blastocysts. The recent evidence stemming from systematic reviews and meta-analyses is supportive on the clinical application of PBMCs as an add-on to improve reproductive outcomes (Sci Rep 2022 Nov 1;12(1):18434, J Reprod Immunol 2021 Jun;145:103323, Sci Rep 2021 Jan 18;11(1):1747, Front Cell Dev Biol. 2021 Mar 16;9:613277).	We consider the text "Other meta-analysis including the same dataset have been published. However, the study populations are small and the definitions for RIF inconsistent. Furthermore, techniques to prepare PBMC differed substantially between studies (co-cultured in the presence of HCG, CRH, HMG, a mixture of fresh and co-cultured PBMC). " covers the comment of the reviewer
154	Georgi Stamenov	24	715	The rationale behind the therapeutic effect of PBMC has been tested in in vivo studies on mice: Yu N, Yang J, Guo Y, Fang J, Yin T, Luo J, Li X, Li W, Zhao Q, Zou Y, Xu W. Intrauterine administration of peripheral blood mononuclear cells (PBMCs) improves endometrial receptivity in mice with embryonic implantation dysfunction. Am J Reprod Immunol. 2014 Jan;71(1):24-33. doi: 10.1111/aji.12150. Epub 2013 Aug 1. PMID: 23909917. Fan L, Sha M, Li W, Kang Q, Wu J, Chen S, Yu N. Intrauterine administration of peripheral blood mononuclear cells (PBMCs) improves embryo implantation in mice by regulating local Treg/Th17 cell balance. J Reprod Dev. 2021 Dec 14;67(6):359-368. doi: 10.1262/jrd.2021-006. Epub 2021 Oct 7. PMID: 34615838; PMCID: PMC8668375.	We have removed the sentence that there are no in vivo studies, and added the 2 refs to the text.
155	Georgi Stamenov	24	716	We may add some other meta-analyses with positive results regarding PBMC administration in RIF patients like: Yang DN, Wu JH, Geng L, Cao LJ, Zhang QJ, Luo JQ, Kallen A, Hou ZH, Qian WP, Shi Y, Xia X. Efficacy of intrauterine perfusion of peripheral blood mononuclear cells (PBMC) for infertile women before embryo transfer: meta-analysis. J Obstet Gynaecol. 2020 Oct;40(7):961-968. doi: 10.1080/01443615.2019.1673711. Epub 2019 Dec 3. PMID: 31791175. Qin Q, Chang H, Zhou S, Zhang S, Yuan D, Yu LL, Qu T. Intrauterine administration of	We have investigated the suggested references, but the studies included in those reviews are all already included in the review by Maleki-Hajiagha, 2019 and the studies listed as more recent. Therefore adding the reference is of little relevance.

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				peripheral blood mononuclear cells activated by human chorionic gonadotropin in patients with repeated implantation failure: A meta-analysis. J Reprod Immunol. 2021 Jun;145:103323. doi: 10.1016/j.jri.2021.103323. Epub 2021 Apr 15. PMID: 33878637. Liu, M., Yuan, Y., Qiao, Y. et al. The effectiveness of immunomodulatory therapies for patients with repeated implantation failure: a systematic review and network meta-analysis. Sci Rep 12, 18434 (2022). https://doi.org/10.1038/s41598-022-21014-9	
156	Georgi Stamenov	24	719	There are other RCTs and studies confirming the positive effect of PBMC on RIF patients: RCT with 248 women included: Zahra Pourmoghadam, Mohammad Sadegh Soltani-Zangbar, Golshan Sheikhansari, Ramyar Azizi, Shadi Eghbal-Fard, Hamed Mohammadi, Homayoon Siahmansouri, Leili Aghebati-Maleki, Shahla Danaii, Amir Mehdizadeh, Mohammad Hojjat-Farsangi, Roza Motavalli, Mehdi Yousefi,Intrauterine administration of autologous hCG- activated peripheral blood mononuclear cells improves pregnancy outcomes in patients with recurrent implantation failure; A double-blind, randomized control trial study, Journal of Reproductive Immunology, Volume 142, 2020, 103182, ISSN 0165-0378, https://doi.org/10.1016/j.jri.2020.103182. RCT with 250 couples included: Nobijari, F. F. et al. Endometrium immunomodulation by intrauterine insemination administration of treated peripheral blood mononuclear cell prior frozen/thawed embryos in patients with repeated implantation failure. Zygote 27, 214–218. https://doi.org/10.1017/S0967199419000145 (2019). Study with 253 cycles included: Okitsu O, Kiyokawa M, Oda T, Miyake K, Sato Y, Fujiwara H. Intrauterine administration of autologous peripheral blood mononuclear cells increases clinical pregnancy rates in frozen/thawed embryo transfer cycles of patients with repeated implantation failure. J Reprod Immunol. 2011 Dec;92(1-2):82-7. doi: 10.1016/j.jri.2011.07.001. Epub 2011 Oct 27. PMID: 22035703.	We had already included the study of Pourmoghadam 2020, and have now added the study of Nobijari 2019, Since these studies are not included in the review of Maleki-Hajiagha, 2019 it is appropriate to list them separately. The study of Okitsu 2011 is included in the review, and hence not individually listed
157	Georgi Stamenov	24	721	The study populations in the proposed studies are around 250 cycles/women while in the cited RCT and study are smaller (95 and 100 patients). We propose Intrauterine autologous blood mononuclear cells (PBMC) infusion to be considered in RIF patients.	The text includes all studies and RCTs that have been suggested by the reviewer, either in the review or separately. The working group confirms the comment on the limitations of the evidence based on all listed evidence, as well as the recommendation.
183	Carlos Calhaz-Jorge	24		Recommendation about Intrauterine autologous PMBC infusion: Although the administration is not recommended, all the descriptive precedent text seems to show	We have added a sentence to the text reading "Taken together, while a role for

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				positive results of its use. I suggest to include some additional sentence that makes clear the reasoning for “non-recommended”	PBMC in specific patients with RIF might be identified, at present their empirical use is not recommended. "
192	Timur Gürgan Antonios S. Makrigiannakis	24	727	Platelet-rich plasma has been previously used in regenerative medicine. The main concept was to take advantage of an array of growth factors secreted by platelets, modulating the local micro-environment of the targeted tissue. In that view, PRP intra-uterine administration has been introduced as an add-on in case of RIF. A series of studies has been published with promising results. Both systematic reviews and meta-analyses have demonstrated a significant improvement of reproductive outcomes in case of autologous PRP intra-uterine administration in women with RIF (Sci Rep 2022 Nov 1;12(1):18434, Sci Rep 2021 Jan 18;11(1):1747, Front Cell Dev Biol. 2021 Mar 16;9:613277). However, due to relatively small sample sizes, properly designed RCTs are needed to further clarify the impact of PRP on reproductive outcomes. Additionally, in order to reduce heterogeneity, it is imperative to establish a consensus upon the method of platelet isolation, along with the platelet concentration applied in the suggested treatment.	We have included the review of Liu 2022 in the text, but not the other suggested reviews as One of them was already included (Busnelli 2021), while the review of Makrigianakis 2021 is not a meta-analysis and it refers, for PRP data, to the review of Maleki-Hajigha 2020. We did add a sentence on the method for platelet isolation and platelet concentration, as suggested.
201	Cristina Magli	25	760	Delete “An older”	This was adapted in the text
90	Aboubakr Mohamed Elnashar	26	768	Intrauterine hCG injection can be considered in cleavage stage transfer not blastocyst transfer	We acknowledge that this is the conclusion that can be drawn from the meta-analysis cited and the text is adapted to express this.
55	Enver Kerem Dirican		751-768	intrauterine hCG administration section seems to be contradictory with GPR on Add-ons page 1260-1316	Based on this and other comments, we have amended the recommendation, which now reads "Intrauterine hCG injection is not recommended." which given the weight of supporting evidence is similar to the other therapies.
45	Marco Sbracia	25	751/ rec1 4	About the role of intrauterine infusion of hCG the extenders of these "Good Practice statement" should report the quality of the studies reported (mostly metanalysis). Furthermore, the most recent papers in literature showed that hCG infusion is not useful at all except that in case of cleavage stage embryo transfer in selected cases (Conforti a et al 2022, Jan XH et al 2022, Abdallah KS et al 2021). Consequently, the statement that “intrauterine hCG injection may be considered” should be deleted, and instead stated that all intrauterine treatments before embryo transfer should be avoided in order to no	We added the review of Conforti et al 2022, which includes the Abdallah KS et al 2021 study so the latter was not individually added. We could not find the Jan XH et al 2022 study and hence this could not be included,

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				alters the endometrium anatomy and physiology, in order avoid the introduction in uterine cavity potential infectious agents or dangerous substances for the embryo.	
184	Carlos Calhaz-Jorge	26		Recommendation about Intrauterine hCG injection : From the text I could not find a reason why this recommendation is different from the previous ones	Based on this and other comments, we have amended the recommendation, which now reads "Intrauterine hCG injection is not recommended." which given the weight of supporting evidence is similar to the other therapies.
71	Baris Ata	26		Recommendation for intrauterine hCG : How do you justify recommendation for considering hCG injection, while you seem to recommend against IV lipid, IVIG, PBMC and PRP with more or less similar evidence? Would you consider using a GRADE approach across the paper to make such decisions more transparent for the reader?	Based on this and other comments, we have amended the recommendation, which now reads "Intrauterine hCG injection is not recommended." which given the weight of supporting evidence is similar to the other therapies.
82	Elvira Grandone	26	LMWH	Other papers should be considered, analysed and discussed. Conditional recommendation to use LMWH should be given.	As the reviewer did not make any suggestions as to which papers are to be added, we did not follow up on this.
81	Elvira Grandone	26		In addition, I would like to underscore that in the Methodology authors state that Cochrane is one literature source, but the interpretation of the findings on LMWH is completely different. This can disorient the readers. Furthermore, other papers below indicated are not quoted and considered for analysis and discussion. 1) Dentali F, et al. Efficacy of low molecular weight heparin in patients undergoing in vitro fertilization or intracytoplasmic sperm injection. J Thromb Haemost. 2011 ;9(12):2503-6. This is a systematic review and meta-analysis suggesting that LMWH may be effective in increasing the rates of clinical pregnancies and live births in patients undergoing IVF or ICSI. 2) Potdar N, et al. Adjunct low-molecular-weight heparin to improve live birth rate after recurrent implantation failure: a systematic review and meta-analysis. Hum Reprod Update. 2013 Nov-Dec;19(6):674-84. In this systematic review and meta-analysis, authors analysed two RCTs and one quasi-randomized trial. One study included women with at least one thrombophilia (Qublan et al., 2008) and two studies included women with unexplained RIF (Urman et al., 2009; Berker et al., 2011). Pooled risk ratios in women with ≥ 3 RIF (N = 245) showed a significant improvement in the LBR (risk ratio (RR) = 1.79, 95%	We have included the review by Potdar. The suggested review by Dentali focusses on ART rather than RIF women and was therefore not quoted. Likewise, studies on treatment in pregnancy were not described as these are not considered appropriate for the specific context of RIF. The conclusion and recommendation are focussed on women with RIF, and LMWH treatment to achieve pregnancy which is not to be confused with LMWH treatment during pregnancy which has been covered by Cochrane reviews.

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				confidence interval (CI) = 1.10-2.90, P = 0.02) and a reduction in the miscarriage rate (RR = 0.22, 95% CI = 0.06-0.78, P = 0.02) with LMWH compared with controls. The IR for ≥ 3 RIF (N = 674) showed a non-significant trend toward improvement (RR = 1.73, 95% CI 0.98-3.03, P = 0.06) with LMWH. However, the beneficial effect of LMWH was not significant when only studies with unexplained RIF were pooled. The summary analysis for the numbers needed to be treated with LMWH showed that approximately eight women would require treatment to achieve one extra live birth. The prudent conclusion of these authors is in favour of LMWH in women with ≥3 RIF, but with caution. Indeed, the overall number of participants in the studies was small. Further evidence from adequately powered multi-centered RCTs is required prior to recommending LMWH for routine clinical use. 3) Grandone E, et al. Low-molecular -weight heparin in pregnancies after ART -a retrospective study-. Thromb Res. 2014 ;134(2):336-9. This is an observational retrospective study involving 327 women (751 cycles) showing that the use of LMWH is significantly associated with both the outcomes, clinical pregnancy (logistic regression OR: 6.0, 95%CI: 2.8-15.6) and live birth (logistic regression OR: 10.7, 95%CI: 3.2-36.1). 4) Grandone E, et al. Clinical utility of antithrombotic prophylaxis in ART procedures: an Italian experience. PLoS One. 2014 ;9(5):e97604. This is a prospective study involving 595 women (1234 cycles). The pregnancy rate was significantly increased by the use of LMWH alone (p: 0.005, OR: 2.6, 95% CI: 1.3-5.0). The efficacy of antithrombotic treatment was confirmed when the outcome " live-birth" was considered.	
46	Marco Sbracia	26	785 / rec 15	The data reported about GnRH agonist plus aromatase inhibitor are very poor and the study group should report this. Furthermore, this treatment should be restricted only patients with uterine problems, such as fibroids and adenomyosis, to reduce the extension of these anomalies. This should be reported.	We have added a sentence reading that "Taken together, while a role for GnRH agonist and aromatase inhibitor pre-treatment in specific patients with RIF might be identified, at present their empirical use is not recommended."
186	Carlos Calhaz-Jorge	27		Recommendation about GnRH agonist and aromatase inhibitor pre-treatment : Again the descriptive text seems not to support the recommendation	We have added a sentence reading that "Taken together, while a role for GnRH agonist and aromatase inhibitor pre-treatment in specific patients with RIF might be identified, at present their empirical use is not recommended."

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93	Dietmar Spitzer Maximilian Murtinger Maximilian Schuff		807	Preimplantation genetic testing for aneuploidy (PGT-A) It should be clearly stated that there is still no proven benefit for PGT-A in all IVF-patient subgroups -based on RCTs , including RIF patients (Cornelisse et al, 2020). Moreover, in fact almost all published trials include good prognosis patients. The conclusion that PGT-A could be considered a good strategy for women with RIF or Preimplantation genetic testing for aneuploidy (PGT-A) can be considered lacks any scientific basis. Moreover, we see this recommendation is too simple and most probably contraindicated for this patient clientele as PGT-A is inevitable linked to a high rate of embryo-drop-out due to non-biopsable embryos, inconclusive results or results with chromosomal mosaic constitutions of numerical or segmental chromosomal aberrations. PGT-A. It should be mentioned that PGT-A is costly procedure, and its application may need additional IVF cycles to gain as euploid diagnosed embryos for transfer -especially for the RIF patient clientele. The shortcomings and problems of PGT-A and the unfulfilled promises of PGT-A were rightly criticised by numerous publications (Gleicher et al, 2022; Gleicher et al, 2021; Gleicher et al, 2020 and many others). This should not be neglected and included in these recommendations. As a brief comment: The recommendation of „Preimplantation genetic testing for aneuploidy (PGT-A) can be considered“ in this document is somewhat detrimental to the recent EHRE draft „Good practice recommendations for add-ons in reproductive medicine“	We acknowledge the controversy around PGT-A, and the issues around the RCTs and reviews evaluating the technique. To our knowledge, there are no data available to support that PGT-A, when adopted to assess non-mosaic full-chromosome aneuploidies may impact RIF patients' chance to conceive. Nor does the list of references mentioned by the reviewer provide hard data to advise against PGT-A. Clearly, PGT-A (as any available embryo selection tool) cannot improve intrinsic embryo competence and/or patients' overall chance to conceive. Nonetheless, it does prevent the unsuccessful and potentially detrimental (i.e., miscarriages and chromosomal syndromes) transfers of aneuploid blastocysts to RIF patients. Such benefit may not be a valuable argument in all ART patients, which is the topic of the Add-ons recommendations paper. It is the conclusion of the working group that PGT-A at the blastocyst stage cannot be advised against in this specific population of patients. Therefore, we chose the "can be considered" statement meaning that it might be adopted to prevent further implantation failures imputable to aneuploid blastocyst transfers.
202	Cristina Magli	27	820	Some text missing	We have corrected the sentence
109	Tarek El-Toukhy	27	825 to 828	The recommendation for PGT-A in RIF "can be considered" seems to be based on the results of two retrospective studies, which have not even been referenced in the document, whilst not taking into account the results of the systematic review of Busnelli	We acknowledge the controversy around PGT-A, and the issues around the RCTs and reviews evaluating the technique. To our

NR	Reviewer	Page	Line	Comment	Action / Reply
				A et al, 2021 which included 2 RCTs, showing no benefit from PGT-A in this group of patients. Whilst the argument about the testing methodology and technique used (FISH vs aCGH or NGS) could be debated, there is no guideline recommendation that would be based on the results of two retrospective studies, thus defying the basis of Evidence-Based Medicine. This particular recommendation should be changed to "not recommended due to lack of sufficiently robust evidence" to avoid exposing many vulnerable RIF patients to an unproven, expensive and invasive technique if ESHRE says "can be considered". This recommendation can not, by any reasonable standard, fulfil the good clinical practice ESHRE is promoting!	knowledge, there are no data available to support that PGT-A, when adopted to assess non-mosaic full-chromosome aneuploidies may impact RIF patients' chance to conceive. Nor does the list of references mentioned by the reviewer provide hard data to advise against PGT-A. Clearly, PGT-A (as any available embryo selection tool) cannot improve intrinsic embryo competence and/or patients' overall chance to conceive. Nonetheless, it does prevent the unsuccessful and potentially detrimental (i.e., miscarriages and chromosomal syndromes) transfers of aneuploid blastocysts to RIF patients. Such benefit may not be a valuable argument in all ART patients, which is the topic of the Add-ons recommendations paper. It is the conclusion of the working group that PGT-A at the blastocyst stage cannot be advised against in this specific population of patients. Therefore, we chose the "can be considered" statement meaning that it might be adopted to prevent further implantation failures imputable to aneuploid blastocyst transfers.
138	Carmen Rubio	27	825 - 828	Add references of the two retrospective mentioned studies. We included some additional suggestions: Jing Tong, Yichao Niu, Anran Wan, Ting Zhang. Next-Generation Sequencing (NGS)-Based Preimplantation Genetic Testing for Aneuploidy (PGT-A) of Trophectoderm Biopsy for Recurrent Implantation Failure (RIF) Patients: a Retrospective Study. Reprod Sci. 2021 Jul; 28(7): 1923–1929. Jayesh Amin, Sr., Ripal Patel, Grishma JayeshAmin, et al. Personalized Embryo Transfer	We have added some relevant references to the section, including some of the ones suggested by the reviewer

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				Outcomes in Recurrent Implantation Failure Patients Following Endometrial Receptivity Array With Pre-Implantation Genetic Testing Cureus. 2022 Jun; 14(6): e26248. Tianxiang Ni, Qianqian Wu, Yueting Zhu et al. Comprehensive analysis of the associations between previous pregnancy failures and blastocyst aneuploidy as well as pregnancy outcomes after PGT-A. J Assist Reprod Genet. 2020 Mar; 37(3): 579–588.	
39	Marco Sbracia	8	217/ rec 8	In the figure 4 the summary of RIF investigations, it has been omitted the PGT-A, that instead has been included in the interventions section. It is a totally misleading statement, since also in the name (the T of PGT IS REFERRED TO A TEST), is clear that it is diagnostic test and no a treatment, especially for RIF. In the reference previously reported (Reig A et al 2020) the live birth rate is rate reported after PGT-A is around 50%	PGT-A is indeed a test conducted on the embryos and that may have clinical implications on the IVF treatment. As such, it should be considered an intervention during IVF and not an investigation on the couple
47	Marco Sbracia	27	807 / rec 16	PGT-A is not a treatment and consequently should be deleted from this section since it is a diagnostic tool and should be reserved for selected cases for counseling patients. Please, remove from this part of the guideline.	PGT-A is indeed a test conducted on the embryos and that may have clinical implications on the IVF treatment. As such, it should be considered an intervention during IVF and not an investigation on the couple
83	Elvira Grandone	27	PGT -A	On the basis of the available evidence, PGT-A cannot be recommended.	We acknowledge the controversy around PGT-A, and the issues around the RCTs and reviews evaluating the technique. To our knowledge, there are no data available to support that PGT-A, when adopted to assess non-mosaic full-chromosome aneuploidies may impact RIF patients' chance to conceive. Nor does the list of references mentioned by the reviewer provide hard data to advise against PGT-A. Clearly, PGT-A (as any available embryo selection tool) cannot improve intrinsic embryo competence and/or patients' overall chance to conceive. Nonetheless, it does prevent the unsuccessful and potentially detrimental (i.e., miscarriages and chromosomal syndromes) transfers of aneuploid blastocysts to RIF patients. Such

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					benefit may not be a valuable argument in all ART patients, which is the topic of the Add-ons recommendations paper. It is the conclusion of the working group that PGT-A at the blastocyst stage cannot be advised against in this specific population of patients. Therefore, we chose the "can be considered" statement meaning that it might be adopted to prevent further implantation failures imputable to aneuploid blastocyst transfers.
79	Fang Ma	22		If PGF-A is considered,is a normal recommened? Based of the cost and technical limitations, it's kind of controversy?	We acknowledge the controversy around PGT-A, and the issues around the RCTs and reviews evaluating the technique. To our knowledge, there are no data available to support that PGT-A, when adopted to assess non-mosaic full-chromosome aneuploidies may impact RIF patients' chance to conceive. Nor does the list of references mentioned by the reviewer provide hard data to advise against PGT-A. Clearly, PGT-A (as any available embryo selection tool) cannot improve intrinsic embryo competence and/or patients' overall chance to conceive. Nonetheless, it does prevent the unsuccessful and potentially detrimental (i.e., miscarriages and chromosomal syndromes) transfers of aneuploid blastocysts to RIF patients. Such benefit may not be a valuable argument in all ART patients, which is the topic of the Add-ons recommendations paper. It is the conclusion of the working group that

NR	Reviewer	Page	Line	Comment	Action / Reply
					PGT-A at the blastocyst stage cannot be advised against in this specific population of patients. Therefore, we chose the “can be considered” statement meaning that it might be adopted to prevent further implantation failures imputable to aneuploid blastocyst transfers.
96	Michael Scholtes	22		Basically PGT-A does not provide the help that is promised. Just meiotic aneuploidy seems to be relevant and exclusion of translocations. Mitotic aneuploidy detection results in rejection of possible viable embryos with a chance on life birth.	We acknowledge the controversy around PGT-A, and the issues around the RCTs and reviews evaluating the technique. To our knowledge, there are no data available to support that PGT-A, when adopted to assess non-mosaic full-chromosome aneuploidies may impact RIF patients’ chance to conceive. Nor does the list of references mentioned by the reviewer provide hard data to advise against PGT-A. Clearly, PGT-A (as any available embryo selection tool) cannot improve intrinsic embryo competence and/or patients’ overall chance to conceive. Nonetheless, it does prevent the unsuccessful and potentially detrimental (i.e., miscarriages and chromosomal syndromes) transfers of aneuploid blastocysts to RIF patients. Such benefit may not be a valuable argument in all ART patients, which is the topic of the Add-ons recommendations paper. It is the conclusion of the working group that PGT-A at the blastocyst stage cannot be advised against in this specific population of patients. Therefore, we chose the “can be considered” statement meaning that it might

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					be adopted to prevent further implantation failures imputable to aneuploid blastocyst transfers.
203	Cristina Magli	28	834	"BR" instead of "LBR"?	This was corrected in the text
110	Elena Kostova		834 - 836	Glujovsky, et al., 2016 was updated in 2022 (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD002118.pub6/full). Authors report "The live birth rate following fresh transfer was higher in the blastocyst-stage transfer group (odds ratio (OR) 1.27, 95% confidence interval (CI) 1.06 to 1.51; I2 = 53%; 15 studies, 2219 women; low-quality evidence)."	The reference as well as the data were amended to the newest version of the Cochrane review
204	Cristina Magli	28	836 and 838	Are the two citations about RIF?	To the best of our knowledge there are no recent studies and/or high-quality data to support blastocyst stage ET in RIF patients. The reasoning for this recommendation is based on the general concept that development to the blastocyst stage is an indication of embryo competence and therefore blastocysts transfer can be considered for RIF patients, even if it is acknowledged that there is no evidence supporting blastocyst transfer as a recommendation for all RIF patients.
23	Anastasia Salame	28	843 - 860	Despite the non supportive results of the systematic reviews, one might consider recommending AH is certain subpopulations.	We have amended the recommendation to read that "Assisted hatching is not routinely recommended".
161	Mark Larman	29	868	There are several prospective studies worth considering as they support that a high HA transfer medium improves implantation and clinical pregnancy rates for patients with previous/recurrent implantation failure. Friedler et al 2005 reported at ESHRE a prospective comparison with patients that had > 4 previous implantation failures following day 2 embryo transfer. 187 patients had transfers using either a transfer medium with no or high HA. Significantly higher implantation and clinical pregnancy rates were observed in the high HA group. Vajolerdi et al 2006 performed a RCT that included the transfer of cleavage stage embryos into patients with previous implantation failure. Over 800 embryos were	We have added a paragraph on HA supplemented ET medium, referring to data in ART patients and the only study in RIF patients, as suggested.

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				randomized between a no or high HA transfer medium. Significantly higher implantation rate was observed in the high HA group. Friedler et al 2007 performed a RCT with patients that had > 4 previous implantation failures following cleavage stage embryo transfer (day 2 and 3). 101 patients were randomized between a no or high HA transfer medium. Significantly higher implantation, clinical pregnancy rate and OPR/LBR were observed in the high HA group. Korosec et al 2007 performed a RCT that included the transfer of blastocysts into patients with previous implantation failure. was significantly higher compared to the no HA transfer medium control. Thirty-one patients were randomized between a no or high HA transfer medium. Significantly higher clinical pregnancy rate was observed in the high HA group. Urman et al 2008 performed a RCT that included the transfer of cleavage stage embryos and blastocysts into patients with previous implantation failure. As the mean number of previously failed cycles was 2.0 if it is likely that many of the patients were recurrent implantation failure patients. Around 1800 embryos/blastocysts were randomized between a low or high HA transfer medium. Significantly higher implantation and clinical pregnancy rates were observed in the high HA group with an overall NNT of 7 for clinical pregnancy. Nakagawa et al 2011 performed a RCT with 314 patients that had ≥ 4 previous implantation failures following cleavage stage embryo transfer. Fresh and frozen transfers were performed. In both groups transfer with a higher HA transfer medium significantly increased implantation and clinical pregnancy rates. Hyaluronan is a macromolecule that can vary in chain length from a few thousand to several million Daltons. EmbryoGlue contains 0.5mg/ml of a particular range of hyaluronan chain lengths. As the Cochrane studies have utilized EmbryoGlue it should be stated that other hyaluronan containing medium might not have the same efficacy. Indeed, evidence for physical difference (viscosity) between embryo transfer media was presented by Reed and Said 2019. Thus, without the equivalent level of clinical testing the efficacy of other hyaluronan transfer media remains uncertain. Therefore, high hyaluronan transfer medium should be considered for RIF patients and readers should be made aware that the clinical data reported, at this time, supports the	

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				efficacy of the particular concentration and chain length range of hyaluronan in EmbryoGlue.	
160	Mark Larman			There is one study that has reported LBR for recurrent implantation failure (Friedler et al 2007) and the high hyaluronan (HA) transfer medium resulted in significantly higher LBR compared to the no HA transfer medium control. LBR was followed up for the overall study population in the Urman et al 2008 publication as an ESHRE abstract (Balaban et al 2011). Unlike the publication the previous implantation failure subgroup was not specified, but the LBR was significantly higher compared to the low HA transfer medium control.	We have added a paragraph on HA supplemented ET medium, referring to data in ART patients and the only study in RIF patients, as suggested.
187	Carlos Calhaz-Jorge	29	874	Shouldn't the title in this line be in a different letter type and dimension? Similar to those used in line 642	The format of the heading was amended
58	Linda Stevens Brentjens	29	880	The article that is referred to (Kuroda et al.) is published in 2021, not 2020.	We have corrected the reference as suggested
139	Carmen Rubio	29	874-882	The text related here looks like this topic is recommended, then CE treated is considered here, it is contradictory not to recommend it.	To avoid confusion, the examples in the sentence were removed
150	Georgi Stamenov			After we find the specific cause of the implantation failure through different investigations, we ought to find an individualized treatment approach, avoiding conveyor-belt, one size fits all treatments. The individualized approach to each patient/couple requires individualized treatment of the specific case (already addressed through specific research into the root causes of failure). These treatments, some of which are discussed in this guideline, have already shown significantly improved results when compared with an untreated control group, and although it is possible to optimize the approaches, the goal for clinicians is to increase the chance of success after each subsequent attempt, not to wait and leave that to luck. This strategy of testing-treating has proven as successful as cited in p.29 line 877, with the results from the OPTIMUM trial. We propose to consider intrauterine autologous blood mononuclear cells (PBMC) infusion and intrauterine G-CSF administration. Also, we propose that the personalised embryo transfer, which is a successful strategy in cases with a displaced window of implantation, to be included in the recommended treatment options.	We have added a sentence reading " These data suggests that using diagnostics to assess the cause of RIF is likely to improve the efficacy of interventions which would then be applied with more rationale than at present. At present few validated tests of value in the context of RIF are available, but this is likely to change in the future. " However, we have not amended the recommendations for intrauterine autologous blood mononuclear cells (PBMC) infusion and intrauterine G-CSF administration,
188	Carlos Calhaz-Jorge		883	Maybe here something similar could be used	Assuming the comment relates to the format of the heading, we have adapted it

NR	Reviewer	Page	Line	Comment	Action / Reply
18	Xingbang Zheng	21	642	For the patients with RIF , the pelvic pathology such as endometriosis and tubal factor which contribute to the implantation failure shouldn't be ignored. Current diagnostic methods for infertility don't totally exclude the pelvic factors. It is well-known that above 50% of normal HSG patients have pelvic pathology ,mainly the endometriosis. Our team have used laparoscopy for the RIF patients for more than 10 years and find that laparoscopy can significantly improve the pregnancy outcome for the RIF patients. In a retrospective case-control study, the ongoing pregnancy rate in the laparoscopy group is significant higher than the control group(41.9% vs 19.6%, P<.05).In another retrospective cohort study (published in Chinese), we have included 72 RIF patients who received laparoscopy, the result is pregnancy rate was 63.9% （46/72） and the live birth rate was 58.3%（42/72). Another important benefit is after laparoscopy, some of the RIF patients can have the chance of natural conception. In the case-control study, among the 19 patients who choose to try natural conception, clinical pregnancy rate was 84.2% and live birth rate was 68.4%. My points are supported with other articles. Soriano et al reported a 42.3% pregnancy rate after endometriosis surgery in women with prior recurrent failed IVF management. Although these studies were not RCT studies, but they provide some unique insight for the treatment of RIF which maybe improve the treatment outcome. Please see the manuscripts in the attachments.	We have added a sentence reading that "While assessment of the presence of adenomyosis, endometriosis and submucosal fibroids should be carried our prior to IVF, if there is renewed suspicion due to emerging clinical signs or ultrasound features noted after RIF, then further investigations including MRI or diagnostic laparoscopy should be considered." More detailed information on endometriosis surgery is outside the scope of the paper. Regarding the addition of laparoscopy as an intervention for RIF, we could not find the paper referred to and hence have not added this.
101	Yezhou Yang XiaoYong Qiao	21	642	As mentioned above, treatment of abnormal uterine contractions and abnormal endometrial peristalsis can be used as a kind of treatments independent of RIF investigations, For the treatment of uterine contractions and endometrial peristalsis, many study suggested that the use of oxytocin antagonist can improve the clinical outcome of RIF patients. The result of meta-analysis suggest that the value of oxytocin antagonist play only a limited role in improving pregnancy outcomes in the general population of women undergoing IVF, and recent RCT study with small sample sizes have not demonstrated their exact effectiveness in RIF patients, however, due to the complexity and variety of causes of RIF populations, the use of oxytocin antagonist therapy may still be considered as a treatment in RIF patients.	We have considered the comment of the reviewer regarding abnormal uterine contraction and uterine peristalsis at the time of embryo transfer, but as mentioned we do not consider these to be relevant for the current paper. We have also not included Oxytocin as a relevant intervention as consider the data specifically in RIF patients are too limited to be considered a valid treatment option.
DISCUSSION					
189	Carlos Calhaz-Jorge	30	929	The word "that" is duplicated.	This was corrected in the text

NR	Reviewer	Page	Line	Comment	Action / Reply
190	Carlos Calhaz-Jorge	31	947	“will reduce homogeneity” seems not being correct. “will reduce heterogeneity” or “will increase homogeneity”, perhaps	This was corrected in the text
140	Carmen Rubio	30	937 -961	Microbiome, CE, Endometrial receptivity are not included for further research. If not recommended, at least these two approaches should be included for further research. Publications included in this document should be considered.	We have added a research recommendation on endometrial receptivity tests, CE evaluation and microbiome profiling,
51	Mitranovici Melinda Ildiko	31	951-956	As priorities for researchers you didn t mention the role of antioxidants in the enhance of endometrium, implantation and angiogenesis	We have added a research recommendation on antioxidant treatment,
GENERAL COMMENTS					
31	Marco Sbracia			The study group of these guidelines has done an enormous job in attempting to summarize all the possible definitions, possible diagnostic tests and possible treatments suggested by the many papers present in the literature on this topic. Despite this, there are several inaccuracies and misleading statements that should be corrected in order not to generate confusion and erroneous conclusions in the readers that could lead to erroneous clinical behavior.	As the reviewer makes clear, creating a guideline on the management of RIF is fraught with complications, not least of which is the inconsistency in its definition, and the lack of high quality evidence. For these reasons, the Working Group has purposefully elected not to write a formal Guideline. Instead it has sought to provide a definition which it feels will be helpful in clinical practice. However, given the uncertainties that remain regarding the underlying causes and appropriate management , a more didactic approach is not possible so what constitutes ‘erroneous clinical behaviour’ remains open to debate.
99	Yezhou Yang XiaoYong Qiao			the definition of RIF and the recommendations in the draft are appropriate based on the limited evidence at present.	Thank you
141	Ahmed Fawzy Galal			Excellent guideline in a very hot area	Thank you
148	Georgi Stamenov			Long years of research on this specific moment/stage of conception –embryo implantation – have proven the importance of a number of factors that can have an impact on the successful outcome. In order for this accumulated knowledge to be used for its intended purpose, it is necessary that it be applied in clinical practice without this leading to adverse consequences for the patient.	The OPTIMUM trial - in which RIF patients were treated based on diagnostic findings - suggests that using diagnostics to assess the cause of RIF is likely to improve the efficacy of interventions which would then be applied

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				The treatment decision can only be made after defining the problem, which is done through clinical investigation of the embryo competence, the embryo transfer timing (day of the embryo transfer), or both. The non-recommendation of treatments (like e.g. autologous PBMC infusion and intrauterine G-CSF administration) that have proven their efficacy and are supported by evidence in numerous meta-analyses would ultimately lead to a decrease in the success rate of implantation after embryo transfer of good quality embryos, which sets clinical practice back in time. We still have a lot to learn about the processes involved in implantation, and this guideline recommends that researchers focus on the core topics as a priority, but the knowledge and results already gained are there, and it is our mission to use them to improve clinical practice in the best interest of the patient. For example, as cited in the guideline on page 29, line 877, in the OPTIMUM trial, RIF patients were treated according to an identified factor, and significantly better outcomes were observed.	with more rationale than at present. At present, however, few validated tests of value in the context of RIF are available.
162	Carlos Calhaz-Jorge			Thank you to the authors for their hard work in such a difficult topic	Thank you
14	Tansu Kucuk	8	214	“GRP” is a typo error (GPR).	This was adjusted in the text.
3	Oluyemisi Famuyiwa	13	382	Add s to the word clinician, it should read clinicians	This was adjusted in the text.
199	Cristina Magli	13	382	“clinician” should be “clinicians”	This was adjusted in the text.
4	Oluyemisi Famuyiwa	14	396	Change the word aims to aimed	This was adjusted in the text.
20	Anastasia Salame	14	410	The title of the paragraph is missing	This was adjusted in the text.
174	Carlos Calhaz-Jorge	14	410	I guess a title is missing at the beginning of this paragraph	This was adjusted in the text.
200	Cristina Magli	19	577	Incomplete citation	We have corrected the citation
73	Baris Ata	19	592	…including 1339 women undergoing 2759	This was adjusted in the text.
5	Oluyemisi Famuyiwa	21	633	Change ad to and	This was adjusted in the text.
178	Carlos Calhaz-Jorge	21	633	Should be “and” instead of “ad”	This was adjusted in the text.

NR	Reviewer	Page	Line	Comment	Action / Reply
185	Carlos Calhaz-Jorge	26	776	“A systematic review and investigated…”Please remove the word “and”	This was adjusted in the text.
6	Oluyemisi Famuyiwa	27	815	Add the word as between such and advanced	This was adjusted in the text.
111	Elena Kostova		834	LBR instead of BR?	This was corrected in the text
107	Chi Chiu Wang	8	Fig 4	wording “high risk” will be better than “suspected”	We have not changed the term "suspected" to "high risk" as linguistically this is not more correct.
115	Carmen Rubio	8	Fig 4	Endometrial receptivity test and microbiome profiling could be considered according to proportion of clinicians that are using them and taking into consideration all published papers (listed below).	We have considered carefully the evidence for Endometrial receptivity test and microbiome profiling , but decided not to amend the recommendations.
19	Anastasia Salame			A very needed review. The language is clear, concise, and precise. In the general the references are chosen carefully. The use of the descriptive diagrams is very helpful.	Thank you
48	Mitranovici Melinda Ildiko			It is a very good work. Thank you for this opportunity.	Thank you
63	Baris Ata			Thank you for this comprehensive paper which required a lot of effort.	Thank you
106	Chi Chiu Wang			wording “high risk” will be better than “suspected”	We have not changed the term "suspected" to "high risk" as linguistically this is not more correct.
164	Carlos Calhaz-Jorge			The sections of the text are a little bit confusing because treatments are included in the section of “Investigation and treatments” (in spite of the title of the subsections refer only “Investigation of…”) and there is another specific section on “Interventions”: Investigation and treatments for RIF - Investigating female factors - Investigating factors related to the embryo - Investigating male factors Interventions for RIF - Treatments independent of RIF investigations - Treatment based on diagnostic findings Patient care and counselling Why not to move all treatment recommendations just to one section?	We have revised and amended the headings and the content of the Investigations for RIF and Interventions for RIF sections