difficulties faced by those seeking to provide clinical guidelines in this area since the evidence base available does not permit robust conclusions to be drawn.

The ESHRE Working Group on Recurrent Implantation Failure recognized that there is a need to look afresh at how RIF should be identified, defined, and managed. While there is an evidence base to scrutinize, it is the view of the RIF working group (WG) that the available literature has not generated clinical data of sufficient quality around an agreed and consistent definition of RIF to permit a didactic guideline to be distilled. However, there is still a need for an evidence-supported document describing what represents 'Good Practice' in this challenging area of reproductive medicine. This document aims to meet that need through a systematic search for and synthesis of published studies on the topic, a survey among professionals on current clinical practice in RIF and considering the practical expertise of selected clinicians and embryologists.

Materials and methods

The current good practice recommendation for RIF terminology, investigations, and treatments have been developed according to the manual for the development of ESHRE good practice recommendations (Vermeulen *et al.*, 2019).

A WG tasked with drafting a document for review was composed of representatives of the relevant ESHRE Special Interest Groups (SIGs), notably the SIGs Implantation and Early Pregnancy, Reproductive Endocrinology, and Embryology, and further completed with an independent chair (N.M.), an expert in statistics (D.J.M.) and support for literature searches and project management. In the first meetings, the ESHRE Working Group on Recurrent Implantation Failure discussed the topics to be covered and divided to work in subgroups with defined tasks. Progress with the different tasks and issues arising was discussed in regular online meetings.

A literature search through PUBMED and Cochrane databases was performed using the key terms 'recurrent reproductive failure' OR 'recurrent implantation failure' OR 'repeated implantation failure'. Studies were included from inception to August 2022, with addition of more recent references where available. All titles and abstracts were screened to identify relevant studies, for which full-text papers were collected and summarized. While the literature search was focused on specific studies in RIF patients (defined as such by the authors) and the main outcomes live birth rate (LBR), pregnancy rate (PR), and side effects, in the absence of studies specifically addressing cases of RIF, the impact on implantation after ART, in general, was considered.

Recommendations for clinical practice were stated based on studies collected through the systematic search of the literature, and recommendations in other guidelines (Coughlan *et al.*, 2014a; Shaulov *et al.*, 2020; Mascarenhas *et al.*, 2022; Sociedad Española de Fertilidad; Grupo de Trabajo de Fracaso Reproductivo), a previously performed survey providing details on current clinical practice (Cimadomo *et al.*, 2021), assessment of biological rationale, and the expert opinion of the WG. While the WG was aware that for most investigations or interventions there may be specific patient groups that may be shown to benefit, or indeed the opposite, in order to aid clinical decision-making, the recommendations were colour-coded to indicate three levels of advice: green, recommended for all patients with suspected RIF; orange, can be considered in RIF patients; red, not recommended. When 'not recommended' is the advice given, this implies that the investigation/intervention is not to be routinely offered, but that does not mean that it is recommended not to be used in any circumstances, since in most cases, the evidence base cannot support such a didactic statement.

While key available evidence was summarized for all investigations and interventions, an exclusively evidence-based approach was not considered possible for the current topic, owing to the lack of consistency in the definition of RIF and the sparse direct and high-quality evidence available for most interventions, including those already established in clinical practice. The recommendations are, therefore, derived from expert interpretation of the available data, their biological rationale, and opinion rather than from the data alone. The evidence assessed and other factors considered for drafting each recommendation are tabulated in Supplementary Data S1 (investigations) and Supplementary Data S2 (interventions).

Specifically concerning the definition of RIF and to define a threshold for considering RIF, an exercise was performed among 10 members of the participating SIGs. In the exercise, three RIF cases were presented and the implications of three different thresholds (70%, 60%, and 50%) for the cumulative success of implantation leading to pregnancy were to be considered. Following the feedback from this exercise, the threshold of 60% was proposed and presented as part of the first draft of the recommendations for investigations and interventions in RIF.

The first draft of the recommendations for good practice was sent for review by the 14 ESHRE SIGs. Feedback was collected on the proposed definition of RIF, criteria for identifying it in an individual patient and on the relevance of diagnostic and treatment options. The feedback was discussed in an in-person WG meeting and adopted by agreement into a final draft of the paper, which was published on the ESHRE website between 1 November and 1 December 2022 for stakeholder review among the ESHRE membership. A total of 204 comments were received, considered by the WG, and incorporated by agreement. The report of the stakeholder review is available on www.eshre.eu/guidelines. The list of experts that contributed to the stakeholder review is included in Supplementary Data S3.

The current document adheres to the previously published definitions for ART, IVF, infertility, pregnancy, and live birth (Zegers-Hochschild *et al.*, 2017). Implantation rate is defined as the number of gestational sacs observed divided by the number of embryos transferred (usually expressed as a percentage) and is preferably calculated per ET procedure (Griesinger, 2016). Implantation is taken to describe the attachment and subsequent penetration by a zona-free blastocyst into the endometrium (Zegers-Hochschild *et al.*, 2017). For the purpose of this document, successful implantation is taken to be the achievement of early pregnancy (i.e. detection of beta hCG in serum or urine indicative of a positive pregnancy test (precise levels will vary depending on the test used)) following an ET procedure.

It is acknowledged that many studies investigating RIF and RIF interventions have primarily looked at PR and/or LBR. Since these outcomes depend on many other factors that can arise after successful implantation, the focus of this document is therefore on determinants of implantation, defined as above rather than as manifest in a live birth. For consideration of factors causing RPL, the reader is referred to the ESHRE Guideline on Recurrent Pregnancy Loss (ESHRE Guideline Group on RPL *et al.*, 2023).

In this document, in line with published research, the terminology and discussion focusses on men and women. The ESHRE Working Group on Recurrent Implantation Failure recognizes that there are individuals confronted with RIF who do not identify with the terms used in the literature. The terminology used in