Unique ID	1	**Study ID**	MIVI 004	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMA resolution	**Results**	binary	**Weight**	10.5

Domain	Signalling question	Response	Description
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
	4.1 Was the method of measuring the outcome inappropriate?	Y	OCTs were centrally read in an expert center.

Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	2	**Study ID**	MIVI 006	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMA resolution	**Results**	binary	**Weight**	28.5
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	There were more women in the active group which could have increased efficacy, but there were also more fewer ERMs in the control group, which would work in the opposite direction. None of this suggests a problem with randomization.
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	No - identical looking active and placebo was administered.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	

	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	Low risk of bias: placebo-controlled and intent-to-treat analysis.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Only 4 of 326 subjects did not have this assessment.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	Yes - this analysis plan was provided.
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	3	**Study ID**	MIVI 007	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

			to-treat' effect)		
Outcome	VMA resolution	**Results**	binary	**Weight**	24.3

Domain	Signalling question	Response	Description
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	No - identical looking active and placebo was administered.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	Low risk of bias: placebo-controlled and intent-to-treat analysis.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	4	**Study ID**	MIVI 005	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMA resolution	**Results**	binary	**Weight**	24.1
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	

Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	5	**Study ID**	MIVI 006	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMA resolution	**Results**	binary	**Weight**	12.7
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.

Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	6	**Study ID**	MIVI 004	**Assessor**	Koenraad Blot

Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	10.5

Domain	Signalling question	Response	Description
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No - readers were blinded to treatment allocation.

	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	7	**Study ID**	MIVI 006	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	28.5
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	There were more women in the active group which could have increased efficacy, but there were also more fewer ERMs in the control group, which would work in the opposite direction. None of this suggests a problem with randomization.
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	No - identical looking active and placebo was administered.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	

	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	Low risk of bias: placebo-controlled and intent-to-treat analysis.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Only 4 of 326 subjects did not have this assessment.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	Yes - this analysis plan was provided.
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	8	**Study ID**	MIVI 007	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	24.3

Domain	Signalling question	Response	Description
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	No - identical looking active and placebo was administered.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	Low risk of bias: placebo-controlled and intent-to-treat analysis.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	Very low. Centralized, blinded reading assessment.

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	9	**Study ID**	MIVI 005	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	24.1
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	

Bias due to missing outcome data	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	10	**Study ID**	MIVI 006	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	12.7
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from	2.1.Were participants aware of their assigned intervention during the trial?			N	

intended interventions	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	11	**Study ID**	MIVI 004	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention	**Source**	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

			(the 'intention-to-treat' effect)		
Outcome	VMAR D 28	**Results**	binary	**Weight**	10.5

Domain	Signalling question	Response	Description
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	12	**Study ID**	MIVI 006	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	28.5
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	There were more women in the active group which could have increased efficacy, but there were also more fewer ERMs in the control group, which would work in the opposite direction. None of this suggests a problem with randomization.
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	No - identical looking active and placebo was administered.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	Low risk of bias: placebo-controlled and intent-to-treat analysis.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Only 4 of 326 subjects did not have this assessment.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	Yes - this analysis plan was provided.
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	13	**Study ID**	MIVI 007	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	24.3
Domain	**Signalling question**			**Response**	**Description**
	1.1 Was the allocation sequence random?			Y	

Bias arising from the randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	No - identical looking active and placebo was administered.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	Low risk of bias: placebo-controlled and intent-to-treat analysis.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	

	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	14	**Study ID**	MIVI 005	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	24.1
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	15	**Study ID**	MIVI 006	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	12.7

Domain	Signalling question	Response	Description
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	

	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	
	Risk of bias judgement			**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	16	**Study ID**	MIVI 004	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

Outcome	VMAR D 28	Results	binary	Weight	10.5

Domain	Signalling question	Response	Description
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	Very low. Centralized, blinded reading assessment.

Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	17	**Study ID**	MIVI 006	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	28.5
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	There were more women in the active group which could have increased efficacy, but there were also more fewer ERMs in the control group, which would work in the opposite direction. None of this suggests a problem with randomization.
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	No - identical looking active and placebo was administered.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?			Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?			NA	

	Risk of bias judgement			**Low**	Low risk of bias: placebo-controlled and intent-to-treat analysis.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?			Y	Only 4 of 326 subjects did not have this assessment.
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?			NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?			NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			NA	
	Risk of bias judgement			**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?			N	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	Yes - this analysis plan was provided.
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	18	**Study ID**	MIVI 007	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	24.3
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	

	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	No - identical looking active and placebo was administered.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	Low risk of bias: placebo-controlled and intent-to-treat analysis.
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?	N	
	Risk of bias judgement	**Low**	Low - pre-specified endpoint.

Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	19	**Study ID**	MIVI 005	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Trial protocol; Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	24.1

Domain	**Signalling question**	**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	
	Risk of bias judgement	**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
	4.1 Was the method of measuring the outcome inappropriate?	Y	OCTs were centrally read in an expert center.

Bias in measurement of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?			N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?			NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?			NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			NA	
	Risk of bias judgement			**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?			Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?			N	
	Risk of bias judgement			**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**			**Low**	
Unique ID	20	**Study ID**	MIVI 006	**Assessor**	Koenraad Blot
Reference	Individually Randomized, Parallel Group Trials	**Aim**	assignment to intervention (the 'intention-to-treat' effect)	**Source**	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
Outcome	VMAR D 28	**Results**	binary	**Weight**	12.7
Domain	**Signalling question**			**Response**	**Description**
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was centrally managed using interactive voice response system (IVRS).
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y	
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			N	
	Risk of bias judgement			**Low**	Randomization was at low risk of bias due to the centrally administered IVRS system.
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?			N	
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?			PN	
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?			NA	
	2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?			NA	
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?			NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	All analyses were done on an intent-to-treat basis. No important change in analysis plan occurred.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	
	Risk of bias judgement	**Low**	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	**Low**	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y	OCTs were centrally read in an expert center.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No - readers were blinded to treatment allocation.
	4.3 Were outcome assessors aware of the intervention received by study participants?	NA	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	**Low**	Very low. Centralized, blinded reading assessment.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	No, the endpoint was clearly planned.
	5.3 ... multiple analyses of the data?	N	
	Risk of bias judgement	**Low**	Low - pre-specified endpoint.
Overall bias	**Risk of bias judgement**	**Low**	