Appendix 1. Search Strategies and Keyword PICOs Framework

Population	Patients diagnosed with general hypercholesterolemia or heterozygous familial hypercholesterolemia (HeFH)
Intervention	Inclisiran 300 mg
Comparison/Control	Placebo
Outcome	Change score of LDL-C and PCSK9
Study Design	Randomized Controlled trials

Appendix 2. Cochrane RoB-2 Tools

Unique ID	1	Study ID	Ray, 2022	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	The study states that randomization was performed using automated interactive response technology and stratified based on LDL-C levels, statin use, and participation in the pharmacokinetic (PK) suubstudy.
	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	The baseline characteristics between groups were described as "well balanced" (p. 877). There were no significant differences between the groups.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	The study was double-blind, so the participants were unaware of their assignments. The investigators, site staff, and clinical team were also blinded.
	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 likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	The analysis used Mixed Models fo Repeated Measures (MMRM) according to standard practice, and the Full Analysis Set (FAS) was used as the primary population (p. 879)
	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	The retention rate was very high: 97.8% completed the study (p. 880)
	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	LDL-C and PCSK9 measurements were performed in a central laboratory, according to standards.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	There was no indication of differences in measurements between groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	All those performing the assessments were blinded to the intervention group.
	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	
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	It is stated that the analysis follows a statistical analysis plan (SAP) prepared by a statistician (p. 880).
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	Primary and secondary endpoints were clearly defined beforehand.
	5.3 ... multiple eligible analyses of the data?			N	There is no indication of outcome selection based on the analysis results. Methods and endpoints are predetermined.
	Risk of bias judgement			Low	
Overall bias	Risk of bias judgement			Low	

Unique ID	2	Study ID	Luo, 2023	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	The study explicitly states that it was a randomized, placebo-controlled trial.
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			NI	

	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	NI	Baseline characteristics (age, sex, BMI) were balanced between groups as per Table 1.
	Risk of bias judgement	Some concerns	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	The study is described as blinded; participants were not aware of group assignment.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY	
	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?	N	No evidence of deviations due to awareness was reported.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	MMRM analysis was conducted based on the

			randomized groups with MAR assumption.
	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	Only one subject was excluded due to protocol deviation; minimal missing 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?	N	Standardized, validated methods (e.g., ELISA, HPLC-MS) were used for measurement.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement protocol and schedule applied across groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Not clearly reported whether lab personnel were blinded.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NI	No direct evidence, but cannot be ruled out due to lack of blinding info.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NI	
	Risk of bias judgement	High	
Bias in selection of	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?	NI	There is no mention of pre-specified statistical analysis plan or protocol publication.

the reported result	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			PN	Only one primary and one secondary outcome domain were reported, but alternative definitions/timings may exist.
	5.3 ... multiple eligible analyses of the data?			PN	While MMRM is appropriate, other analytical methods are not mentioned or ruled out.
	Risk of bias judgement			Some concerns	
Overall bias	Risk of bias judgement			High	
Unique ID	3	Study ID	Raal, 2020	Assessor	

Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomization was computer-generated and stratified by site. Allocation was concealed using interactive voice/web response system.
	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	Baseline demographics were similar across groups.
	Risk of bias judgement			Low	

Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Participants were blinded. Caregivers and investigators were blinded.
	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 likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Appropriate ITT analysis and MMRM were used.
	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	Follow-up completion was high.
	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	LDL-C was measured centrally.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	No differential measurement between arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Assessment was blinded.

	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	
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	Analyses followed the pre-specified statistical plan.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Single primary endpoint.
	5.3 ... multiple eligible analyses of the data?	N	No evidence of selective analysis.
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	4	Study ID	Leiter, 2019	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the	1.1 Was the allocation sequence random?			Y	Randomization was conducted using a

randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	computerized system in a double-blind, placebo-controlled design. The allocation sequence was centrally controlled through an interactive system.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics were balanced between group, with no significant differences.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	The study employed a double-blind design. Neither the investigators nor the participants were aware of the intervention being 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 likely to have affected the outcome?	NA	

	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	The statistical analysis was conducted using a pre-specified model in accordance with the SAP.
	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	The majority of participants completed the study through day 540.
	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	LDL-C and ApoB were measured at a central laboratory.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	There was no indication that the methods differed between groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The assesors were unaware of the intervention received by the participants.
	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	
Bias in selection of	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	The analysis was conducted according to the pre-specified plan.

the reported result	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	The primary and secondary endpoints were pre-specified.
	5.3 ... multiple eligible analyses of the data?			N	No multiple anayles were selectively chosen.
	Risk of bias judgement			Low	
Overall bias	Risk of bias judgement			Low	
Unique ID	5	Study ID	Fitzgerald, 2017	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		

Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Participants were randomized 3:1 to inclisiran or placebo in each cohort. Randomization used block sizes; syringe masking used to preserve blinding.
	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	Demographics and lipid levels balanced between groups.
	Risk of bias judgement			Low	
Bias due to deviations	2.1.Were participants aware of their assigned intervention during the trial?			N	Single-blind (participants blinded); no evidence of

from intended interventions	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	awareness. Likely unblinded site staff; study is single-blind.
	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?	N	No deviations reported.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Analysis of covariance (ANCOVA) and repeated measures used.
	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	Only 1–2 exclusions from PD analysis due to protocol deviation.

	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	LDL-C and PCSK9 measured with validated methods (e.g., beta-quantification).
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	All participants followed identical protocols.
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Not specified for lab staff.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	Objective outcome, but full blinding unclear.

	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	
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	Protocol approved; analysis methods pre-defined.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			PN	Different doses and timing were assessed; unclear if selection occurred.
	5.3 ... multiple eligible analyses of the data?			PN	ANCOVA and descriptive stats used; alternate models not discussed.
	Risk of bias judgement			Low	
Overall bias	Risk of bias judgement			Low	

Unique ID	6	Study ID	Ray, 2017	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Centralized, computer-generated randomisation was applied. Allocation concealment maintained through secure systems.
	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	Balanced baseline characteristics between treatment arms.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Participants were blinded. Investigators were also blinded.
	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 likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	MMRM and ANCOVA applied as specified.

	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	High retention and follow-up across study groups.
	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	4.1 Was the method of measuring the outcome inappropriate?	N	Measurement of LDL-C followed standard protocol.

of the outcome	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Identical methods across groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Blinded outcome assessment.
	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	
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	Followed the pre-defined SAP.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Primary and key secondary outcomes clearly defined.
	5.3 ... multiple eligible analyses of the data?	N	Analyses followed specified plan.

	Risk of bias judgement			Low	
Overall bias	Risk of bias judgement			Low	
Unique ID	7	Study ID	Wright, 2021	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1

Domain	Signalling question	Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Randomized 1:1 to inclisiran or placebo across ORION-9, -10, -11 trials. Randomization was stratified and managed centrally; concealment procedures implied.
	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	Baseline demographics and lipid profiles were well balanced (Table 2).
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Study was double-blind. Blinded healthcare professionals administered the treatment.
	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 likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Intention-to-treat analysis with multiple imputation and prespecified analysis plan.
	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	94.3% (inclisiran) and 92.8% (placebo) completed follow-up.
	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	Standard lab measures (LDL-C, PCSK9) used.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Same measurement and timing across arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Not explicitly stated for lab analysts.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	Doubtful; LDL-C is objective, but lab blinding not specified.
	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	

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	Protocol was prospectively defined; coprimary and secondary endpoints pre-specified.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	LDL-C measurement timepoints were pre-defined.
	5.3 ... multiple eligible analyses of the data?			N	Analysis plan detailed in the supplement and adhered to.
	Risk of bias judgement			Low	
Overall bias	Risk of bias judgement			Low	
Unique ID	8	Study ID	Ray, 2023	Assessor	

Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	This study is an extension of the ORION-1 randomized trial, which used valid randomization. The allocation in ORION-1 was made before unbinding.
	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 no baseline imbalances in either ORION-3 or ORION-1.
	Risk of bias judgement			Low	

Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	Y	The ORION-3 study was open-label. Both the researchers and participants were aware of the treatment (open-label).
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	
	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?	N	No major protocol deviations were reported.
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	The analysis followed the protocol and SAP, using an intention-to-treat approach.
	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	Retention was fairly good, with around 80% of participants completing the 4-year study.
	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	LDL-C was measured using a valid method.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	The likelihood of differences due to the open-label design was low.
	4.3 Were outcome assessors aware of the intervention received by study participants?	Y	The assessors were aware of the intervention.

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY	LDL-C assessment was objective (laboratory-based), so the risk of bias was minimal. It is unlikely to have had a major impact on the result.
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N	
	Risk of bias judgement	Some concerns	
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	The SAP was available and clearly defined.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The outcomes and analysis methods were pre-defined.
	5.3 ... multiple eligible analyses of the data?	N	There was no selective reporting,
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Some concerns	

Unique ID	9	Study ID	Wiegman, 2025	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the	1.1 Was the allocation sequence random?			Y	Randomization was done in a 1:1 ratio using a

randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	computerized system with stratification based on FH diagnosis and ASCVD status. Allocation concealment was maintained through a double-blind procedure.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics were similiar between the groups.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	Patients were unaware of their group assignments. Researchers and medical staff were blinded.
	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 likely to have affected the outcome?	NA	

	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	MMRM was used, and the intention-to-treat population was applied.
	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	The follow-up rate was high (>95%).
	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	The method used for LDL-C was valid and standard.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Identical procedures were used in both groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	The outcome assessor was blinded.
	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	
Bias in selection of	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	The analysis was pre-specified in the SAP.

the reported result	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?			N	The outcome was clear and primary.
	5.3 ... multiple eligible analyses of the data?			N	No selective analysis was identified.
	Risk of bias judgement			Low	
Overall bias	Risk of bias judgement			Low	
Unique ID	10	Study ID	Yamashita, 2024	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		

Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?			Y	Randomisation was computer-generated using an interactive response system with stratification factors. Allocation was concealed via automated system prior to assignment.
	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	Baseline characteristics were well balanced between inclisiran and placebo groups.
	Risk of bias judgement			Low	

Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	The trial was double-blind. Participants were unaware of assignment. Investigators and care staff were blinded.
	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 likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Mixed models for repeated measures (MMRM) used as per protocol.
	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	97.8% of participants completed the trial.
	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	LDL-C was measured in a central laboratory using standard validated methods.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Uniform procedures were applied to all groups.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded.

	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	
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	Outcomes were analysed per a pre-specified statistical analysis plan.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Only one primary outcome measure was used.
	5.3 ... multiple eligible analyses of the data?	N	No evidence of selective analysis was noted.
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

Unique ID	11	Study ID	Koenig, 2023	Assessor	
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental		Comparator		Source	
Outcome		Results		Weight	1
Domain	Signalling question			Response	Comments
Bias arising from the	1.1 Was the allocation sequence random?			Y	Original ORION trials were randomized and placebo-

randomization process	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	controlled. Allocation was concealed using a central system.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	Baseline characteristics of CeVD subgroup were balanced.
	Risk of bias judgement	Low	
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	N	The trials were double-blinded. Investigators and staff were blinded to allocation.
	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 likely to have affected the outcome?	NA	
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	

	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	MMRM and ANCOVA models were used as specified.
	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?	PY	Specific data on follow-up for CeVD subgroup was not provided.
	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	LDL-C measured centrally.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Procedures were identical between arms.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Assessors were blinded.
	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	
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?	PY	This was a post hoc subgroup analysis, not pre-specified in original trials.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PY	Multiple endpoints analyzed; selection may not be fully predefined.

	5.3 ... multiple eligible analyses of the data?	PY	Subgroup results might reflect selective interest after initial findings.
	Risk of bias judgement	High	
Overall bias	Risk of bias judgement	High	

Appendix 3. Egger's Regression Test for Small-Study Effects in the Inclisiran Meta-analysis

```
. meta bias, egger random(reml) detail nometashow

Random-effects meta-regression                  Number of obs  =        11
Method: REML                                    Residual heterogeneity:
                                                          tau2 =    257.2
                                                       I2 (%)  =    99.95
                                                          H2   =  1988.48
                                                R-squared (%)  =     0.00
                                                Wald chi2(1)   =     0.00
                                                Prob > chi2    =   0.9791
```

_meta_es	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
_meta_se	-.4599493	17.59764	-0.03	0.979	-34.95068	34.03078
_cons	6.523159	11.17012	0.58	0.559	-15.36987	28.41618

```
Test of residual homogeneity: Q_res = chi2(9) = 7846.80  Prob > Q_res = 0.0000

Regression-based Egger test for small-study effects
Random-effects model
Method: REML

H0: beta1 = 0; no small-study effects
           beta1 =     -0.46
      SE of beta1 =    17.598
               z =     -0.03
        Prob > |z| =    0.9791
```

Appendix 4. Random-Effects Meta-Regression Evaluating Study-Level Moderators of Inclisiran Treatment Effect

```
  Effect-size label: Hedges's g
        Effect size: _meta_es
          Std. err.: _meta_se

Random-effects meta-regression                  Number of obs  =        11
Method: REML                                    Residual heterogeneity:
                                                          tau2 =    81.29
                                                       I2 (%)  =    99.73
                                                          H2   =   371.92
                                                R-squared (%)  =    64.88
                                                Wald chi2(3)   =    21.38
                                                Prob > chi2    =   0.0001
```

_meta_es	Coefficient	Std. err.	z	P>|z|	[95% conf.	interval]
samplesizeinclisiran	.1311322	.1153849	1.14	0.256	-.0950181	.3572825
samplesizeplacebo	-.1042025	.113084	-0.92	0.357	-.3258431	.1174381
drugmg	0	(omitted)				
durationdays	-.0209046	.0177005	-1.18	0.238	-.055597	.0137878
_cons	6.612217	6.165169	1.07	0.283	-5.471293	18.69573

```
Test of residual homogeneity: Q_res = chi2(7) = 1445.05  Prob > Q_res = 0.0000
```