Reference Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014; 370: 2478-86. [CRYSTAL-AF]

Study design

- ☑ Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

Specify which outcome is being assessed for risk of bias	AF detection at 6, 12 and 36 months
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Time to first AF, ITT N=221 ICM, N=220 control *By 6 months* (primary analysis, unadjusted): Median 41 days (IQR 4 to 84) ICM vs 32 days (2 to 73) control; HR 6.4 (95% CI 1.9 to 21.7; p < 0.001) *By 12 months:* Median 84 days (18 to 265) ICM vs 53 days (17 to 212) control; HR 7.3 (95% CI 2.6 to 20.8; p < 0.001) *By 36 months:* HR 8.8 (95% CI 3.5 to 22.2; (p < 0.001)

Is the review team's aim for this result…?

- ☑ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ☑ Journal article(s) with results of the trial
- ☑ Trial protocol
- ☐ Statistical analysis plan (SAP)
- ☑ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☑ Conference abstract(s) about the trial
- ☑ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☑ Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Description	Response options
1.1 Was the allocation sequence random?	"Randomization lists were created with the use of permuted blocks of random size, with assignments made sequentially." (Sanna 2014)	Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	"Randomization will use an interactive voice response telephone system." (Sinha 2010)	Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	All p values >0.05 although slightly higher rates of patent foramen ovale, hypertension, and coronary artery disease in the ICM group than in the control group at baseline. (Sanna 2014)	Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?	N/A	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?	"Patients and physicians were aware of the study-group assignments, because patients in the ICM group underwent insertion of the device." (Sanna 2014)	Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
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?	12 (5.4%) patients assigned to ICM received standard care and 6 (2.7%) patients in standard care arm received ICM. (Sanna 2014) ICM insertion within 10 days of randomisation was not implemented in 24 patients in the ICM arm: "…scheduling delays (22 patients) or medical justification (2 patients) accounting for delayed insertions (median delay, 6 days; interquartile range, 1 to 32)." (Sanna 2014)	NA / Y / PY / PN / N / NI
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	Slightly higher cross over in ICM group: 12 (5.4%) patients assigned to ICM received standard care and 6 (2.7%) patients in standard care arm received ICM. (Sanna 2014) Delay in insertion of ICM not relevant to standard care arm.	NA / Y / PY / PN / N / NI
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	Only small numbers crossed over from assigned interventions: 5.4% in ICM group and 2.7% in standard care. Delay in insertion of ICM was mostly short (median 6 days) so the impact on AF detection is likely to be small. Delays to insertion are also expected to reflect clinical practice.	NA / Y / PY / PN / N / NI

2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	"The rate of detection of atrial fibrillation was estimated with the use of the Kaplan–Meier method and was compared between groups on an intention-to-treat basis with the use of a log-rank test." (Sanna 2014) Only small numbers deviated from assigned interventions.	Y / PY / PN / N / NI
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 / Y / PY / PN / N / NI
Risk-of-bias judgement	Lack of blinding unlikely to affect relative AF detection rates between groups. Only small numbers of patients received the alternative interventions (12 [5.4%] patients assigned to ICM and 6 [2.7%] patients in standard care arm). Results analysed for ITT population (Sanna 2014) so, by including patients who did not receive an ICM, received one late, or crossed over to standard care, the estimated benefit of receiving an ICM may be conservative. Delays in ICM insertion were mostly short and unlikely to impact this outcome.	Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?	N/A	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Description	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	All patients included in analysis, only 12 (5.4%) in ICM arm and 13 (5.9%) in standard care arm withdrew from the study by 6 months. 194 (88.8%) patients in ICM arm and 185 (84.1%) in standard care arm completed 12 months follow-up. Only 88 patients completed 24 months follow-up in ICM arm and 89 in standard care arm, and this dropped to only 24 patients in each study arm by 36 months follow-up although an ITT analysis used.	6 months: Y / PY / PN / N / NI 12 months: Y / PY / PN / N / NI ≥24 months: Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Although there were only 177 patients who completed 24 months follow-up and 48 patients that completed 36 months follow-up, there were similar patient numbers in each study arm and an ITT analysis was used. However, the reasons for loss to follow-up beyond 6 months are not reported and a large number of patients are censored in the analyses.	6 and 12 months: NA ≥24 months: NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Unlikely given that balanced across treatment arms and adjucation panel used for the outcome assessment.	6 and 12 months: NA ≥24 months: NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?		6 and 12 months: NA ≥24 months: NA / Y / PY / PN / N / NI

3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		6 and 12 months: NA ≥24 months: NA / Y / PY / PN / N / NI
Risk-of-bias judgement		6 and 12 months: **Low** ≥24 months : **Some concerns**
Optional: What is the predicted direction of bias due to missing outcome data?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Description	Response options
4.1 Was the method of measuring the outcome inappropriate?	Patients assigned to the control group underwent assessment at scheduled and unscheduled visits, with ECG monitoring performed at the discretion of the site investigator. Monitoring type, duration, and all results were recorded. Patients assigned to the ICM group had the ICM settings programmed in a standardized fashion. The ICM (REVEAL XT, Medtronic) automatically detected and recorded episodes of suspected atrial fibrillation, irrespective of heart rate or symptoms.	Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups ?	The purpose of the study was to assess to different methods of measuring AF: ECG or ICM but the threshold/definition for diagnosing AF was consistent between the two treatment groups. "Episodes of atrial fibrillation that qualified for analysis were adjudicated by an independent committee." (Sanna 2014) Adjudication committee were blinded to the treatment arm, where possible. (Sinha 2010)	Y / PY / PN / N / NI
4.3 Were outcome assessors aware of the intervention received by study participants?	"Patients and physicians were aware of the study-group assignments, because patients in the ICM group underwent insertion of the device." (Sanna 2014) However, the adjudication committee were blinded to the treatment arm, where possible. (Sinha 2010)	Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	There was a clear threshold and definition of AF applied by the adjudication panel.	NA / Y / PY / PN / N / NI
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 / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?	N/A	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Description	Response options
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis ?	Analysis plan reported in published trial protocol	(Y) / PY / PN / N
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Discrete outcome of AF presence/absence assessed by adjudication committee	Y / PY / PN / (N) / NI
5.3 ... multiple analyses of the data?		Y / PY / PN / (N) / NI
Risk-of-bias judgement		(Low) / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / (Some concerns)
Optional: What is the predicted direction of bias due to selection of the reported result?	Including patients who did not receive an ICM, received one late, or crossed over to standard care in the ITT analysis may give a conservative estimate of the true benefit of ICM, although these issues may reflect clinical practice. Incomplete follow-up at later that 24 months+ is likely to make these results less reliable than those at 6 and 12 months, although the direction of this bias is unpredictable.	Favours experimental / Favours comparator / Towards null /Away from null / (Unpredictable)