# Appendix A4. Definitions of "Per-protocol" and "As-treated" Populations

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| **Systematic, Collaborative, PFO closure Evaluation (SCOPE)** | **Per-Protocol population (if possible to identify across trials): all patients who: i) received the randomly assigned treatment, ii) adhered at least moderately to the trial-mandated long-term medical treatment specific to their allocated treatment group (including long-term antithrombotic therapy in the medical therapy-only treatment group and long-term post-device antithrombotic therapy in the closure device plus medical therapy group, iii) did not have a major inclusion or exclusion violation, classified according to the treatment group to which they were randomly assigned and iv) patients who are NOT lost to follow up, when these patients are able to be identified (special considerations for PC and RESPECT trials)** |
| CLOSE | *An additional analysis was performed in the per-protocol cohort, which included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment **until the end of the trial**, and did not have a major protocol violation.* |
| PC Trial | *In a per-protocol analysis, we restricted the analysis to data from patients in the closure group in whom implantation of a device was attempted and patients in the medical-therapy group who received treatment as assigned at the time of randomization; if patients in the medical-therapy group crossed over to the closure group, the data were censored at the time of crossover.*<br>**Special consideration:**<br>• PC Trial censored people who crossed over at the time of crossover in their PP analysis. We decided we would not do this, and instead exclude patients who crossed over.<br>• In their publication, they used the **LTFU at 3 years** to identify and report. Using the 3 year variable would hopefully be consistent with their publication and make their definition closer to the other trials. |
| CLOSURE | *Defined as all randomized patients who received the treatment to which they were randomized, who had no major inclusion/exclusion criteria violations, and **who had a follow-up of at least 22 months.*** |
| RESPECT | *The per-protocol cohort included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion violation.*<br>**Special consideration:**<br>• Respect did not exclude patients who were lost to follow up in their per protocol analysis. In their short-term publication, they identified *119* patients who "discontinued prior to primary endpoint", and in their long-term follow-up publication, they identified *264* patients who "discontinued prior to primary endpoint."<br>• In the data they provided, they provided information about *226* patients who discontinued, these patients have been excluded from the SCOPE per-protocol analysis. |

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| REDUCE | *For per-protocol (PP) analysis, only subjects who were randomized and treated according to critical protocol requirements were analyzed, according to treatment assigned at randomization. Specifically, subjects randomized to the closure group who received antiplatelet medical therapy and PFO closure with a study device within 90 days post-randomization, and subjects randomized to medical therapy who received antiplatelet medical therapy and no PFO closure by any means at any time, were included in the PP analysis. The PP population excludes subjects who violated key eligibility criteria, did not receive the therapy to which they were randomized, or did not comply with one of the protocol required medical regimens.* |
| DEFENSE | *Included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment until the end of the trial, and did not have a major protocol violation.* |

**SCOPE "As treated" population definition:**

All the patients in the study classified according to the treatment actually received (i.e., this analysis will compare patients who "got device" versus those that did not). Patients randomized to medication but got device are censored at time of crossover to the device arm.

**Special consideration:** PC trial did not provide device procedure dates for all patients.