**Supplementary Table 1 Summary of outcome definitions for fistula closure in included studies**

| **Study** | **Definition of Fistula Closure** | **Output Reduction Threshold** | **Imaging or Other Confirmation** | **Notes on Heterogeneity** |
| --- | --- | --- | --- | --- |
| Torres 1992[1] | Cessation of fistula output for 48 hours, without recurrence. (Location: Results section, page 2: "A definitive healing of the fistula was observed when the fistula had been unproductive for 48 hours.") | Zero output for 48 hours. | Not mentioned; primarily clinical assessment. | Short duration threshold without imaging, potentially underestimating incomplete closures. |
| Scott 1993[19] | No fistula output for 2 or more successive days during the 12-day therapy period. (Location: Methods and patients section, page 267: "Fistula closure was defined as 2 or more successive days with no fistula losses in the 12 day therapy period.") | Zero output for ≥2 days. | Not mentioned; clinical only. | Short duration threshold without imaging, similar to Torres 1992 but emphasizes therapy period. |
| Isenmann 1994[20] | Fistula secretion volume <5 mL/day, confirmed radiologically or by ultrasonography. (Location: " The outcome “fistula closure” was defined as a drainage volume of less than 5 mL per day and was confirmed radiologically or by ultrasonography.") | <5 mL/day. | Radiological or ultrasonographic confirmation. | Stricter definition with low threshold and imaging confirmation, differing from output-only definitions. |
| Sancho 1995[21] | Absence of fistula output for at least 2 days, confirmed by clinical examination. (Location: Patients and methods section, page 639: "Closure within 20 days was observed..."; inferred from output reduction and clinical confirmation, but explicit: "No fistula output for at least 2 days, confirmed by clinical examination.") | Zero output for ≥2 days. | Clinical examination; imaging if doubt persists. (Location: Patients and methods, page 639: "imaging if doubt persists.") | Includes optional imaging, adding variability compared to purely clinical definitions. |
| Hernández-Aranda 1996[2] | Spontaneous closure of the fistula, defined as cessation of fistula output. (Location: Abstract and Results, page 226-227: "Spontaneous healing of Fistula" based on cessation of output; no explicit duration.) | Zero output (duration not specified). | Not explicitly for closure; radiological means mentioned for assessment of perpetuating factors or complications. (Location: Not directly stated for closure; general mention in methods for evaluation.) | Definition based on output cessation, with imaging used optionally for general evaluation (not confirmed as mandatory for closure), increasing heterogeneity. |
| Leandros 2004[22] | Not explicitly defined; referred to as spontaneous closure without specifying criteria. (Location: Throughout the article, e.g., Abstract and Results, pages 303-305: Terms like "fistula closure rate" and "spontaneous closure" used without detailed criteria such as output threshold, duration, or confirmation methods.) | Not specified. | Diagnosis of fistula origin attained by computed tomography scan or fistulography when necessary; not mentioned for closure confirmation. (Location: Methods and Materials section, page 304: "The diagnosis of fistula origin was attained, when necessary, by computed tomography scan or fistulography (Table 1).") | Lacks specific closure criteria, contributing to heterogeneity; imaging used for origin, not closure. |
| Jamil 2004[23] | Fistula considered healed when its secretions ceased and remained nil for three months. (Location: Patients and Methods section, page 238: "Fistula considered healed when its secretions ceased and remained nil for three months.") | Zero output (duration not specified, but nil for 3 months). | Not mentioned; primarily clinical. | Long-term confirmation (3 months) without threshold or imaging, increasing heterogeneity. |
| Gayral 2009[7] | Output of less than 15 mL for 24 hours without any recurrence within the next 10 days, and confirmation 30 days later. (Location: "Fistula closure was defined as an output of less than 15 mL for 24 hours without any recurrence within the next 10 days, and confirmation 30 days later.") | <15 mL for 24 hours. | Not mentioned for closure; clinical assessment with recurrence check and later confirmation. | Low output threshold with recurrence verification over 10 days and 30-day confirmation, differing from zero-output or imaging-based definitions. |
| Timmer 2024[24] | Not explicitly defined in the provided excerpts; study focuses on output reduction rather than closure. (Location: Abstract and Background, pages 727-728: Primary outcome is responders with output reduction ≥25%; no mention of closure criteria in excerpts.) | Not applicable (focus on reduction, not closure). | Not mentioned in excerpts. | Study emphasizes output reduction, not closure; limited excerpt information may miss closure criteria, contributing to heterogeneity. |

**Supplementary Table 2 Risk of bias assessment**

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| --- | --- | --- | --- | --- | --- | --- |
| **Author, year of publication** | **Randomization Process** | **Deviations from Intended Interventions** | **Missing Outcome Data** | **Measurement of Outcome** | **Selection of Reported Result** | **Other Bias** |
| **Torres 1992**[1] | High risk: The article does not specify how the randomization sequence was generated or concealed. Baseline imbalance between groups is not addressed. | Some concerns: It is unclear whether participants and personnel were blinded. Lack of this information introduces potential performance bias. | Low risk: Most participants completed the trial and data appears complete. | Low risk: Primary outcomes (e.g., fistula closure) are objective and not subject to measurement bias. | High risk: No trial registration or protocol available; potential for selective outcome reporting. | High risk – Very small study with unclear funding and reporting structure. |
| **Scott 1993[19]** | Some concerns: The study was described as double-blind and randomized, but the method of sequence generation and allocation concealment was not reported. | Low risk: No deviations from intended interventions are reported. Patients received the assigned treatment and blinding was maintained. | Low risk: No missing outcome data were reported for the analyzed 19 patients. Dropouts and exclusions were clearly explained. | Low risk: Outcomes (fistula output and closure) were objectively measured and not susceptible to detection bias. | Some concerns: No trial registration or protocol was available, raising the possibility of selective outcome reporting. | High risk: Very small sample size (n=19 vs. planned 200); underpowered and limited generalizability. |
| **Isenmann 1994**[20] | Some concerns: The study is described as randomized, but the method of sequence generation or allocation concealment is not reported. Groups are balanced, but lack of methodological detail raises concern. | Low risk: No deviations from intended interventions are reported. Patients appear to have received allocated treatments as planned. | Low risk: All or nearly all participants were accounted for. There is no evidence of differential dropout or missing data between groups. | Low risk: Outcomes such as fistula closure time and volume are objective and unlikely to be affected by lack of blinding. | Some concerns: No protocol or trial registration is available. It is unclear if all predefined outcomes were reported, raising the possibility of selective reporting. | Low risk: Multicenter study with balanced groups; no financial or methodological concerns were identified. |
| **Sancho 1995**[21] | High risk: The paper does not describe the method of random sequence generation or allocation concealment. This lack of information raises concerns about possible selection bias. | Low risk: There is no evidence of deviation from intended interventions in either group. The interventions appear to have been applied as planned. | Some concerns: While the outcomes are mostly reported, the handling of withdrawals is unclear, and no intention-to-treat analysis is mentioned. | Low risk: Outcomes such as fistula closure are objective and unlikely to be influenced by lack of blinding. | High risk: There is no trial registration or protocol available. This raises concern that outcomes may have been selectively reported. | Some concerns – Small sample size and limited reporting on baseline comparability. |
| **Hernández-Aranda 1996**[2] | Some concerns: Randomized but no method described | Low: Blinding appears to be maintained | Low: Low dropout rate and accounted for | Low: Objective outcomes, unlikely measurement bias | High: Selective reporting likely as only positive results emphasized | Some concerns: Unclear funding or conflict of interest |
| **Leandros 2004** [22] | Some concerns: Randomization stated but method not described, age imbalance (P=0.049) | Some concerns: Open-label design, no blinding, but no evidence of co-interventions | Low risk: All randomized patients analyzed | Some concerns: Outcomes objective but assessors not blinded | Some concerns: No protocol or registry available | Low: No other concerns |
| **Jamil 2004[23]** | High risk – The method of randomization was not described, and there is no mention of allocation concealment. | Some concerns – No mention of blinding; deviation from intended interventions may have occurred due to lack of masking. | Low risk – All 33 patients were accounted for, and outcomes were reported. | Some concerns – Unclear whether outcome assessors were blinded; subjective outcomes (e.g., fistula closure time) could be biased. | Some concerns – No protocol or trial registration available; potential for selective reporting. | High risk – Small sample size, single center, no power calculation, and cost outcomes not standardized. |
| **Gayral, 2009[7]** | Some concerns: Centralized randomization stratified by fistula location, but no details on sequence generation or allocation concealment | Low (primary endpoint): Double-blind phase and ITT analysis protect primary endpoint; Some concerns (secondary endpoints): Open-label phase may introduce performance bias | Low: Minimal missing data (4/111), appropriate handling with censoring | Low: Objective outcomes, double-blind for primary endpoint | Some concerns: All outcomes reported, but protocol unavailable | Some concerns: Potential industry influence, though robust design mitigates major concerns |
| **Timmer 2024**[24] | Low risk: Stratified randomization by fistula/enterostomy type. | Some concerns: Open-label study (no blinding). | Low risk: Complete data for ITT analysis. | Low risk: Output measured objectively. | Low risk: All pre-specified outcomes reported. | Some concerns: Partial industry funding (Ipsen). |

**Supplementary Table 3 Summary of qualitative publication bias assessment**

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| **Dimension** | **Key Findings** | **Level of Concern** |
| **Small-Study Effects** | Small studies (e.g., Sancho 1995[21], n = 31) include non-significant results; no clear pattern of exaggerated effects. | Low |
| **Effect Size Distribution by Sample Size** | Mixed effects; smaller studies (e.g., Jamil 2004[23]) show modest benefits, while larger studies (e.g., Isenmann 1994[20]) report larger effects, but not consistently. | Low |
| **Temporal Distribution** | Studies from 1992 to 2024, concentrated in the 1990s with a gap from 2009 to 2024; neutral results from the 1990s reduce concern. | Mild |
| **Geographic Pattern** | Diverse origins (Mexico, Spain, Italy, Pakistan, Germany, Swiss, Russia, Greece, UK, Netherlands); with no overrepresentation from a single region. | Low |
| **Selective Outcome Reporting** | Inconsistent reporting of secondary outcomes (e.g., complications, costs); non-significant primary outcomes mitigate but raise moderate concern. | Moderate |

**Supplementary Table 4 GRADE for Somatostatin-Based Therapies in the Management of External Gastrointestinal Fistulas**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **No. of Studies (Participants)** | **Risk of Bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other Considerations** | **Effect Size (95% CI)** | **Certainty of Evidence** | **Comments** |
| **Fistula Closure Rate** | 7 (363) | Serious a | Not serious b | Serious**d** | Not serious | None | RR 1.11 (0.95 to 1.28) | Low ⊕⊕◯◯ | No significant difference in closure rates. Downgraded for high RoB across most trials and indirectness due to protocol heterogeneity (drug class, dose, duration, co-interventions, and outcome definitions). |
| **Time to Fistula Closure** | 5 (240) | Serious a | Not serious b | Not serious | Not serious | None | MD -6.16 days (-7.44 to -4.88) | Moderate ⊕⊕⊕◯ | Significant reduction in closure time. Consistent effect across studies (I² = 0%). |
| **Hospital Length of Stay** | 2 (118) | Serious a | Not serious b | Not serious | Serious c | None | MD -4.00 days (-7.99 to -0.01) | Low ⊕⊕◯◯ | Significant reduction in hospital stay, but limited by few studies and small sample size. |
| **Clinical Complications** | 6 (254) | Serious a | Not serious b | Not serious | Serious c | None | RR 0.76 (0.55 to 1.05) | Low ⊕⊕◯◯ | No significant difference. Wide CI and moderate sample size limit precision. |
| **Surgical Intervention** | 6 (268) | Serious a | Not serious b | Not serious | Serious c | None | RR 0.67 (0.38 to 1.19) | Low ⊕⊕◯◯ | No significant difference. Wide CI and moderate heterogeneity (I² = 31%) reduce certainty. |
| **Mortality** | 6 (324) | Serious a | Not serious b | Not serious | Serious c | None | RR 0.77 (0.44 to 1.35) | Low ⊕⊕◯◯ | No significant difference. Wide CI and moderate sample size limit precision. |

### Legend: a ****Risk of Bias****: Downgraded due to concerns in randomization processes, lack of blinding in some trials, and potential selective reporting, as assessed by Cochrane RoB 2.0. Most studies had at least "some concerns" or "high risk" in one or more domains. b ****Inconsistency****: Not downgraded, as heterogeneity was low (I² = 0% for most outcomes, 31% for surgical intervention), and effect estimates were generally consistent in direction. c ****Imprecision****: Downgraded for outcomes with wide confidence intervals that include the null effect or for outcomes with limited studies/small sample sizes (e.g., hospital length of stay). dIndirectness: Downgraded due to notable protocol heterogeneity across trials, including differences in agents (somatostatin vs analogues), dosing schedules and durations, co-interventions, and non-standardized definitions of fistula closure, which limit direct applicability of the pooled estimate.

### Explanation of Certainty Levels

* **Moderate (⊕⊕⊕◯)**: Evidence is reliable but limited by risk of bias in included studies.
* **Low (⊕⊕◯◯)**: Confidence in effect estimates is limited due to risk of bias and imprecision from small sample sizes or wide confidence intervals.