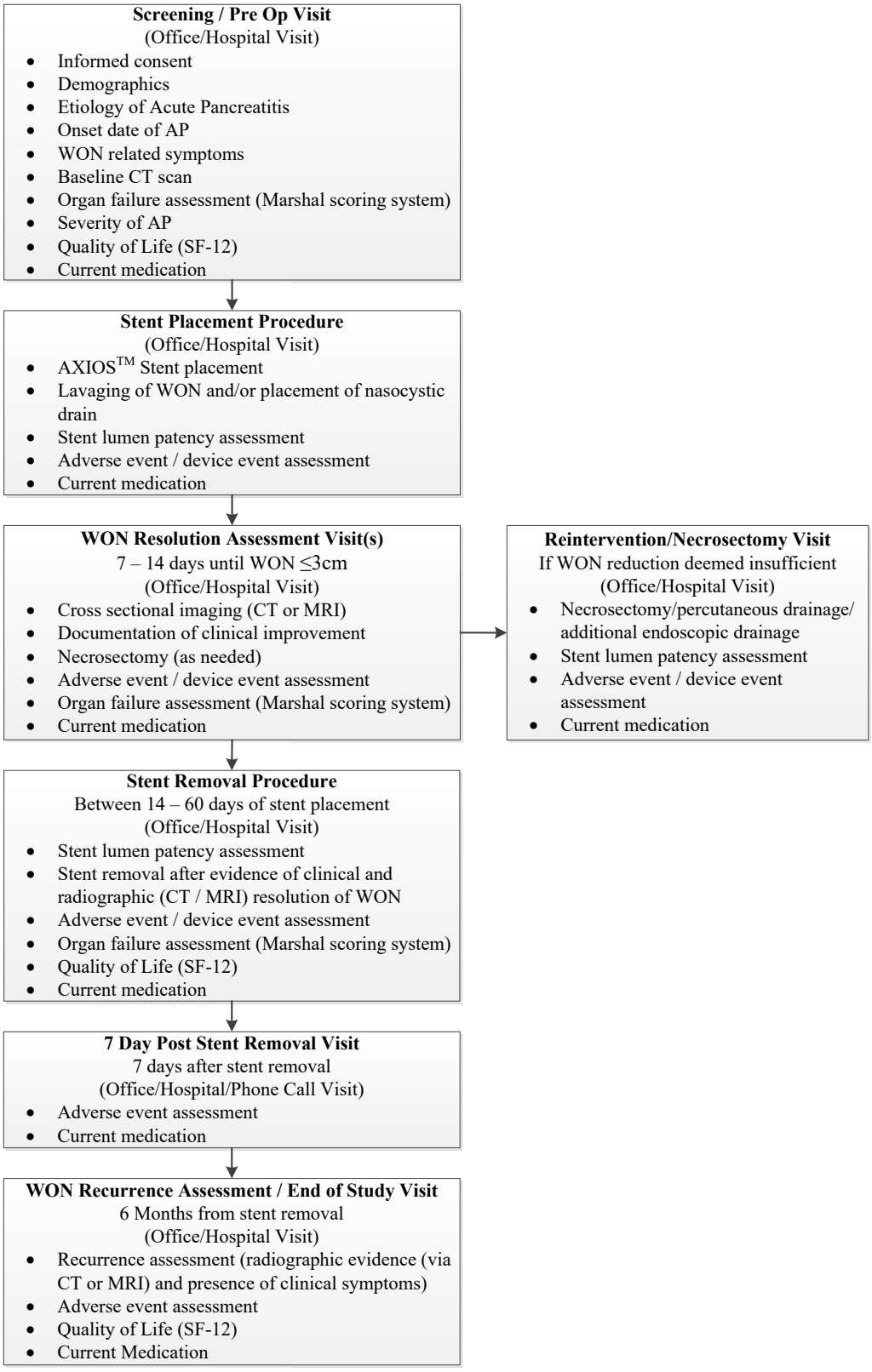
4.3 *Additional Endpoints*

1. Reduction of WON-related clinical symptoms.
   Note: WON-related symptoms as defined in Inclusion Criteria #4
2. Technical AXIOS™ stent placement success, defined as placement in desired location using endoscopic/EUS techniques per standard of practice.
3. Technical AXIOS™ stent removal success, defined as ability to remove the AXIOS™ stent using an endoscopic snare or forceps or graspers without AXIOS™ stent removal related serious adverse events.
4. Drainage procedural time: Time elapsed between initial puncture of the WON with electrocautery to endoscope retrieval.
5. Resolution of WON with or without necrosectomy by 6 months post AXIOS™ stent removal.
6. Time to WON resolution using same definition as for primary endpoint, namely:
   - Resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI.
7. Recurrence of WON after initial resolution and up to 6 months post AXIOS™ stent removal.
8. Stent lumen patency, evaluated via imaging or direct visual inspection with endoscope, and defined as one or both of the following:
   - Drainage through AXIOS™ stent visualized from the stomach or bowel, and/or
   - Visual confirmation of AXIOS™ stent lumen patency
9. Fluoroscopy (time) per endoscopic procedure.
10. Incidence of new organ failure from drainage procedure to WON resolution.
11. Change in Quality of life score (SF-12 questionnaire) from baseline to stent removal and end of study

4.4 *Study Design*

This study is a prospective, multi-center, single arm, consecutive series study. Treatment of up to 40 subjects will take place at up to 6 clinical centers. Subjects who meet all eligibility criteria will receive the AXIOS™ stent for up to 60 days stent indwell and 6 months follow-up after stent removal.

Figure 4.4-1: WON Drainage IDE Study Design



and where it is possible to place the AXIOS™ stent in a position such that the inner flange (inside WON) has enough space to expand.

- Lavaging of WON under endoscopic visualization and/or placement of nasocystic drain, or a single, 7fr double pigtail plastic stent (Boston Scientific 7Fr Advanix™ Biliary Stent) through the AXIOS™ stent at the discretion of investigator
- Stent lumen patency assessment
- Adverse event assessment/device event assessment
- Current medication
- Labs (as needed)
  Note: Labs need to be repeated at this visit ONLY IF they were collected more than 3 days before the stent placement procedure.

Multiple Interventions During Index Procedure:
Once stent is placed into the WON, dilation of the AXIOS™ stent is allowed to expand the stent if needed. Dilation can be performed to the maximal diameter of the AXIOS™ stent. A single, 7 fr double pigtail plastic stent (Boston Scientific 7Fr Advanix™ Biliary Stent) may be placed through the AXIOS™ stent at the discretion of the investigator. Access to the WON with a forward viewing diagnostic or therapeutic upper gastroscope is allowed up to 20 minutes (from time of endoscopic access of the WON) to break-up large chunks of necrosis and lavage collection at the discrection of the physician.

<u>WON Resolution Assessment - 7 days (+/- 3 days) for inpatients and 14 (+/- 5 days) days for outpatients (needed until radiographic decrease of WON size to ≤ 3cm) – Office/Hospital Visit:</u>

- Cross sectional imaging (CT or MRI) to assess reduction in WON size. If reduction in size is deemed insufficient, necrosectomy will be initiated
- Documentation of clinical improvement defined as improvement of principal WON-related symptoms
- Necrosectomy (as needed)
- Adverse event assessment/device event assessment
- Organ failure assessment (Marshal scoring system)
- Current medication
- Labs (as needed)

<u>Reintervention/Necrosectomy Visits when needed during AXIOS™ stent indwell – Office/Hospital Visit:</u>

- Necrosectomy initiated if WON reduction in size is deemed insufficient during WON Resolution Assessment Visit. Duration of each necrosectomy session is limited to 60 minutes
- Percutaneous drainage or additional endoscopic drainage may be needed if reduction in WON size is insufficient or in cases of continued WON related symptoms such as infection/sepsis despite necrosectomy. Choice of stent (AXIOS™ or plastic double pigtail

stent(s)) for repeat endoscopic drainage procedures will be left to the discretion of the investigator. The double pigtail plastic stent(s) or new AXIOS™ stent may be placed through the tract established by the original AXIOS™ stent or in a separate location.
- Stent lumen patency assessment
- Imaging (as applicable)
- Labs (as needed)
- Adverse event assessment/device event assessment
- Current medication

Stent Removal Visit - between 14 days and 60 days (+/- 7 days) of stent placement – Office/Hospital Visit

- Stent lumen patency assessment
- Stent removal after evidence of clinical and radiographic (via CT or MRI) resolution of WON
  Note: Removal of stent by 60 days is required if WON not resolved. Patients with unsuccessful or incomplete WON resolution by 60 days will proceed to standard of care treatment outside of this protocol after removal of the AXIOS™ stent; however, the patient outcome will continue to be followed. Alternative interventions may include surgery, endoscopic drainage with double pigtail plastic stents, percutaneous catheter drainage and necrosectomy (video-assisted retroperitoneal debridement (VARD), or endoscopic transluminal debridement, or open necrosectomy).
- Adverse event assessment/device event assessment
- Organ failure assessment (Marshal scoring system)
- Quality of Life (SF-12)
- Current medication

7 Day (+/-3 days) Post Stent Removal Visit – (Office or phone call):

- Adverse Event assessment
- Current medication

WON Recurrence Assessment Visit/End of Study – at 6 Months (+/- 14 days) from stent removal:
- Recurrence assessment (presence of clinical symptoms and further diagnosis per standard of care (e.g. labs and imaging)
- Adverse Events assessment
- Quality of Life (SF-12)
- Current medication

6.4 *Study Completion*

Subjects will be followed for 6 months after stent removal.

- If a single, 7fr plastic stent is used at the same drainage site, through the AXIOS™ stent, and the entire fluid collection drains to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered a single collection drainage success.
- If a plastic stent is used at a new drainage site and the entire fluid collection does not drain to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered a single drainage failure.

Hypothesis:

As in the original IDE, #G130264, there is no formal statistical hypothesis for this study. The proportion of AXIOS patients with reduction of WON size to ≤ 3cm within 60 days from AXIOS™ stent placement in the original IDE is 76.7% (23/30) [95% CI (57.7%, 90.0%)] patients. Given that the WONs in the proposed IDE will have an estimated necrotic material content above 30%, namely larger than in IDE #G130264, a slightly lower success rate of 70% is expected in this study. This success rate is within the range of reported WON resolution rates in several recent publications [2-8] representing 448 patients for which a random effects meta-analysis yields a mid-point WON resolution rate of 67.0% [95% CI (60.0%, 73.4%)] for WON drainage with plastic stents (Table 7.1), an established WON drainage method as described in the ASGE guidelines on treatment of pancreatic fluid collections [9].

Table 7.1 Plastic Stent WON Resolution Rates from Recent Publications

Study	% Resolution (x/N)	95% Confidence Interval
Bapaye (2017)	73.8% (45/61)	(60.9%, 84.2%)
Gardner et al (2009)	68.9% (31/45)	(53.4%, 81.8%)
Papachristou (2007)	52.8% (28/53)	(38.6%, 66.7%)
Schmidt (2015)	61.7% (50/81)	(50.3%, 72.3%)
Smoczynski (2015)	75.9% (85/112)	(66.9%, 83.5%)
Abu Dayyeh (2017)	75.0% (27/36)	(57.8%, 87.9%)
Varadarajulu (2011)	60.0% (36/60)	(46.5%, 72.4%)
Random-Effects Meta-Analysis	**67.0%**	**(60.0%, 73.4%)**

Statistical Methods:

The primary effectiveness endpoint will be summarized as the proportion of patients who have resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI out of all patients who have an AXIOS™ stent successfully implanted. A Clopper-Pearson exact 95% confidence interval will also be calculated.

7.2 *Safety Endpoint*

Primary Safety Endpoint:

The Primary Safety Endpoint is AXIOS™ stent related or WON drainage procedure related serious adverse events.

Primary Safety Endpoint Assessment:

If it is determined that the patient has an infection, then the primary safety success of the AXIOS™ device or the drainage procedure will be assessed as follows:

- If the patient presents with an infected collection at the initial drainage procedure, the infection will be classified as a localized infection and will not be considered a stent related or WON drainage related serious adverse event
- If the patient presents with a sterile collection at the initial drainage procedure and post-procedurally develops an infected collection, the infection will be classified as a localized infection and will not be considered a stent related or WON drainage related serious adverse event as this is a known consequence of any endoscopic drainage procedure, where the access route to the collection is through a non-sterile GI lumen and is not a function of a particular stent or device

  (*Note: If the stent is occluded at the onset of infection, then the infection will be attributed to the device. If the stent remains unobstructed at the time of infection, then the infection will not be attributed to the device.)*
- If the patient presents with a sterile collection at the initial drainage procedure and then post-procedurally develops a wide-spread infection in the form of sepsis or blood stream infection, then the infection will be classified as systemic and will be considered a stent related or WON drainage related serious adverse event only if the AXIOS stent was clearly and visually occluded by solid necrosis at the time of repeat endoscopy. This determination will be made by the operating physician at the time of endoscopy

Hypothesis:

As in the original IDE, #G130264, there is no formal statistical hypothesis for this study. The proportion of AXIOS patients with AXIOS™ stent related or WON drainage procedure related serious adverse events in the original IDE is 10.0% (3/30) [95% CI (2.1%, 26.5%)] patients. A similar rate of AXIOS™ stent related or WON drainage procedure related serious adverse events is expected in this study. This event rate is within the range of reported stent related or WON drainage procedure related serious adverse event rates in several recent publications [3-5, 10] representing 306 patients for which a random effects meta-analysis yields a mid-point related SAE rate of 16.7% [95% CI (10.1%, 26.3%)] for WON drainage with plastic stents (see Table 7.2 and Table 7.3 (categorized events from Table 7.2)), an established WON drainage method as described in the ASGE guidelines on treatment of pancreatic fluid collections [9].

15.2 *Definitions and Classification*

Adverse event definitions are provided in Table 15.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 15.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device NOTE 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, as defined by either: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Table 15.2-1: Safety Definitions

Term	Definition
Ref: ISO 14155 *Ref: MEDDEV 2.7/3*	
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	A device deficiency is any inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance.This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

15.3 *Relationship to Study Device(s)*

The Investigator must assess the relationship of any SAE or AE to the study device, study stent placement or removal procedure, and necrosectomy procedure. See criteria in Table 15.3-1:

VARD	Video-Assisted Retroperitoneal Debridement
WON	Walled-off Pancreatic Necrosis

5 Subject Selection

5.1 *Inclusion Criteria*

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criteria is met.

1. Age between 22 and 75 years old
2. Severe or moderately severe acute necrotizing pancreatitis, defined per the 2012 Revised Atlanta Classification[1]
3. WON resulting from necrotizing pancreatitis per contrast-enhanced CT with the following characteristics, per the 2012 Revised Atlanta Classification: [1]

   • Heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous)

   • Well defined wall

   • Location-intrapancreatic and/or extrapancreatic
4. Infected WON or symptomatic sterile WON

   Note: WON-related symptoms may include: pain, fever, leukocytosis, failure to thrive or deterioration of overall heath score, gastric outlet obstruction (GOO), weight loss, biliary obstructive symptoms, systemic inflammatory response syndrome (SIRS), deteriorating organ function, chronic nausea, lethargy, and inability to eat or gain weight
5. Imaging suggestive of greater than 30% necrotic material
6. WON ≥ 6cm in size
7. Eligible for endoscopic intervention
8. Acceptable candidate for endoscopic transluminal drainage
9. Patient understands the study requirements and the treatment procedures and provides written Informed Consent
10. Patient is willing to comply with all specified follow-up evaluations, including willingness to undergo a pre/post CT imaging study

5.2 *Exclusion Criteria*

Subjects who meet any one of the following criteria will be excluded from this clinical study.

1. Pseudocyst
2. Cystic neoplasm
3. Untreated Pseudoaneurysm > 1cm within the WON
4. More than one WON clearly separated and requiring drainage

Additional visits may be conducted at the Investigator's discretion in accordance with Adverse Event or Device Event data collection. A subject will be considered lost to follow-up if the subject remains unresponsive to communication after three documented attempts by study staff.

6.5 *Source Documents*

The Investigator/institution guarantees direct access to original source documents, including imaging documentation, by BSC personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review.

7 Statistical Considerations

7.1 *Effectiveness Endpoint*

Primary Effectiveness Endpoint:

The primary effectiveness endpoint for this study is the resolution of WON with endoscopic drainage defined as radiographic decrease of WON size to ≤ 3cm evaluated by CT scan or MRI

Primary Effectiveness Endpoint Assessment:

Note: Success will be based on the number of WONs resolved, not on the number of AXIOS™ Stents required to achieve resolution.

- If it is determined that the fluid collection is actually two separate collections, and each collection is drained via an AXIOS™ stent, then each collection will be assessed individually via the drainage success criteria of ≤3cm.
- If it is determined that the fluid collection is a single collection but the drainage is inadequate via a single AXIOS™ stent, then the success of the AXIOS™ drainage will be assessed as follows:
    - If a second AXIOS™ stent is used at a new drainage site/original drainage site and the entire fluid collection is drained to meet the success criteria of ≤3cm then the collection will be considered to be a single collection drainage success.
    - If a second AXIOS™ stent is used at a new drainage site and the entire fluid collection does not drain adequately to meet the drainage success criteria of ≤3cm then the fluid drainage of the collection will be considered to be a single drainage failure.
    - If a plastic stent is used at a new drainage site and the entire fluid collection drains to meet the drainage success criteria of ≤3cm then the fluid drainage will be considered indeterminate.

Table 7.2 Plastic Stent-related or WON Drainage-procedure related Serious Adverse Events Rates from Recent Publications [3-5, 10]

Study	% Related SAEs (x/N)	95% Confidence Interval
Papachristou (2007)	20.8% (11/53)	(10.8%, 34.1%)
Schmidt (2015)	12.3% (10/81)	(6.1%, 21.5%)
Smoczynski (2015)	25.9% (29/112)	(18.1%, 35.0%)
Varadarajulu (2011)	8.3% (5/60)	(2.8%, 18.4%)
Random-Effect Meta-Analysis	**16.7%**	**(10.1%, 26.3%)**

Table 7.3 Categorized Plastic Stent-related or WON Drainage-procedure related Serious Adverse Events Rates from Recent Publications [3-5, 10]

SAE	% (x/N)
Bleeding	11.1% (34/306)
Perforation	2.6% (8/306) [5 GI; 2 Collections; 1 Undefined]
Pneumoperitoneum	1.3% (4/306)
Sepsis	0.7% (2/306)*
Stent migration	1.0% (3/306)
Multiple organ failure	1.0% (3/306)
Other - loss of access to the collection (due to hypertension)	0.3% (1/306)

*Note: 1 patient with septic shock also had multiple organ failure (death)

Statistical Methods:

The primary safety endpoint will be summarized as the proportion of patients who have AXIOS™ stent related or WON drainage procedure related serious adverse events out of all patients who have an AXIOS stent successfully implanted. A Clopper-Pearson exact 95% confidence interval will also be calculated.

7.3 *Sample Size and Success Criteria*

The WON resolution rates and related SAE rates reported in the above provided study references are similar to those reported for WON drainage using plastic stents in a recent systematic review and meta-analysis comparing plastic stents to metal stents, including lumen-apposing metal stents (LAMS) for the management of WONs [28]. Appendix I in Section 21 provides a few key points from this systematic review.

Although reported effectiveness and safety event rates from different sources appear similar, 95% confidence intervals are fairly wide, mostly due to small sample sizes and heterogeneity in WONs and in detailed procedural WON drainage steps. Therefore we chose to increase the sample size of the present study to be slightly larger than in the original IDE study #G130264, which was 30 patients.

Table 15.3-1: Criteria for Assessing Relationship of Study Device, Procedure, Stent Removal and any Complete Distal Migration to Adverse Event

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to;

21 Appendix A. Key points extracted from Bazerbachi et al (GIE 2017) [28]

The WON drainage stent types for cases represented in the Bazerbachi et al (GIE 2017)[28] systematic review and meta-analysis included 2213 patients

- 1202 patients with WON drainage using plastic stents
- 1011 patients with WON drainage using metal stents
    - 871 patients with WON drainage using Lumen Apposing Metal Stents (LAMS)
        - 503 patients with WON drainage using AXIOS LAMS
        - 368 patients with WON drainage using non-AXIOS LAMS
    - 140 patients with WON drainage using non-LAMS

Table A1. Summary of Meta-Analysis Metrics Results

Metric	Plastic stents	Metal stents	Lumen-apposing metal stents
Two arm-studies			
Overall resolution	80.9%	92.1% (OR: 2.8; 95% CI, 1.7-4.6; $P < .001$)	91.5% (OR, 2.5; 95% CI, 1.4-4.3; $P = .001$)
Rate of resolution with a single procedure	43.4%	47.1% (OR: 1.3; 95% CI, 0.7-2.4; $P = .2$)	52.3% (OR, 1.4; 95% CI, 0.56-3.6; $P = .4$)
Number of procedures to achieve resolution	Mean difference −.92 (95% CI, −1.283-.561, $p < 0.001$) (favoring metal stents)		
Bleeding	7.1%	3.6% (OR: 0.5; 95% CI, 0.15-1.7; $P = .2$)	5% (OR, 0.64; 95% CI, 0.13-3.1; $P = .5$)
Perforation	3%	1.9% (OR: 0.6; 95% CI, 0.15-2.7; $P = .5$)	4% (OR, 1.2; 95% CI, 0.24-6.18; $P = .8$)
Stent migration	5.3%	6.7% (OR: 1.3; 95% CI, 0.6-2.6; $P = .4$)	6.3% (OR, 1.12; 95% CI, 0.51-2.47; $P = .7$)
Stent occlusion	16.9%	11.7% (OR: 0.6; 95% CI, 0.34-1.1; $P = .1$)	3.8%(OR, 0.36; 95% CI, 0.03-4; $P = .4$)
One-arm studies			
Bleeding	12.6% [95% CI, 9.5%-16.5%]	5.6% [95% CI, 3.6%-8.6%] ($P = .002$)	6.2% [95% CI, 3.9%-9.6%] ($P = .007$)
Perforation	4.3% [95% CI, 3.1%-6%]	2.8% [95% CI, 1.6%-5%] ($P = .2$)	3.8% [95% CI, 2.1%-6.9%] ($P = .7$)
Stent migration	5.1% [95% CI, 2.6%-10.1%]	8.1% [95% CI, 5.1%-12.6%] ($P = .2$)	7.8% [95% CI, 4.7%-12.5%] ($P = .3$)
Stent occlusion	17.4% [95% CI, 9.4%-29.9%]	9.5% [95% CI, 7.5%-12.1%] ($P = .07$)	7.5% [95% CI, 5.6%-9.9%] ($P = .015$)