City of Hope

Annual

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

How to Design a Procedure-focused Clinical Trial in Oncology – The Endoscopist Perspective

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Learning objectives

1

Describe what makes procedure trials different

Understand why endoscopy trials aren't just drug trials with a scope — operator, device, blinding, and learning-curve realities.

2

Identify challenges and mitigation strategies

Recognize the eight operational challenges — and pre-specified fixes for each — that separate credible procedure trials from case series.

3

Compare design archetypes across two landmark trials

Contrast the design choices in Barrett's RFA (AIM-Dysplasia), and EUS-GE for malignant GOO (ENDURO).

4

Apply a practical framework to your own next protocol

Take away a pre-flight checklist and a stepwise pathway from pilot data through pivotal trial to guideline change.

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Procedure trials are under-represented in oncology evidence

Most

Pivotal GI oncology RCTs test drugs or surgery — not endoscopic interventions

Few

Multicenter randomized trials of endoscopic oncologic therapy reach Phase III

Wide

Variability between operators, devices, and centers — often unmeasured

Why this matters

Endoscopic oncology is moving fast — Endoscopic ablation, EMR/ESD, EUS-guided ablation, AI detection, MRD-guided surveillance.

Adoption, reimbursement, and guideline status all hinge on the quality of the trials WE design.

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Start with a sharp PICO question



Population

Adults with non-dysplastic Barrett's ≥ 3 cm



Intervention

Endoscopic ablation + PPI



Comparator

Surveillance endoscopy + PPI



Outcome

Histologic eradication at 12 months

Procedural twist: the "I" must specify the device, the technique, and the operator credentialing — not just "ablation."

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Phases — reframed for procedures and devices

PHASE 0	PHASE 1	PHASE 2	PHASE 3	PHASE 4
Pre-clinical / Bench	**First-in-Human / Feasibility**	**Pilot / Phase II**	**Pivotal / Phase III**	**Post-market / Real-world**
Ex vivo, animal, simulator	Safety, technical success, dose-finding (energy, depth)	Efficacy signal, learning curve, refine protocol	Multicenter RCT vs standard of care or comparator device	Registry, durability, generalizability, rare AEs

Key insight: The device-development cycle (IDEAL framework — Idea → Development → Exploration → Assessment → Long-term study) maps better to procedure trials than the classical drug Phase I–IV pipeline.

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Eight challenges the endoscopist must plan around

Operator variability

Outcome depends on who performs the procedure

Learning curves

Performance changes during the trial itself

Blinding is hard

Operator always knows the arm; often the patient does too

Device evolves mid-trial

v2.0 launches before enrollment ends

Sham-controlled designs

Ethically and logistically demanding

Equipoise and ethics

Procedural risk creates a higher consent bar

Multicenter standardization

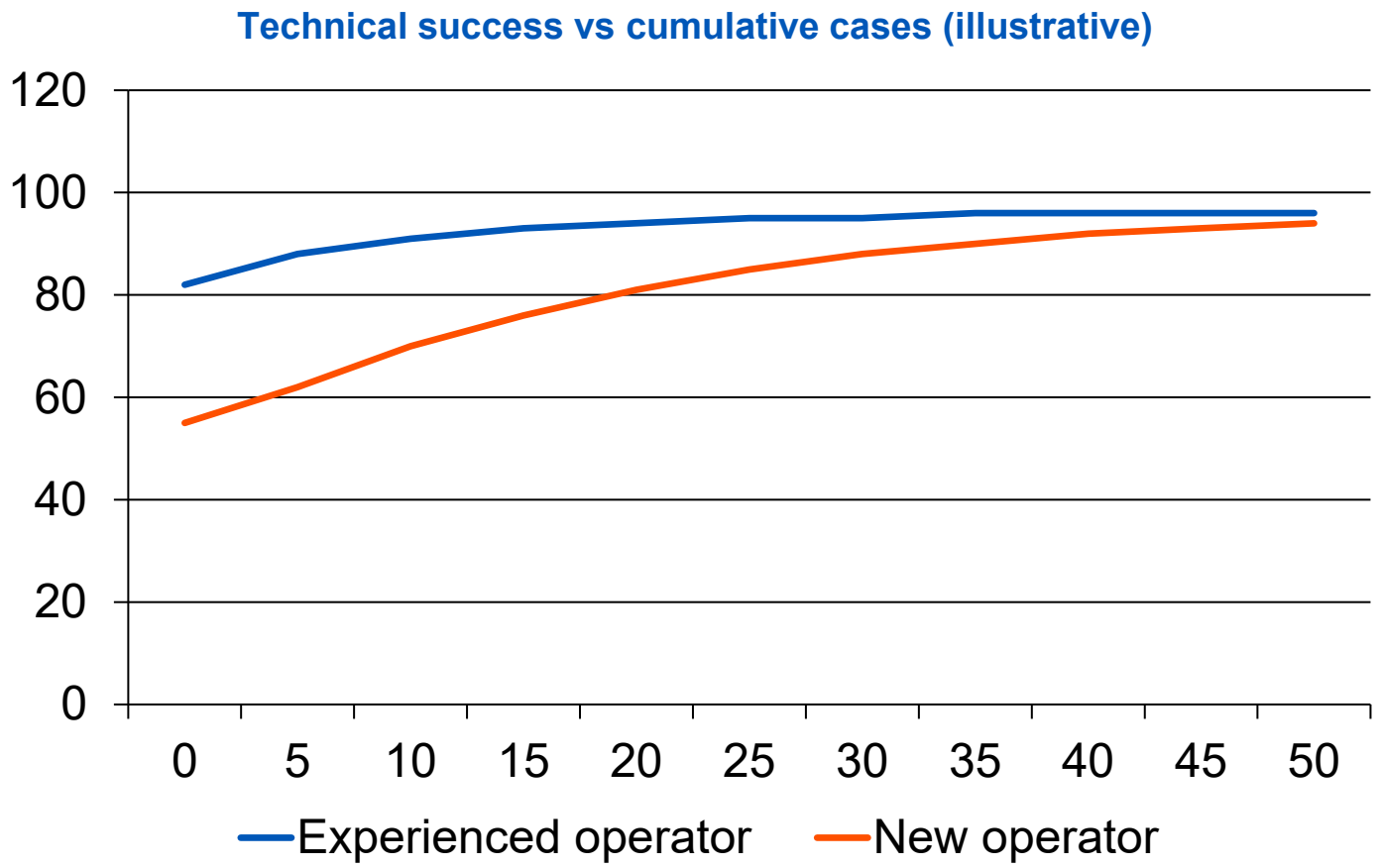
Same protocol ≠ same procedure across sites

Endpoint definitions

"Technical" vs "clinical" success may diverge

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The operator learning curve can be a significant confounder



Design mitigations

- Pre-specify a credentialing threshold (e.g., ≥ N supervised cases or competency assessment)
- Run a lead-in phase before randomization begins
- Stratify randomization by site AND operator volume
- Pre-plan analyses by case-order to detect curve effects
- Centralized procedure video review for QA

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When you can't blind the operator — what then?

Open-label

Most common — but most biased

Strengths

- Pragmatic
- Simple consent
- Reflects practice

Trade-offs

- Performance bias
- Outcome assessment bias
- Crossover risk

Single-blind

Patient blinded; assessor blinded to arm

Strengths

- Reduces ascertainment bias
- Often feasible
- Central reads add rigor

Trade-offs

- Operator still unblinded
- Maintaining patient blinding is hard

Sham-controlled

Highest internal validity

Strengths

- Quantifies placebo effect
- Gold standard for subjective endpoints

Trade-offs

- Ethics committee scrutiny : SOC
- Cost and complexity
- Recruitment is harder

Endoscopist's reality check: Sham endoscopy is feasible — landmark Barrett's RFA and bariatric endoscopy trials have done it — but it requires anesthesia teams, dedicated unblinded staff, and IRB partnership from day one.

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Three Outcomes — Tailor to the Trial

Technical / Procedural
Did the procedure work?

Clinical / Oncologic
Did the patient benefit?

Patient-centered
Did it matter to patients?

Examples in GI endoscopic oncology

Technical

R0 resection rate, en-bloc rate, complete eradication of intestinal metaplasia (CE-IM), depth of ablation, technical success of stent placement

Clinical / Oncologic

Recurrence-free survival, progression to cancer, need for surgery, dysplasia at 1 year, MRD clearance

Patient-centered

Dysphagia score, QoL (FACT-E, EORTC), days alive and out of hospital, return to oral intake

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Outcomes : Surrogate versus Robust Clinical

Surrogate endpoints

Faster, cheaper — but require validation

- CE-IM in Barrett's
- ctDNA / MRD clearance
- Polyp recurrence at 1 year
- Pathologic complete response after CRT
- Progression-free survival

Hard / clinical endpoints

What patients and payers ultimately want

- Cancer-specific mortality
- All-cause mortality
- Need for esophagectomy / colectomy
- Symptom-free survival
- Quality-adjusted life years (QALY)

Rule of thumb: If you want FDA labeling or NCCN inclusion, a validated surrogate may suffice for accelerated approval — but plan a confirmatory study with hard endpoints.

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Statistical Considerations

α / β

Type I and II error

Conventionally 0.05 / 0.20 — but pre-specify

Δ

Effect size

Driven by clinical importance, not what makes the math work

n

Sample size

Inflate for cluster effects, drop-outs, crossovers

Statistical considerations unique to procedure trials

Cluster effects: patients within an operator are correlated — use multilevel / mixed-effects models, not naïve t-tests.

Non-inferiority vs superiority: if the new procedure is less invasive, NI may be the right framing — but the margin must be clinically defensible.

Adaptive designs: Bayesian and group-sequential designs let you stop for futility or efficacy — well-suited to small, expensive procedural cohorts.

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Recruitment is critical for success : Tips

1

Know the epidemiology

Many endoscopic-oncology indications are uncommon. Pre-screen registries and EHRs before committing to a sample size.

2

Map the referral pathway

Patients with early esophageal or pancreatic neoplasia don't walk in — they're referred. **Identify the referrers before activation.**

3

Pick sites that DO the procedure

Site selection by case-volume beats geographic distribution. **One high-volume center can outpace ten naïve sites.**

4

Mind the patient burden

Multiple endoscopies, biopsies, imaging — each visit erodes consent. **Build the protocol around what patients will actually finish.**

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Pitfalls : Same protocol ≠ Same procedure, How to avoid

1

Manualize

Detailed procedure manual; videos; common technique algorithm

2

Credential

Operator-level credentialing before activation; document the threshold

3

Calibrate

Pre-trial workshops; shared phantoms / ex-vivo models for technique drift

4

Capture

Procedure videos uploaded for every case; standardized image protocols

5

Audit

Central core-lab review of pathology, imaging, and procedure videos

The unsexy work of standardization is what makes a multicenter procedure trial actually generalizable. Skip a step and your effect size belongs to one operator, not your intervention.

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Beyond the classic two-arm RCT

Adaptive / Bayesian

Pre-specified rules to modify sample size, randomization ratio, or arms based on accumulating data. **Useful when prior precision is low.**

Platform / umbrella

One master protocol, multiple devices or techniques, shared control. **Efficient for crowded device spaces.**

Registry-embedded RCT

Randomization layered on a high-quality clinical registry — lean cost, real-world generalizability, durable follow-up.

Stepped-wedge

Sites cross from control to intervention in sequence. Handy when **blinding is impossible** and the intervention will be implemented anyway.

Hybrid effectiveness-implementation

Co-primary endpoints: clinical effect AND adoption / fidelity. **Speeds the path from positive trial to real-world uptake.**

Real-world evidence (RWE)

Propensity-matched cohorts from EMR / claims / registries — **increasingly accepted by FDA for label expansion**.

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CASE STUDY 1 — DIAGNOSTIC / EARLY-CANCER

Barrett's RFA — sham-controlled, pathology-anchored

From feasibility to guideline — the arc

1	**Feasibility**	Single-arm dosimetry, depth-of-injury studies in resected esophagus
2	**Pilot**	Open-label efficacy in non-dysplastic and dysplastic Barrett's
3	**Pivotal**	Sham-controlled multicenter RCT with central pathology review
4	**Real-world**	Multicenter consortia / registries — durability, recurrence, surveillance
5	**Guideline**	Endorsed by GI society guidelines as standard of care for dysplastic Barrett's

What worked

- A sham control was feasible AND informative
- Central, blinded pathology review gave the trial credibility
- Pre-specified surrogate (CE-IM) was clinically meaningful
- Industry partnership did not undermine independence
- Long-term registries answered durability and recurrence

Shaheen, NEJM 2009

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CASE STUDY 3 — PALLIATIVE / PANCREATICOBILIARY

EUS-GE for malignant GOO — endoscopy vs surgery

From LAMS clearance to head-to-head RCT — the arc

1	**Foundation**	Hot AXIOS LAMS already FDA / CE cleared for pseudocyst and WON drainage
2	**Evolution**	Off-label case series extended LAMS to EUS-guided gastroenterostomy for GOO
3	**Pilot**	Multicenter cohorts established feasibility and safety
4	**Pivotal**	ENDURO — 12 Dutch centers, 1:1 open-label RCT vs surgical GJ (2025)
5	**Next**	DRA-GOO vs duodenal stenting; guideline updates; US replication

Design choices that worked

- Competence gating — ≥ 20 LAMS and ≥ 10 EUS-GE per site
- Co-primary endpoints — soft solids AND reintervention; objective, no blinding
- Endoscopy vs surgery head-to-head — cross-specialty equipoise built in
- Real-world palliative population — reflected actual clinical use
- Label-expansion pathway — evidence gap was indication, not safety

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Different questions may demand different designs

	Barrett's RFA *AIM-Dysplasia*	EUS-GE for malignant GOO *ENDURO*
Question	Can we eradicate dysplasia in Barrett's?	Endoscopy or surgery to palliate GOO?
Design	Sham-controlled, blinded, multicenter RCT	Open-label superiority RCT vs surgery
Primary endpoint	Histologic eradication (CE-IM, CE-D)	Time to soft solids; reintervention rate
Randomization unit	Patient-level, 2:1	Patient-level, 1:1
Regulatory path	Device clearance → society guidelines	Pre-existing FDA / CE clearance for LAMS
Design lesson	***Sham works when blinding matters most***	***Competence gating when blinding is impossible***

The right design isn't the most rigorous one — it's the one that answers the actual question

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The pathway to NCCN and society guidelines

STEP 1

Publish

Peer-reviewed, transparent reporting (CONSORT extensions for non-pharm / device interventions)

STEP 2

Replicate

Independent confirmation, ideally in a different population or system

STEP 3

Synthesize

Systematic review / meta-analysis; **cost-effectiveness modeling**

STEP 4

Advocate

Society guideline panels (ASGE, ACG, AGA); NCCN nomination via panel members

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What can undermine procedure trials — and how to mitigate

DON'T

Conflate technical success with clinical benefit

DON'T

Underestimate operator and learning-curve effects

Pre-specify them, measure them, adjust for them.

DON'T

Let the device update mid-trial without a plan

Pre-specify how protocol amendments will handle hardware changes.

DON'T

Skip pre-registration

ClinicalTrials.gov before first patient — non-negotiable.

DO

Build a statistical analysis plan BEFORE unblinding

Lock the SAP. Lock it. Follow the plan

DO

Plan for missing data and crossovers

Procedural cohorts have more dropouts than you think.

DO

Engage patients in design

What they value is often not what we measure.

DO

Report negative trials

The literature needs them more than positive ones.

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TAKE-HOME MESSAGES

Five things to carry into your next protocol

1. Procedure trials demand the same rigor as drug trials — and then some. The operator IS part of the intervention.
2. Pre-specify : endpoints, credentialing, statistical plan, handling of device updates.
3. Can choose surrogate endpoints carefully and validate them — but plan a confirmatory study with clinically relevant and guideline level outcomes.
4. Adaptive, registry-embedded, and hybrid implementation designs may fit our world better than the classical phased pipeline.
5. Design the trial with adoption in mind from day one : guidelines, payers, real-world delivery.

Thank You

Questions and discussion

- *What's your primary endpoint — is this clinically defensible/acceptable ?*
- *How will you handle device evolution mid-trial?*
- *Proactively think of guideline level evidence generation*

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