



# Treatment of perianal Crohn's fistulas: Seton vs. Anti-TNF vs. Surgical closure

*Christianne Buskens, Colorectal surgeon, AMC*



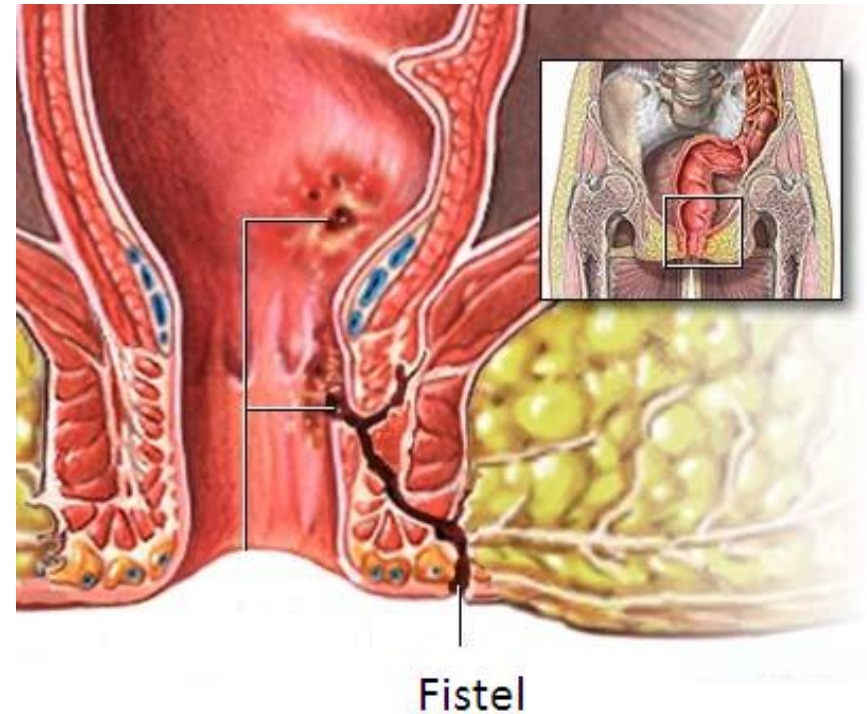
Up to 30% perianal fistula in Crohn's disease

Decreased QoL

- Pain
- Production
- Abscess

High use of medical resources

High costs

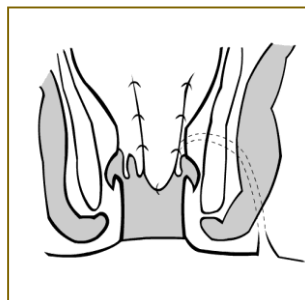
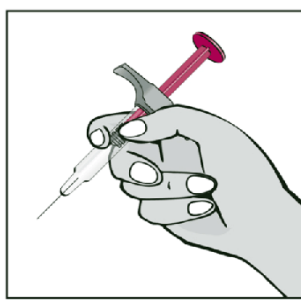
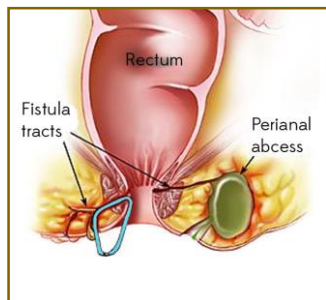


Complex fistula (involvement upper 2/3 sphincter):

- Seton drainage
- Anti-TNF
- Surgical closure

Advancement plasty

Ligation intersphincteric tract



#### 6.2.6. ECCO Statement 9G

Seton placement after surgical treatment of sepsis is recommended for complex fistulas [EL2]. The timing of removal depends on subsequent therapy.

#### 6.2.10. ECCO Statement 9L

Thiopurines [EL2], infliximab [EL1], or adalimumab [EL2], seton drainage, or a combination of drainage and medical therapy [EL3] should be used as maintenance therapy.

#### 6.3.1. ECCO-ESCP Statement 5A

The indications for surgery aiming to close a fistula-in-ano in CD include a symptomatic patient, with no concomitant abscess, with medically controlled proctitis, and a preferably anatomically defined fistula tract [EL3]

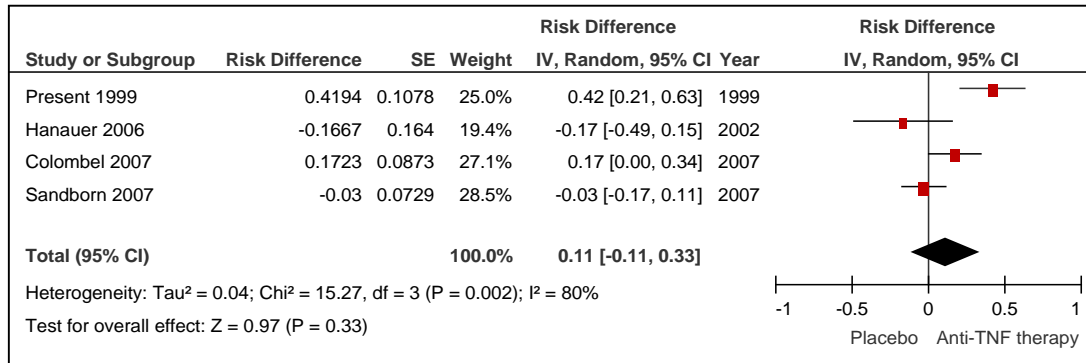
## Seton drainage

- Cheap, prevention of abscesses and recurrent tracts
- Low re-intervention rates (10-20%)
- Fistula will not close with seton in situ: QoL?
- Closure rates after removal?

Studies	No patients	No patients seton + removal	FU months (range)	Fistula closure (%)	Recurrence (%)	Applicability study
Morrison 1989	35	6	120 (ns)	6 (100)	1 (17)	low
Williams 1991	55	22	54 (6-120)	3 (14)	0	low
Scott 1996	59	27	20 (12-35)	23 (85)	4 (15)	low
Takesue 2002	32	9	62 (25-133)	0 (0)	3 (33)	low
Chung 2010	51	32	3 (endpoint)	10 (31)	ns	low

## Anti-TNF

- Expensive (25.000/year)
- Reduces production (increase QoL)
- External opening heals first -> increased risk abscess/ re-intervention



## Complete fistula closure

- Placebo: 13/109 (12%)
- anti-TNF: 32/109 (29%)
- 44% re-interventions

# Treatment Crohn's perianal fistula

**TABLE 3.** Outcome — success rates

Author	Breakdown etiology			Success rates (%)		
	Cryptoglandular	Crohn	Unknown	Overall	Cryptoglandular	Crohn
Oh <sup>6</sup>	15	X		86.7	86.7	X
Aguilar et al <sup>7</sup>	189	X		98.5	98.5	X
Jones et al <sup>8</sup>	6	6		66.7	100.0	33.3
Wedell et al <sup>9</sup>	27	X		96.7	96.7	X
Shemesh et al <sup>10</sup>	4	4		87.5	← 87.5 →	
Lewis and Bartolo <sup>11</sup>	2	6		75.0	50.0	83.3
Kodner et al <sup>12</sup>			36	80.0	(87.1)	(70.8)
Makowiec et al <sup>13</sup>	X	20		75.0	X	75.0
Lewis et al <sup>14</sup>	11	X		90.9	90.9	X
Ozuner et al <sup>15</sup>			46	69.8	(74.1)	(68.1)
Golub et al <sup>16</sup>	164	X		96.7	96.7	X
Joo et al <sup>17</sup>	X	8		73.1	X	73.1
Kreis et al <sup>18</sup>			6	62.5	(75.0)	(56.3)
Marchesa et al <sup>19</sup>	X	9		61.5	X	61.5
Miller and Finan <sup>20</sup>	18	X		83.3	83.3	X
Hyman <sup>21</sup>	6	14		75.0	83.3	71.4
Schouten et al <sup>22</sup>	44	X		75.0	75.0	X
Ortiz and Marzo <sup>23</sup>	103	X		93.0	93.0	X
Mizrahi et al <sup>24</sup>			53	57.0	(66.7)	(42.9)
Sonoda et al <sup>25</sup>			62	75.8	(77.1)	(50.0)
Zimmerman et al <sup>26</sup>	105	X		69.0	69.0	X
Dixon et al <sup>27</sup>	29	X		69.0	69.0	X
Koehler et al <sup>28</sup>	42	X		73.8		
Van der Hagen et al <sup>29</sup>	23	7		76.7		
Ellis and Clark <sup>30</sup>	35	X		62.9		
Gustafsson and Graf <sup>31</sup>	82	X		57.0		
Perez et al <sup>32</sup>	27	X		92.6		
Van der Hagen et al <sup>33</sup>	29	12		36.6		
Uribe et al <sup>34</sup>	51	5		92.9		
Zbar et al <sup>35</sup>	11	X		81.8		
Mitalas et al <sup>36</sup>	87	X		66.7		
Dubsky et al <sup>37</sup>	54	X		75.9		
Ortiz et al <sup>38</sup>	91	X		82.4		
van Koperen et al <sup>39</sup>	80	X		73.8		
Abbas et al <sup>40</sup>			25	76.0	← 76.0 →	
				76.2	78.1	67.5
				79.2	80.8	64.0

**Results Crohn's fistula**

- Initial success: 68%(12%)
- Recurrence rate: 50%
- Re-intervention rate: 50%

Current treatment: up to discretion of treating physician



Hypothesis:

- All treatment interventions comparable closure rates
- Seton less re-interventions and most cost-effective

**Group I**  
**Seton for 1 yr**

**Group II**  
**Anti-TNF for 1 yr**

**Group III**  
**Surgical closure**  
**anti-TNF for 4 mnths**

## Primary endpoint:

- Re-interventions

## Secondary endpoints:

- Closed fistulas (based on MRI)
- Perianal disease activity (PDAI)
- Quality of life
- Costs

Sample size re-intervention

50% anti-TNF  
surg. closure

20% seton

42 patients per group  
(total n=126)



## Inclusion

- Age  $\geq$  18 year
- Crohn's disease
- New or reactive fistula
- High fistula (>2/3 externe sfincter)
- 1 internal opening (MRI)

## Exclusion

- Proctitis or anorectale stenosis
- Submucosal, low intersfincterice fistulas or rectovaginale fistulas
- Seton in situ > 3 months
- Anti-TNF use during past 3 months or prior anti-TNF use without any effect on fistula (failure)
- Patients with stompy

Seton insertion & AB

Group I:  
**Chronisc seton drainage**  
 + 6MP  
 (N=42)

Group II:  
**Anti-TNF**  
 + 6MP  
 (N=42)

Group III:  
**Chirurgical closure**  
 + 6MP + anti-TNF  
 (N=42)

Stop treatment after 1 year

Follow-up 1 year

**Analyses primAry outcme:**  
 Rate patients with re-interventions

Follow-up 6 months

**Analysis secundaRy outcomes:**

- Rate re-interventions
- Rate closed fistulas
- Rate closed fistula tracts (MRI)
- Rate antibiotics
- Quality of life (EQ-5D & IBDQ)
- Disease activity (PDAI score)
- Days sick leave
- Days hospital admission
- Costs with CEA and BIA (Modified Health & Labour)



The work of many of the greatest men, inspired by duty, has been done amidst suffering and trial and difficulty. They have struggled against the tide, and reached the shore exhausted.

(Samuel Smiles)

izquotes.com

Jan 2014 – Nov 2018:

- 44 inclusions (slow inclusion rate!)

DSMB: interim analysis (AE = re-intervention)

Arm	Re-interventions, n (%)
Seton (n=15)	7/15 (47%)
Anti-TNF (n=15)	1/15 (7%)
Surgery (n=14)	2/14 (14%)
Total	10/44 (24%)

**Re-interventions**  
Significantly higher in  
seton-arm  $p=0.046$

Arm	Cross-over (without reintervention)
Seton (n=15)	6/15 (40%)
Anti-TNF (n=15)	0
Surgery (n=14)	0

Secondary outcome parameter: PDAI [scale 25 points]

- Seton                                    20 → 15
- Anti-TNF                                21 → 11
- Surgical closure                      21 → 9

**PDAI**  
Significantly higher in  
seton group

## Recommendations

- Safety: stop randomisation seton-arm



- Futility: Incidence re-intervention in remaining two arms too low to reveal significant differences

→ clinically relevant primary outcome parameter?

# RCT vs patient and doctor's preference

	RCT (n=44)	Patient preference (n=47)	Doctor's preference (n=35)
Age (mean (SD))	33 (10)	39 (11)	33 (21)
Gender (M:F)	16:28	18:29	18:17
Previous anti-TNF use	13 (28%)	14 (30%)	27 (77%)
Disease duration	7 (9)	6 (14)	7 (10)
No previous interventions	0.7 (0.4)	1.0 (0.3)	2.2 (0.3)
PDAI (total 42 points)	21 (5)	22 (6)	21 (5)
No of external openings	1.3 (0.6)	1.2 (0.4)	2.5 (0.5)

# RCT vs patient preference: results

	Seton	Anti-TNF	Surgery
<b>Reinterventions</b>			
RCT	7/15	1/15	2/14
Patient preference	4/16 (25%)	7/21 (33%)	1/10 (10%)
<b>Cross-overs</b>			
RCT	6		0
Patient preference	1		1

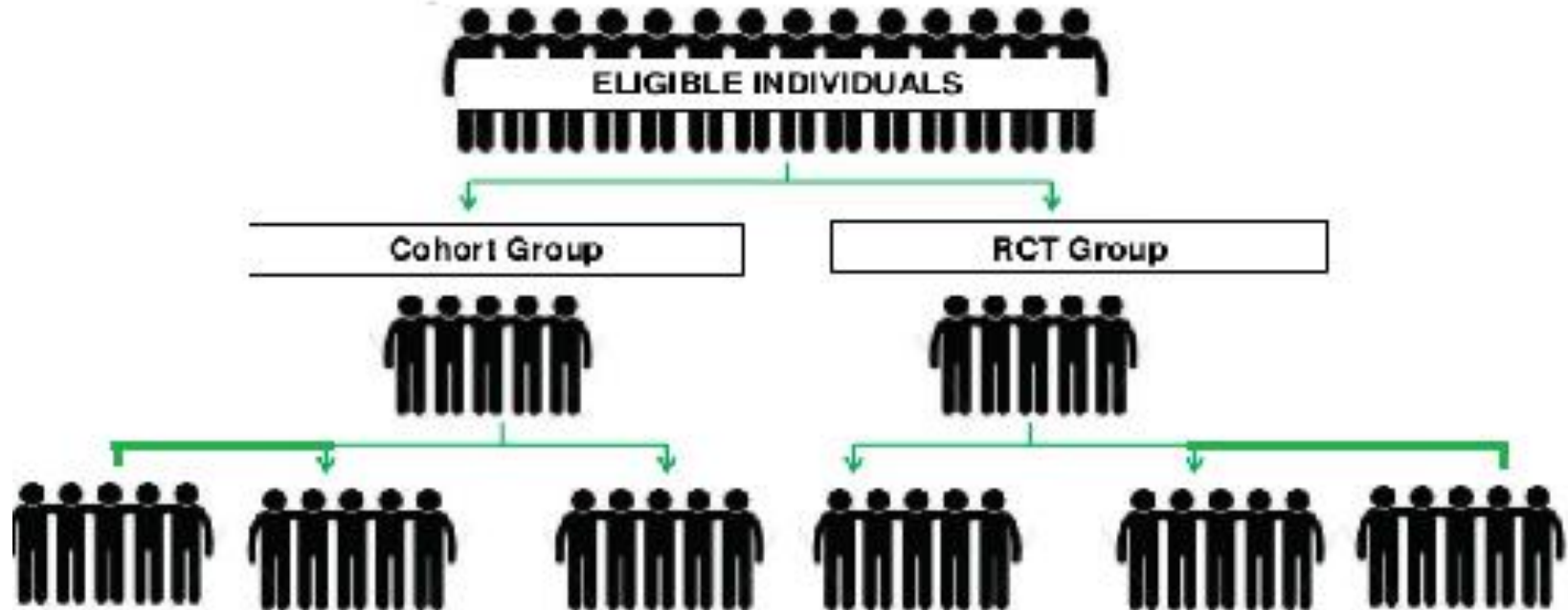


RCT best design for trials comparing medication to surgery?

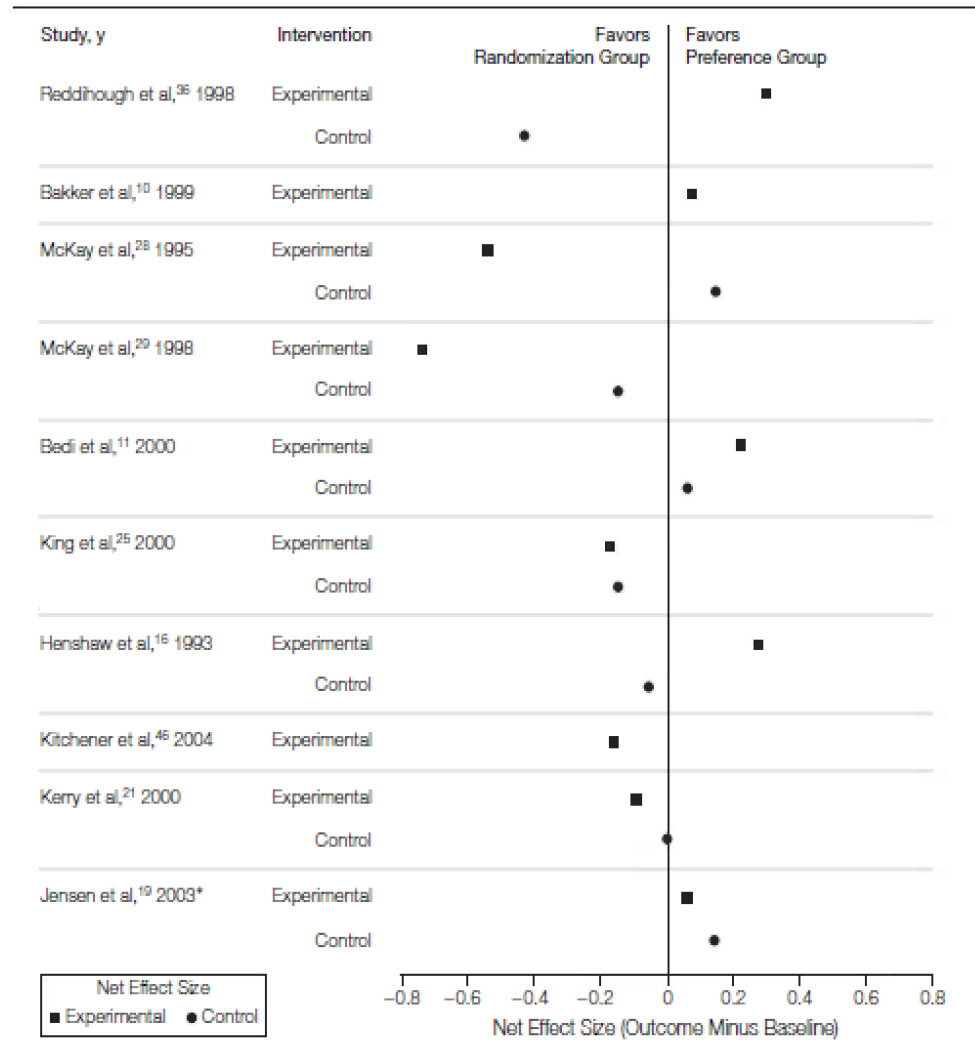
- Randomisation bias: low inclusion rate
- Preference bias: influencing subjective outcomes

Re-intervention objective outcome parameter?

- **Compromising external and internal validity**

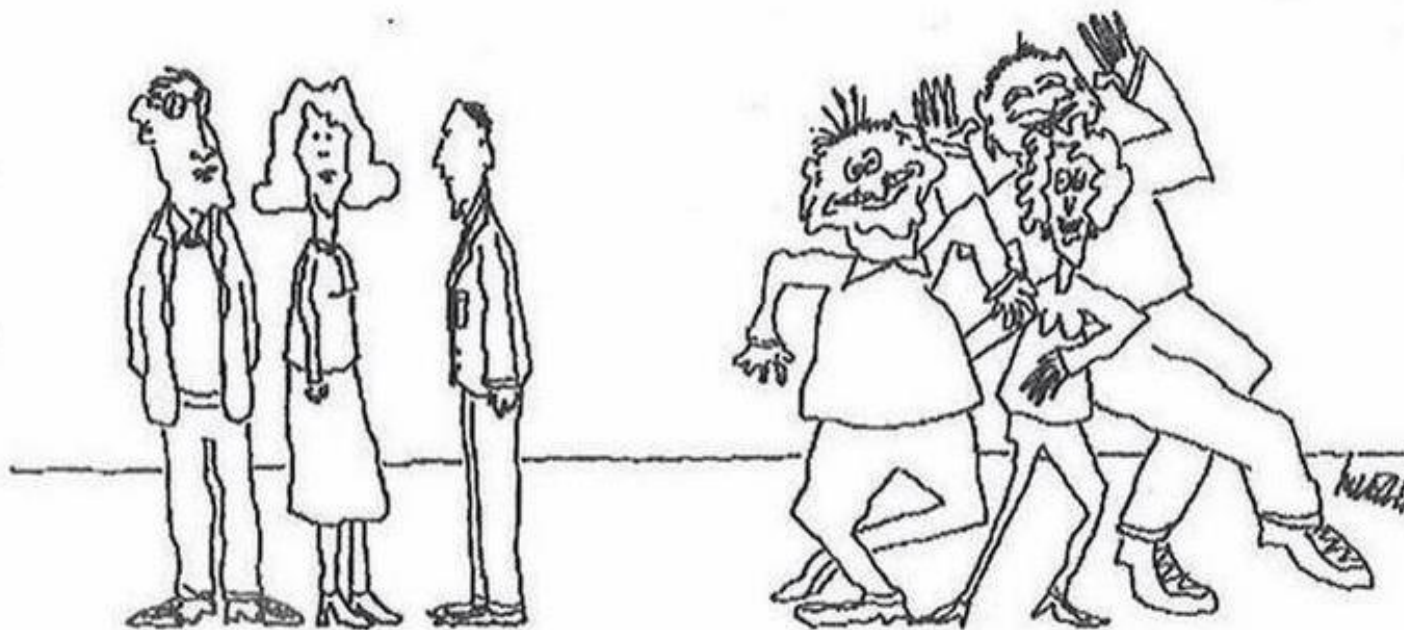


**Figure 2.** Net Effect Sizes for Preference vs Randomization Comparisons, by Study and Intervention Group



## Systematic review:

- *Baseline characteristics usually comparable*
- *Allocating patients to treatments that do not accord with their preferences influences internal and external validity of RCTs*



CONTROL GROUP

OUT OF CONTROL GROUP.

DSMB recommendation:

- Continue as a two-armed trial [anti-TNF & surgical closure]
- Choose more relevant primary outcome parameter

## P426 Meta-analysis of endorectal advancement flap vs. ligation of the intersphincteric fistula tract for Crohn's and cryptoglandular high perianal fistulas

January 2018 · Journal of Crohn's and Colitis 12(supplement\_1):S320-S320

DOI · 10.1093/ecco-jcc/jjx180.553

Merle Stellingwerf · E M van Praag · Willem A Bemelman · Christianne J Buskens

Surgical closure  
60-70% closure rate

## Efficacy of Medical Therapies for Fistulizing Crohn's Disease: Systematic Review and Meta-Analysis

MJ Lee et al. Clin Gastroenterol Hepatol. 2018 Jan 25. [more](#)

Anti-TNF  
40% remission

## Design:

- Comprehensive cohort design

## Hypothesis:

- Surgical closure most successful

## Primary endpoint:

- Fistula closure after 18 months (MRI based)

## Sample size

Fistula closure

50% surg. closure

25% anti-TNF

70 patients per group  
(total n=140)

- Every trial gives new and unexpected insights!
- RCT not optimal design for trials comparing surgery to medical treatment [*in case of subjective outcome parameter*]?
- Chronic seton drainage inferior for Crohn's fistulas [*acceptable if patient prefers*]
- Results of PISA II should be awaited....



# Thank you, PISA collaboration group



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