

# Autologous Stem Cell Transplantation in Crohn's Disease

The ASTIC trial

# Incidental allogeneic transplantation and CD: Seattle

- 1 Inactive → remained inactive 15 yrs
- 3 active → inactive for 6-10 yrs
- 1 active → active, resection at 2 yrs
- 1 died septic shock at day 97
  
- 1 improved (6/12 FU)

Lopez-Cubero GE 1998; 114:433

Drakos Am J Haematol 1993;43:157

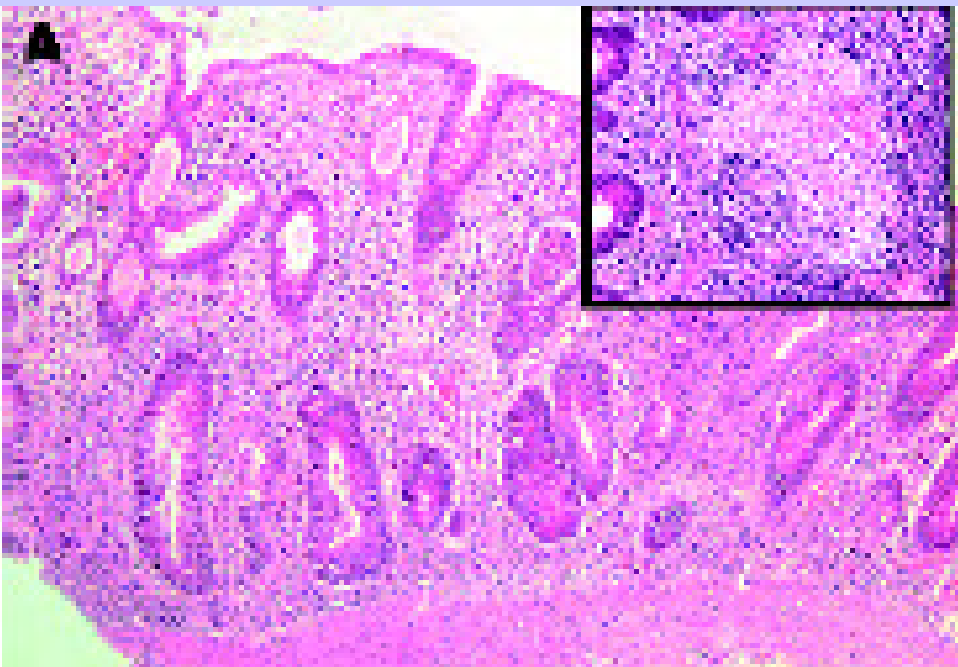
# Allogeneic transplantation and CD Germany

- 11 patients (CD 7, UC 4)
- History: 10 (0.5-22) years
- Follow up: 34 (3-117) months
- 6 patients active at conditioning (4 SASP / steroids)
- 10 inactive after transplant (3 initial symptoms or “atypical” histology, 1 CMV colitis, 2 GVHD)
- 2 remission of extraintestinal manifestations
- 2 off immunosuppression

# Incidental allogeneic SCT, Conclusions

- Allogeneic SCT may ameliorate CD
  - ? Replace a defined genetic defect
- Could allogeneic SCT give you CD?
  - ? Impose a defined genetic defect

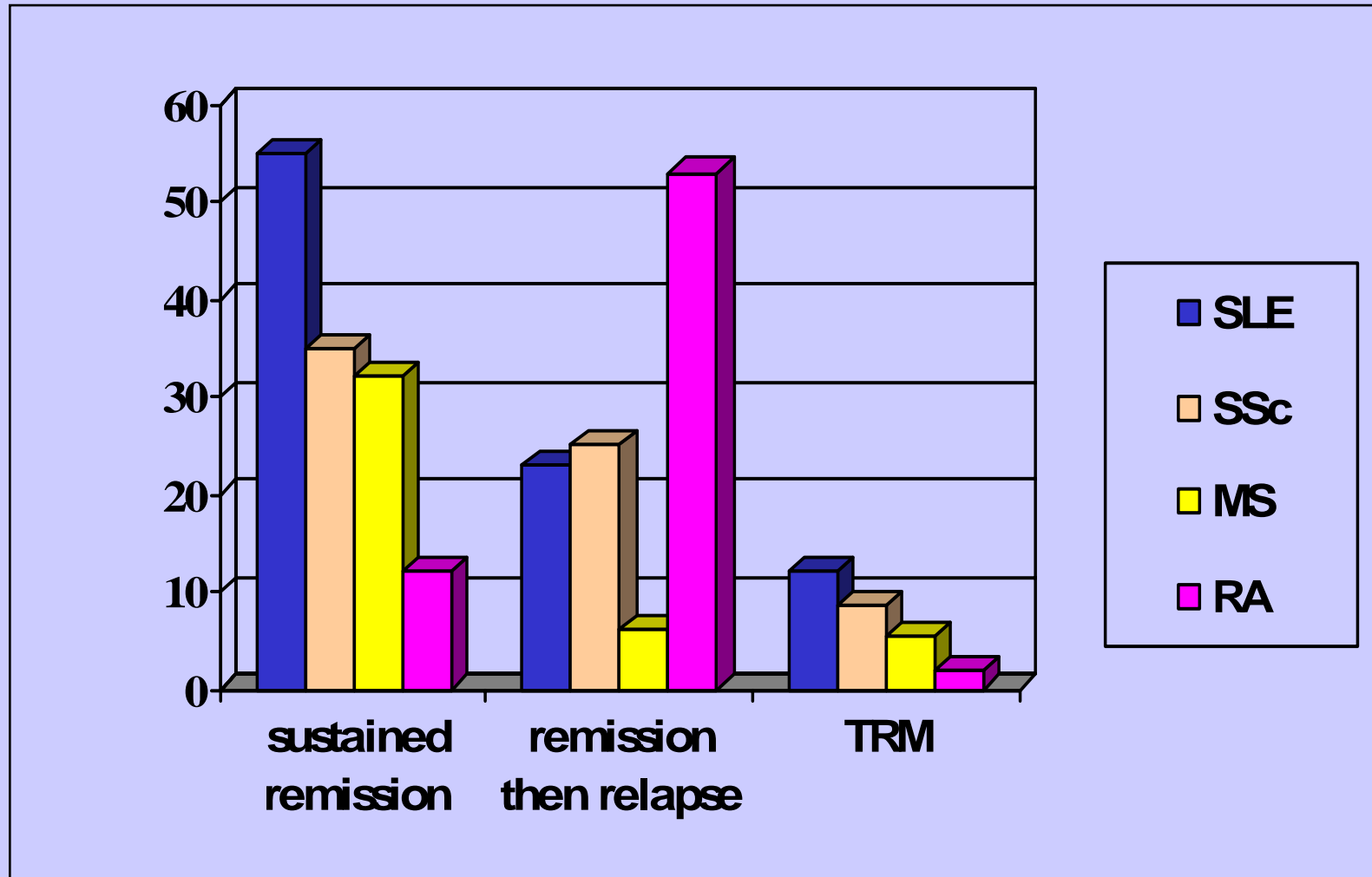
# CD developing after allogeneic SCT



# Autologous transplantation in autoimmune disease

- Eradicate committed clone and allow autologous uncommitted repopulation
  - Patients return to being prone to Crohn's Disease but not actually having it
  - They may not meet environmental trigger again
  - Profound immunosuppression (? of mobilisation) may have pivotal effect

# ASCT in Autoimmune Diseases: Data from EBMT



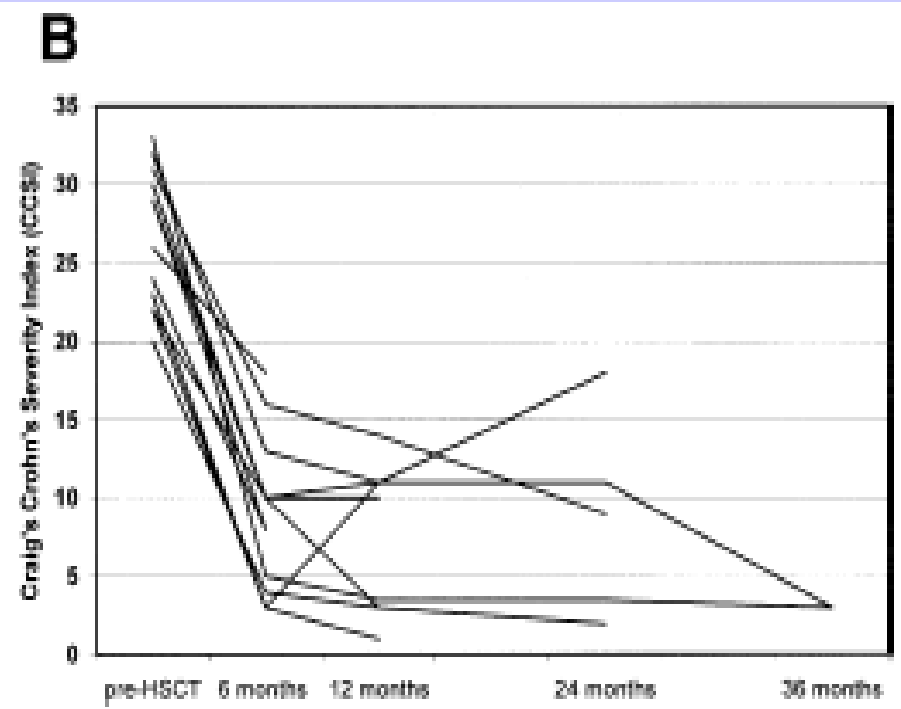
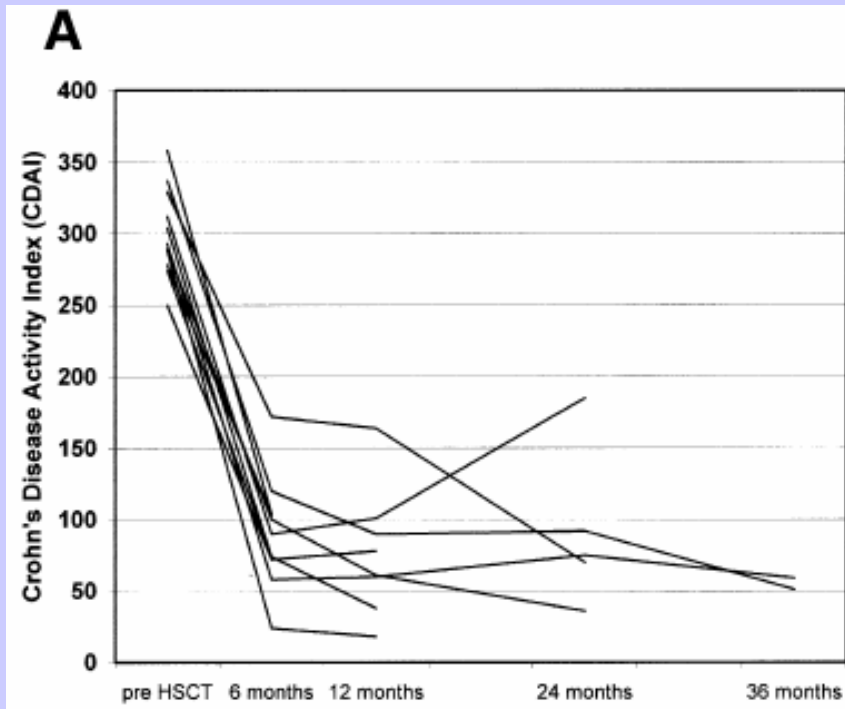
# Incidental autologous transplantation and CD

- 11 years active CD → Inactive 7 years
  - Kashayup B J Haematol 1998 103:651
- Diffuse CD pan colitis → asymptomatic, but inflamed 3 yr later
  - Castro Blood 1996; 88: 133A
- CD: 2 years symptoms, sugery → 5 years free of disease
  - Soderholm Scand J Gastro 2002; 37: 613
- Active CD 10 year: asymptomatic 3 years
  - Musso BMT 2000
- CD 10 year low level symptoms/inflammation → both normal at >5 years
  - Hawkey Best Pract Res Clin Haematol. 2004 17:317
- Ulcerative colitis → asymptomatic off Rx 2 years
  - Castro Blood 1996; 88: 133A
- Ulcerative colitis → asymptomatic off Rx 4 year
  - Tyndall B J Rheum 1997; 36:390

# Autologous SCT for CD: 10 patient Chicago study

CDAI

CCSI



# SCT in CD: Questions

- Mechanisms
  - (Temporary) immunosuppression from mobilisation (or conditioning)
  - Ablation of pathogenic clones
  - Other mechanisms: myofibroblasts
- Benefit
  - Remission (how long?) or cure, in all or some
  - Generalisable across centres?
- Risks
  - NOD-2, TRM / GVH and infection
- Patients
  - Extreme cases not necessarily the best

**ASTIC trial**  
**Autologous Stem Cell Transplantation In**  
**Chrohn's Disease**

**ECCO / EBMT Trial**



EUROPEAN CROHN'S & COLITIS  
ORGANIZATION



The University of  
**Nottingham**



### Patient Information

The ASTIC trial is an international clinical study for patients suffering from severe Crohn's Disease.

- [Why is the study being conducted?](#)
- [What will happen to me if I take part in the study?](#)
- [Which patients can take part in the study?](#)
- [Where is the study happening?](#)
- [Detailed information about the study](#)
- [General information about clinical trials](#)

#### **Why is the study being conducted?**

Unfortunately, some patients fail to respond to best clinical treatment in Crohn's disease and some only experience temporary benefit, which is why the search for more effective treatments is continuing. Recently, an experimental treatment has been developed for severe Crohn's disease, called 'high dose immunoablation followed by autologous hematopoietic stem cell transplantation'. Hematopoietic blood stem cells are young, undifferentiated blood cells that can develop into differentiated ones, including lymphocytes, and over-reactive lymphocytes are thought to contribute to the development of Crohn's disease. These stem cells have nothing to do with embryonal stem cells or cloning of organs or individuals. This study involves removing your over-active lymphocytes (immunoablation) and replacing them using blood stem cells that had been taken (harvested) from your body earlier in the study. Conventional medication only temporarily suppresses the over-reactive lymphocytes.

At present, about 30 patients suffering from Crohn's disease have been treated with stem cell transplantation worldwide. The results from those studies suggest that the therapy may be effective, but it cannot be concluded yet whether this treatment is better than any best clinical practice. An international collaborative group of medical specialists has agreed that this issue can

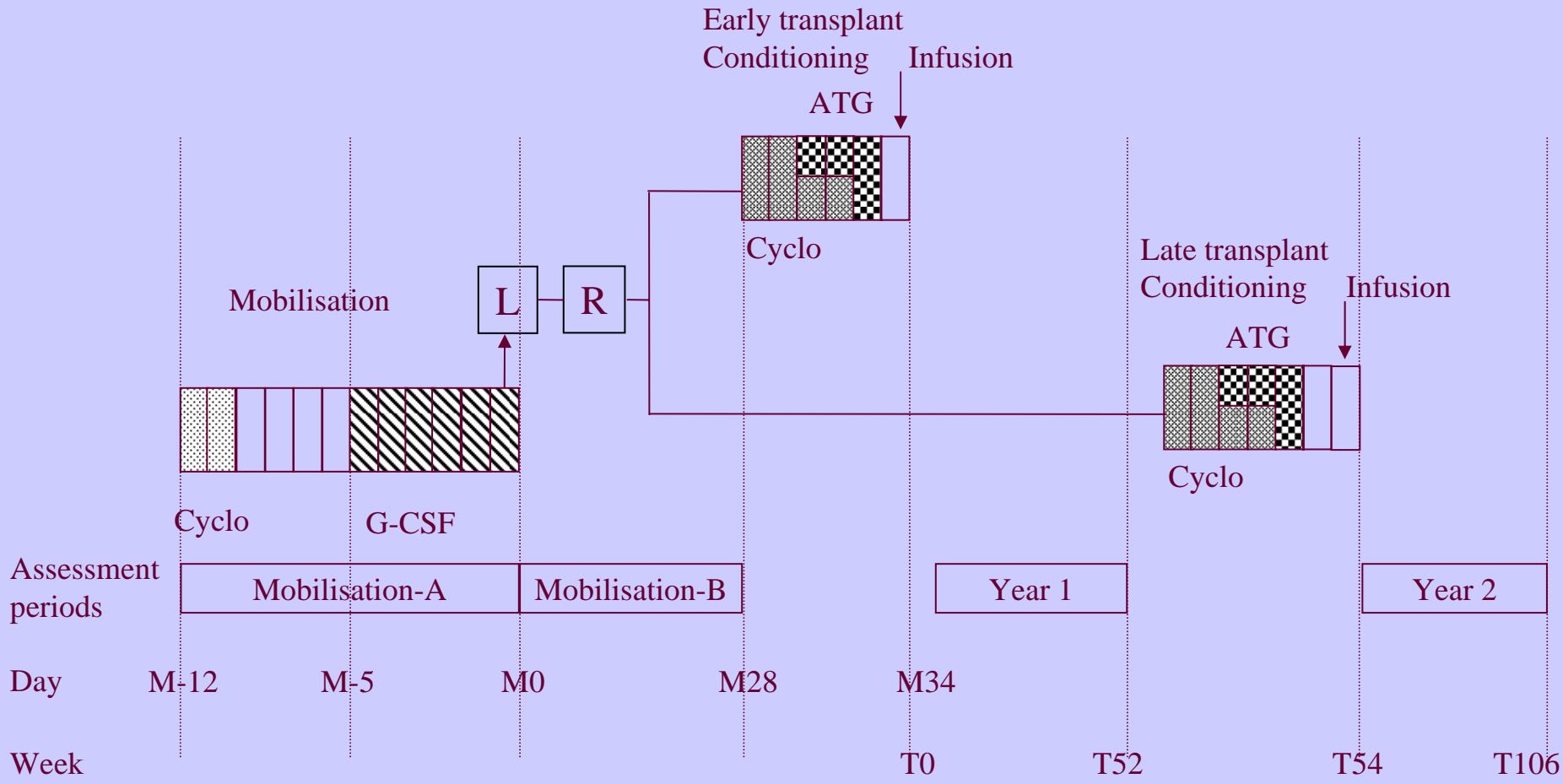
# Entry Criteria

- **INCLUSION**

- 18 - 50 years (or more)
- Unsatisfactory course despite 3 immunosuppressive agents
- CDAI  $\geq$  250
- Impaired function and quality of life
- Unsuitable for surgery
- Normal cardiac and pulmonary function
- Smoking advice
- Informed consent

- **EXCLUSION**

- Pregnancy
- Severe medical or psychological (co)morbidity
- Symptoms believed due to fibrous stenosis
- Diarrhoea due to  $\leq$  30 cm small or large bowel
- Significant infection or risk thereof
- Previous poor compliance
- Lack of funding



- Activity
- Barium
- Endoscopy
- Histology
- Dexa
- Lymphocytes
- Cytokines
- Stop im supp

•Weekly 2x2 g/m<sup>2</sup> 28 days or 56 weeks  
 •Activity  
 •Barium  
 •Endoscopy  
 •Histology  
 •Dexa  
 •Lymphocytes  
 •Cytokines  
 •Stop im supp

•Weekly 10 μg/kg daily-4: Cyclo 50 mg/kg  
 •Bloods  
 •Reinstate CD34 cells methylprednisolone  
 •Im supp 8 x 10<sup>6</sup> CD34-D6 infusion  
 •Cells/kg

•Activity  
 •Barium  
 •Endoscopy  
 •Histology  
 •Dexa  
 •Lymphocytes  
 •Cytokines  
 •Stop im supp

•Activity  
 •Barium  
 •Endoscopy  
 •Histology  
 •Dexa  
 •Lymphocytes  
 •Cytokines

•6 Weekly  
 •Activity  
 •Bloods  
 •Sig and bx  
 6, 13, 26 W

# Primary endpoint: Sustained remission

- 3 month period of CDAI < 150 without steroids and infliximab and mucosal healing at 12 months as evaluated by ileocolonoscopy and small bowel barium studies

# Power: transplantation

Control patients	HSCT patients	
	80% power	90% power
10%	48%	58%
20%	60%	65%
30%	70%	75%

# ASTIC Study: practical issues

- Sponsorship, registration, ethics, insurance and R&D
  - 72 documents, 39 contractual agreements, >350 pages
- Transplant costs
- Informed consent: Patient advocate
  - Pregnancy and fertility
- Sepsis
  - Specific DSMB brief
- Endpoints
- Eminent collaborators
- Patient identification (17/23 approved, 7 awaiting)
- Web site with public and restricted areas
  - Publicity campaign

# Participating Countries and Chief Investigators

	National	Local	Cost problems
<b>UK: Hawkey / (Russell)</b>	<b>Nottingham</b>	(Oxford, London, Leeds)	Whole proc
<b>France: Lemann / Farge</b>	<b>Paris</b>	Lille	Marginal costs
N'lands: Hommes / Kersten/ van Laar	Leiden		OK
<b>Czech: Lukas / Kozak</b>	<b>Prague</b>		?OK
Belgium Vermeire	Leeuven		OK
Germany: Kreisel / Finke	F'bourg		OK
Italy: Gionchetti / Saccardi	Bologna	(Milan)	
Switzerland: Beglinger / Gratwohl	Basel		
Austria: Reinisch / Greinix	Vienna		
Spain: Gassull / de Sevilla Riboda	Badalona		

Please complete pages 1 and 2 of the patient registration form, and fax to the Study Centre (01865 9422242).

<b>Centre Number</b>	___ : ___
<b>Principal Investigator (PI)</b>	Travis
<b>Hospital name and address</b>	John Radcliffe Hospital Oxford OX3 9DU
<b>PI Phone Number</b>	+44 1865 851072
<b>PI Fax Number</b>	+44 1865 220320
<b>Patient's Initials</b>	__ L : H _ : H (First / Mid / Last initial)
<b>Patient's Trial Number</b>	___ : ___ : ___ : ___ : ___ (First three digits = centre number, last three sequentially allocated)
<b>Date of Birth</b>	15 : 12 : 84 (Day / Month / Year)
<b>Sex</b>	Male Female

**Inclusion Criteria** (all inclusion criteria, or corresponding discretionary inclusion criteria)

Yes	No	Age between 18 and 50 years. If No ↓
	Yes No	Age between 50 and 65
Yes	No	Confirmed diagnosis of Crohn's Disease (histology and confirmed active Crohn's disease (CDAI) and endoscopic evidence, evidence from barium studies)
	Yes No	Diseased tissue can't be accessed (e.g. due to strictures of duodenum or terminal ileum?)
Yes	No	Unsatisfactory course despite 3 immunosuppressants
Yes	No	Impaired function and quality of life
Yes	No	Current problems unsuitable for surgery, risk of surgery
Yes	No	Informed consent <b>Not yet!</b>

**Exclusion Criteria** (all should be No)

Yes	No	Pregnancy or unwillingness to use contraception
Yes	No	Concomitant severe disease
Yes	No	Significant infection or risk thereof
Yes	No	Significant malnutrition <b>On enteral supplementation</b>
Yes	No	Previous poor compliance
Yes	No	Concurrent enrolment in another study
Yes	No	Lack of funding <b>Hope not! Haematologists must be consulted</b>

<b>Centre Number</b>	___ : ___
<b>Patient's Initials</b>	L : H : H (First / Mid / Last initial)
<b>Patient's Trial Number</b>	___ : ___ : ___ : ___

**Narrative explanation of why patient should be considered for trial**  
Extensive small bowel, colonic and perianal disease that is refractory to immunomodulators (Aza caused pancreatitis, so MP not tried, MTX intolerant), biologic agents (IFX and adalimumab) and surgery (multiple). Recent MRE confirms active disease. Enquiring about prospects for SCT.

**Narrative history of patient's Crohn's disease. Summarise major events by date**

1993 CD diagnosed (age 9)  
 - treated by elemental diet and steroids  
 2001 – referred to adult gastro, Oxford; SBE: ileal disease  
 2002 – budesonide  
 4.03 Obstruction; laparoscopic ileocaecal resection 55cm, ischaemic perforation – subsequent stoma  
 9.03 reversal; small bowel looked normal  
 12.03 early relapse (steroids and aza)  
 1.04 aza pancreatitis  
 2.04 perianal abscess drained, seton, IFX 3 infusions – good response, but only 2-3 weeks; MTX started; nausea, vomiting  
 8.04 laparotomy for obstruction – adhesions only; transsphincteric fistula drained; further setons  
 11.04 WCE – scattered aphthoid ulcers throughout bowel  
 12.04 IFX – perianal/labial abscess 10 days later, with arthralgia; polymeric diet  
 3.05 obstruction; 15cm ileal segment resected; multiple adhesions; TPN  
 5.05 gastrostomy for PEG feeding  
 8.05 recurrent perianal abscess, setons, abiotics  
 9.05 double balloon enteroscopy around 20 discrete ulcers in distal duodenum and jejunum, confirmed active disease and strictures on MRE  
 9.05 IFX 10mg/kg with hydrocortisone pre-treatment – arthralgia  
 11.05 9.05 IFX 10mg/kg with hydrocortisone pre-treatment – arthralgia/rash  
 1.06 IFX anaphylactoid reaction  
 2.06 Adalimumab (160mg/40mg weekly, 6 weeks) excellent response  
 4.06 Perianal abscess/fistula  
 7.06 More ADL arranged...waiting for ASTIC or certolizumab study!

# Summary

- Stem cell transplantation now widely used for autoimmune disease
- Preliminary evidence suggests possible benefit in CD
- Trial desirable, possible and set up
- Mechanisms not yet clear