



A Clinical Trial involving Endobarrier



Randomisation to Endobarrier alone Versus with Incretin analogue in SustainEd Diabetes



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Background: limited treatment options for diabetes



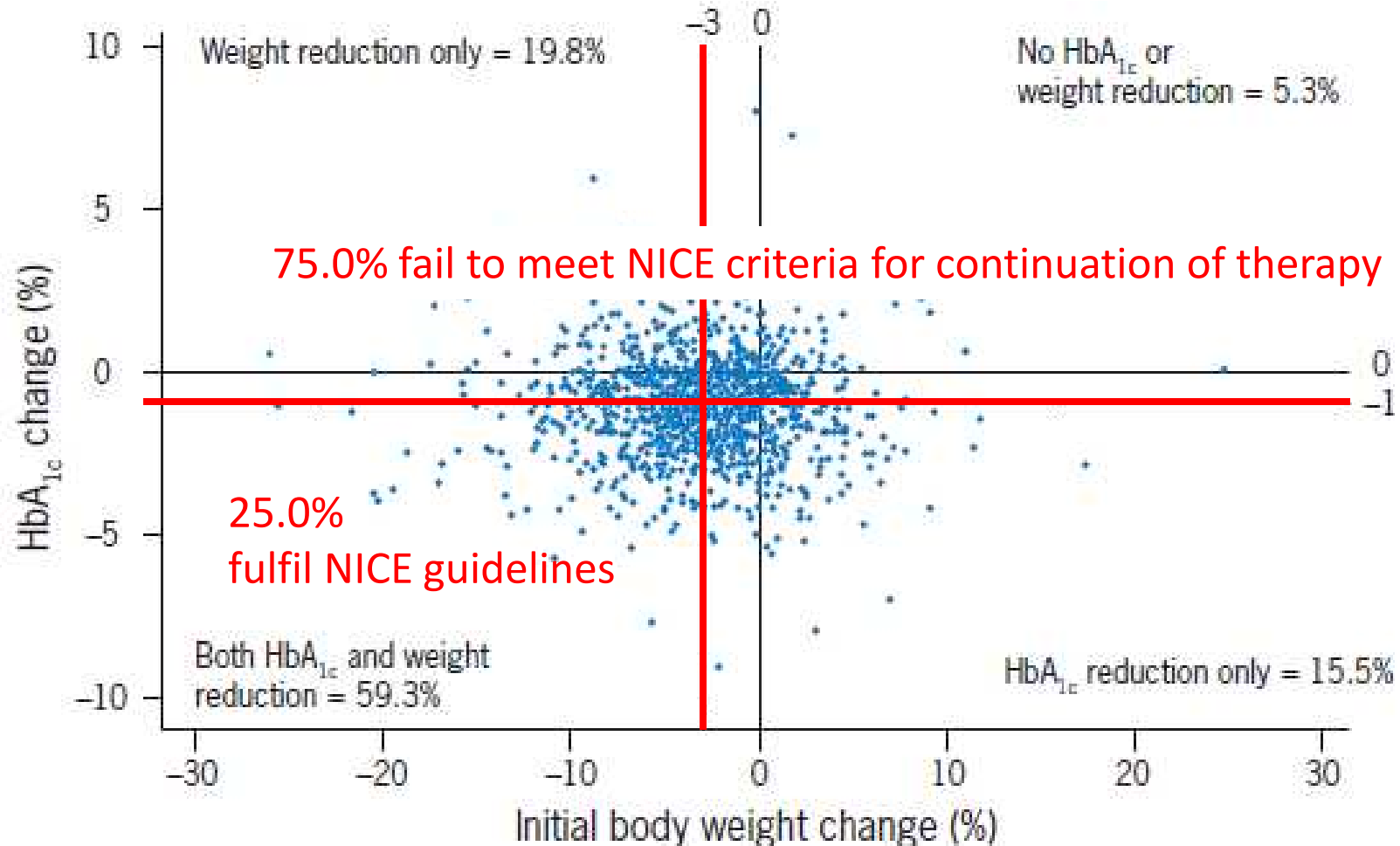
...New, effective therapies are
urgently needed

GLP-1
receptor
agonists



Failure rate of GLP-1RA ABCD liraglutide audit (n1023) data (2009-14)

Scatterplot of HbA1c and initial body weight change at 6 months (± 6 weeks) in liraglutide treated patients



Proof of Principle: Newcastle Diabetes Diet Study 8-week 600kCal dietary intervention reverses diabetes

n11 new onset diabetes (n8 age-, sex-, weight-matched non-diabetic subjects)

Liver triacylglycerol content measured using three-point Dixon MRI

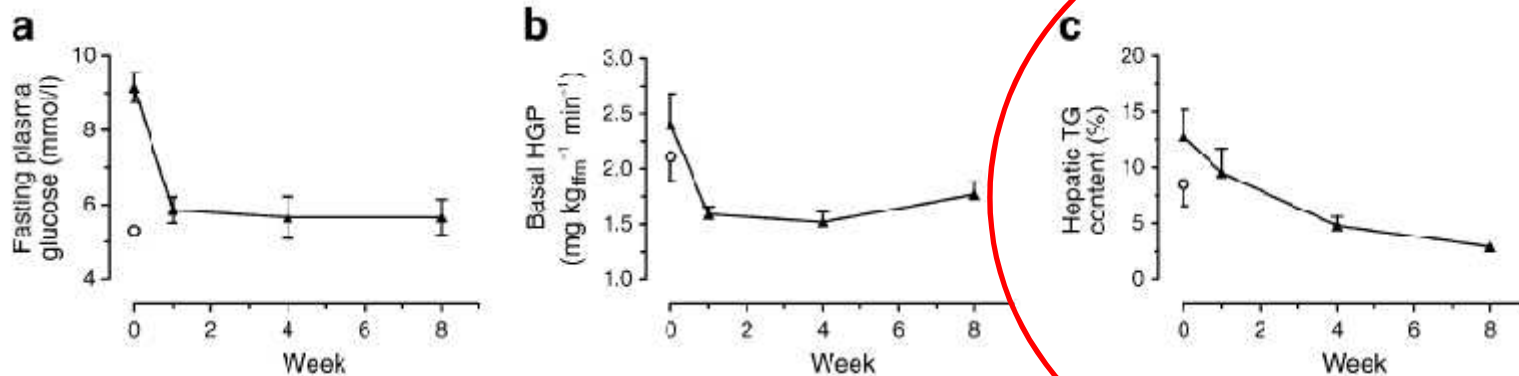


Fig. 1 Effect of 8 weeks of dietary intervention on (a) plasma glucose, (b) hepatic glucose production (HGP) and (c) hepatic triacylglycerol content (TG) for diabetic participants (black triangles).

White circles indicate the mean for the weight-matched non-diabetic control group. Data are shown as mean \pm SE

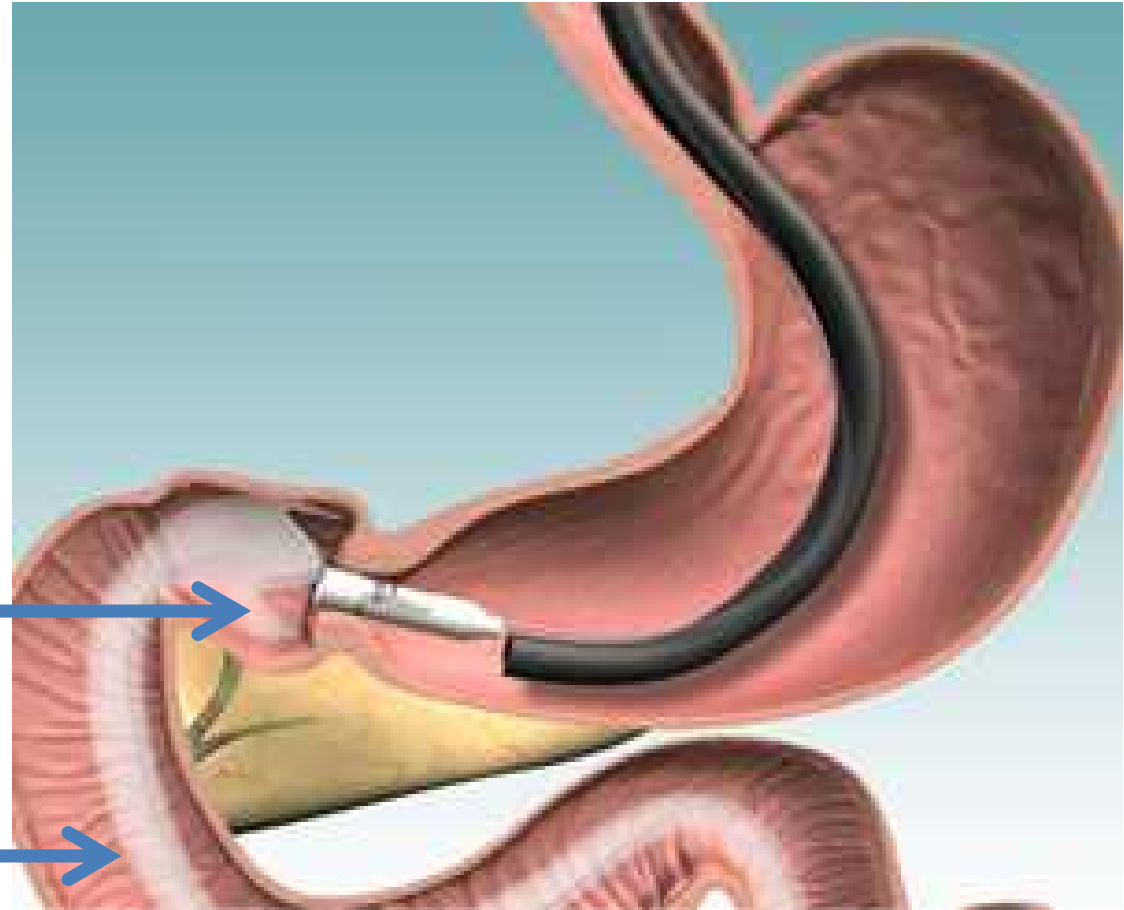
Ref. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R.
Diabetologia 2011. 54(10):2506-14

What is Endobarrier?

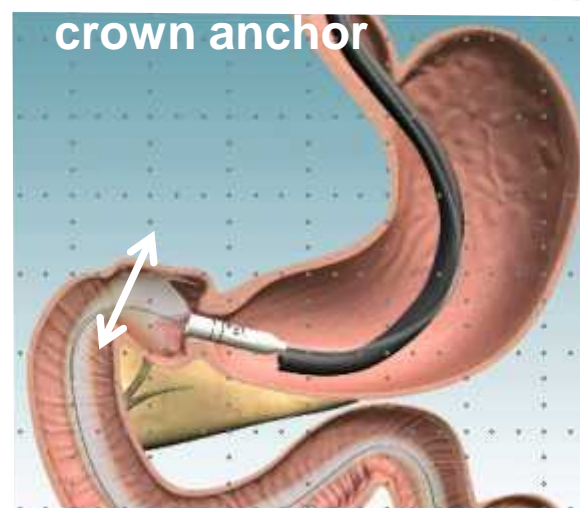
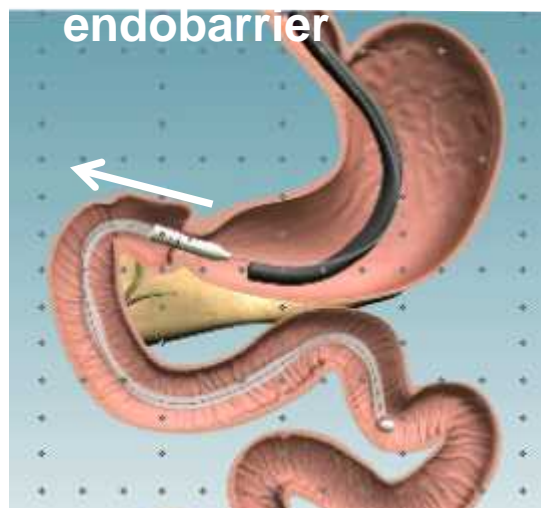
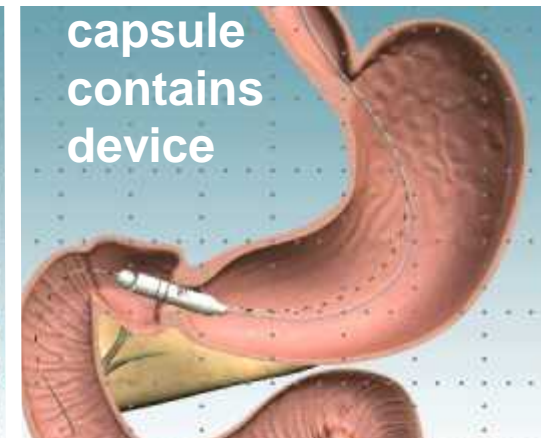
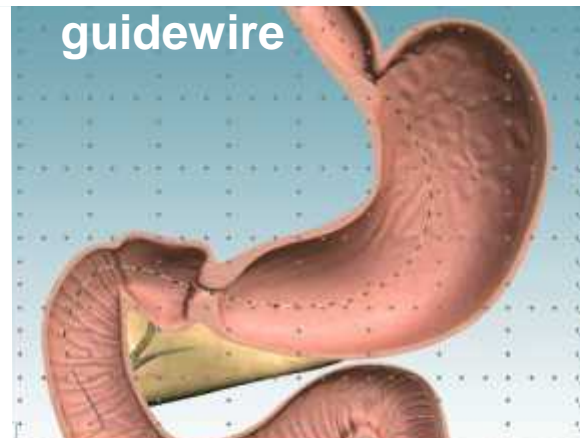


Nitinol
Anchor

Fluoropolymer
wall



Endobarrier – a duodenal-jejunal liner



- endoscopy procedure
- general anaesthetic
- day case
- 2-week diet, chew food
- implant for 1 year
- reversible
- Omeprazole, multivitamin

Liraglutide maintains weight loss attained

- SCALE Maintenance RCT n422¹ obese/ overweight
 - ≥5% initial body weight loss on low calorie diet
 - Randomised to liraglutide or placebo for 56 weeks
 - 81.4% liraglutide vs 48.9% placebo group maintained weight loss (p<0.0001)
- RCT n268², BMI 30-40kg/m²
 - randomised to liraglutide/ orlistat/ placebo for 2 years
 - 52% liraglutide vs 29% orlistat maintained >5%IBW (P<0.001)

1. Wadden TA et al, Int J Obes 2013. 37(11): 1443-51.
2. Astrup A et al, Int J Obes 2012. 36(6): 843-54

Study Aims

To investigate

- 1.** in people who have failed to adequately respond to GLP-1RA therapy, whether combined Endobarrier-liraglutide achieves and maintains greater metabolic control than Endobarrier without liraglutide
- 2.** the mechanisms by which proximal intestinal exclusion affects metabolic improvement

Recruitment: study centres

Target n=72



Selection Criteria

INCLUSION CRITERIA:

Type 2 Diabetes
HbA1c \geq 7.5%

Liraglutide
 \geq 6 months

Obesity
BMI \geq 35 kg/m²

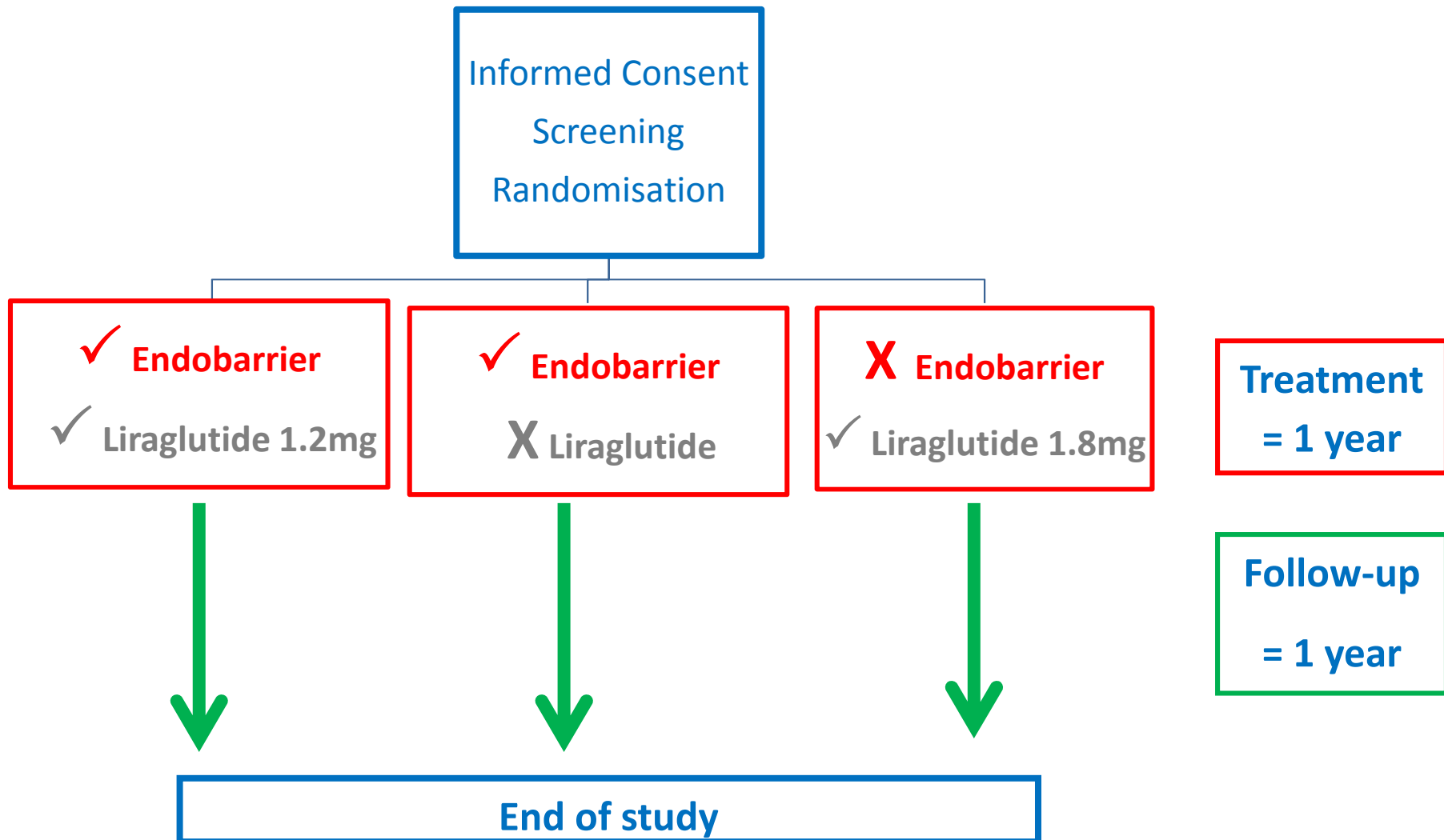
Stable weight
(3 months)

EXCLUSION CRITERIA:

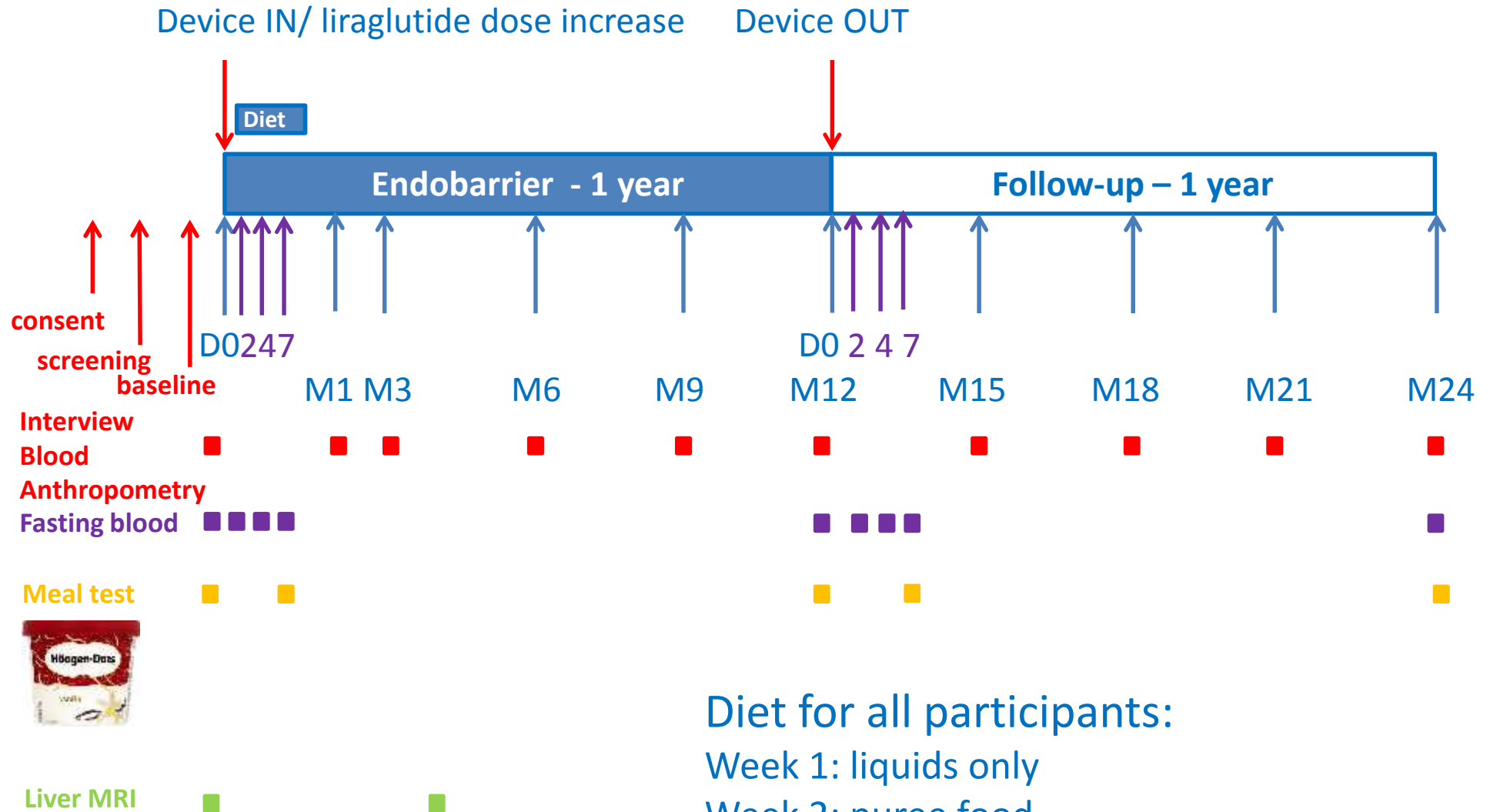
Safety considerations: e.g. aspirin, warfarin, INR $>$ 1.3, pregnancy, contra-indication to OGD, eGFR $<$ 30, portal hypertension, pancreatitis, amylase $>$ 3 times upper lab limit, uncontrolled cardiovascular disease

- **Conditions that may interfere with Endobarrier placement/ findings:** abnormal intestinal anatomy, previous bariatric surgery or bowel surgery excess anaesthetic risk as identified by the anaesthetist or investigator (e.g. uncontrolled obstructive sleep apnoea).

3 Treatment Groups



Visit Schedule



Diet for all participants:
 Week 1: liquids only
 Week 2: puree food
 Week 3 onwards: solid food

Baseline characteristics n68 (94% target)

Parameter		Endobarrier +liraglutide	Endobarrier	liraglutide	P- value
Number		23	24	21	-
Age (years)		51.6±12.0	49.5±9.8	52.1±9.6	0.68
Sex (F-M)		15-8	17-7	14-7	0.91
Ethnicity	Caucasian	17	17	14	0.94
	South Asian	3	3	3	
	Afro-caribbean	1	3	1	
	Other	2	1	1	
BMI		40.3±4.7	41.9±4.7	40.3±4.2	0.38
HbA1c (%)		9.5±1.4	9.6±1.5	9.8±1.4	0.79
HbA1c (mmol/mol)		79.9±15.1	81.4±16.8	83.2±15.3	

'before and during' endobarrier

Before:

- 84.4kg
- HbA1c 9.1% (76mmol/mol)
- Insulin 150 units daily

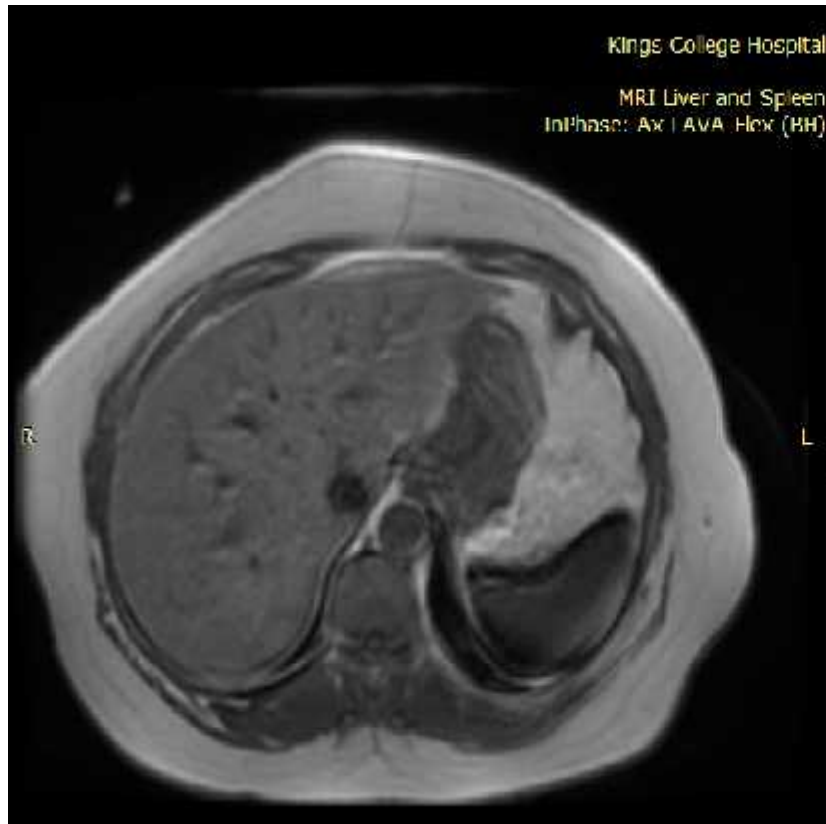
6-months:

- 76.7kg
- HbA1c 6.8% (51mmol/mol)
- Insulin 64 units daily



MRI liver: pre-Endobarrier

In Phase

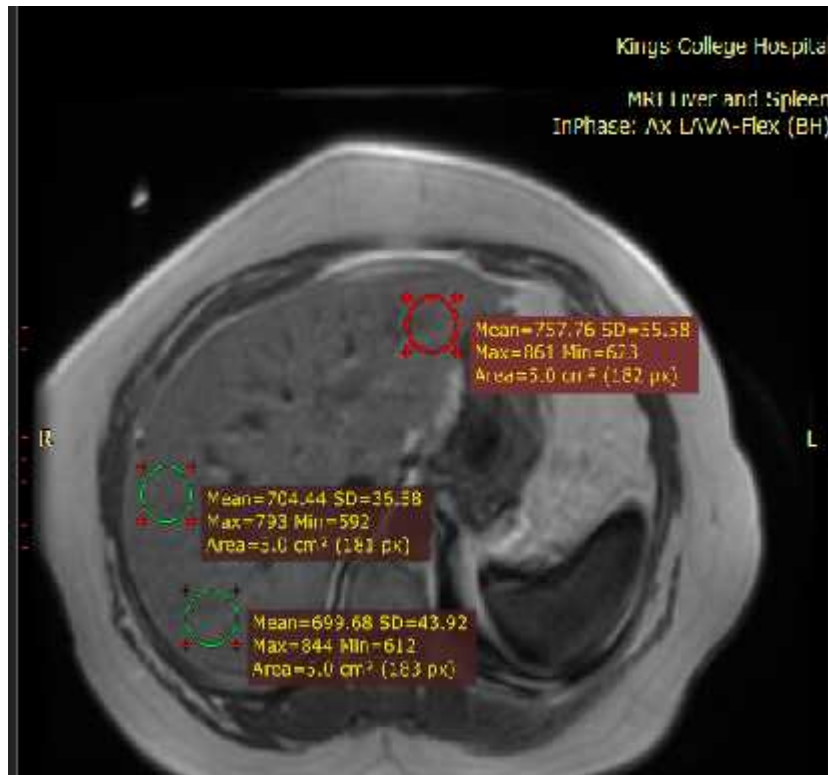


Out of Phase

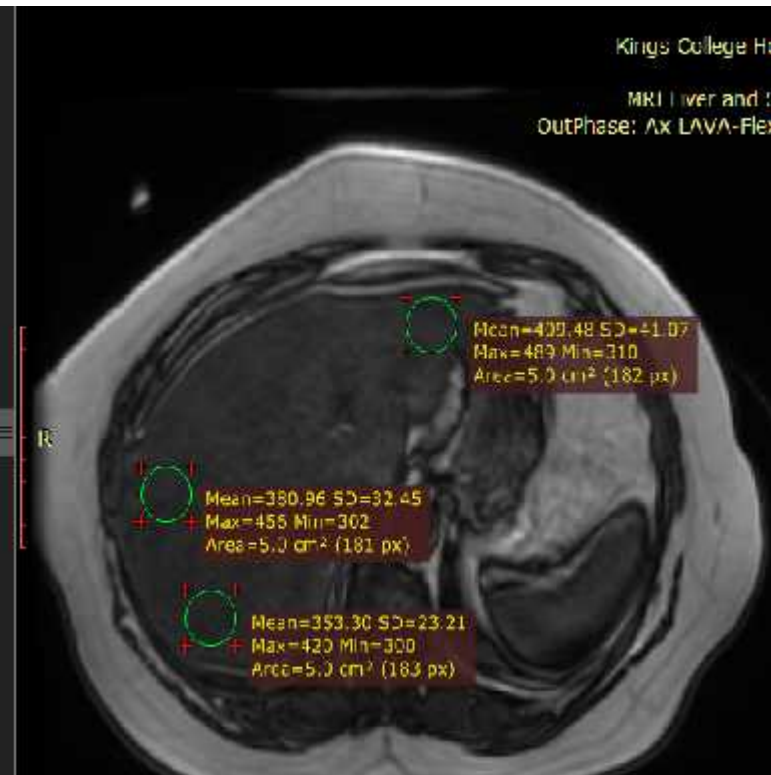


MRI liver: pre-Endobarrier

In Phase

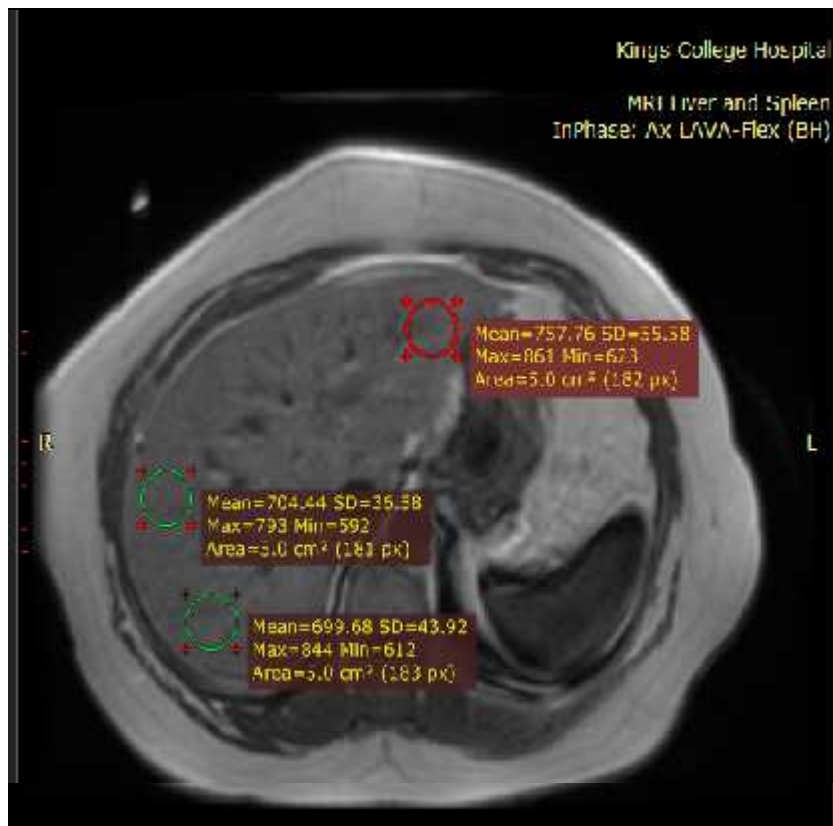


Out of Phase

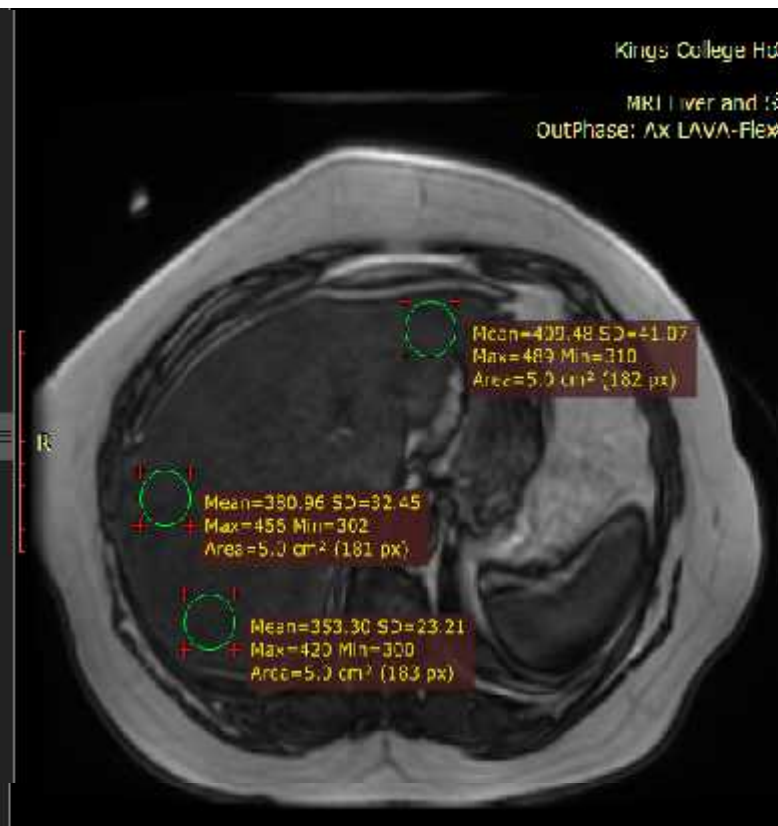


MRI liver: pre-Endobarrier liver fat fraction 22.4%

In Phase



Out of Phase

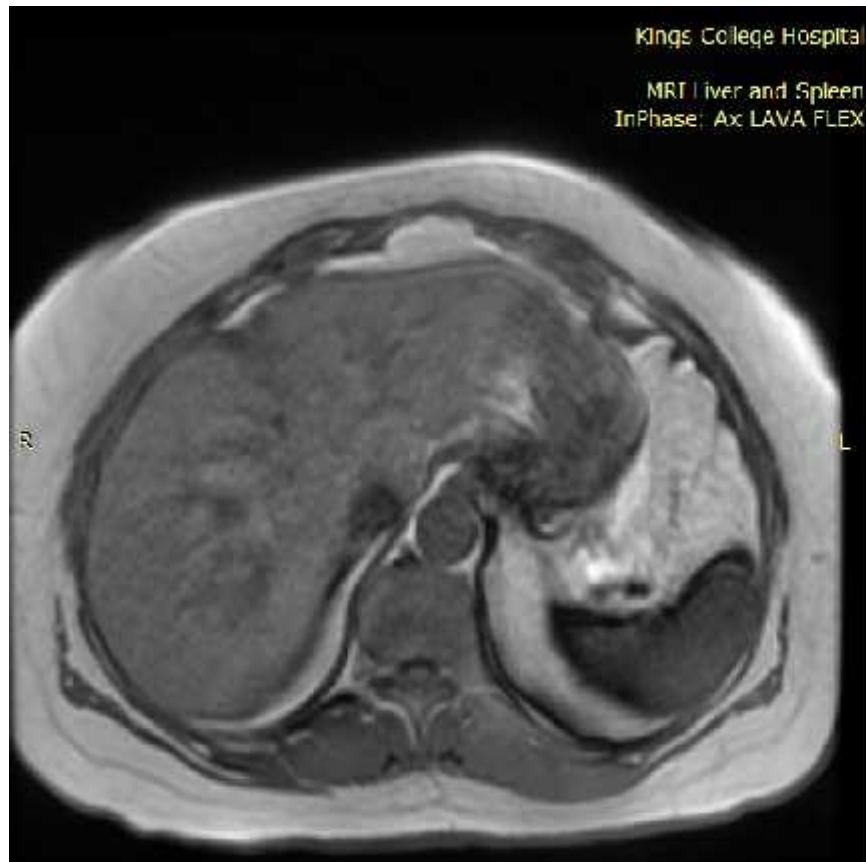


Liver-fat fraction calculation:

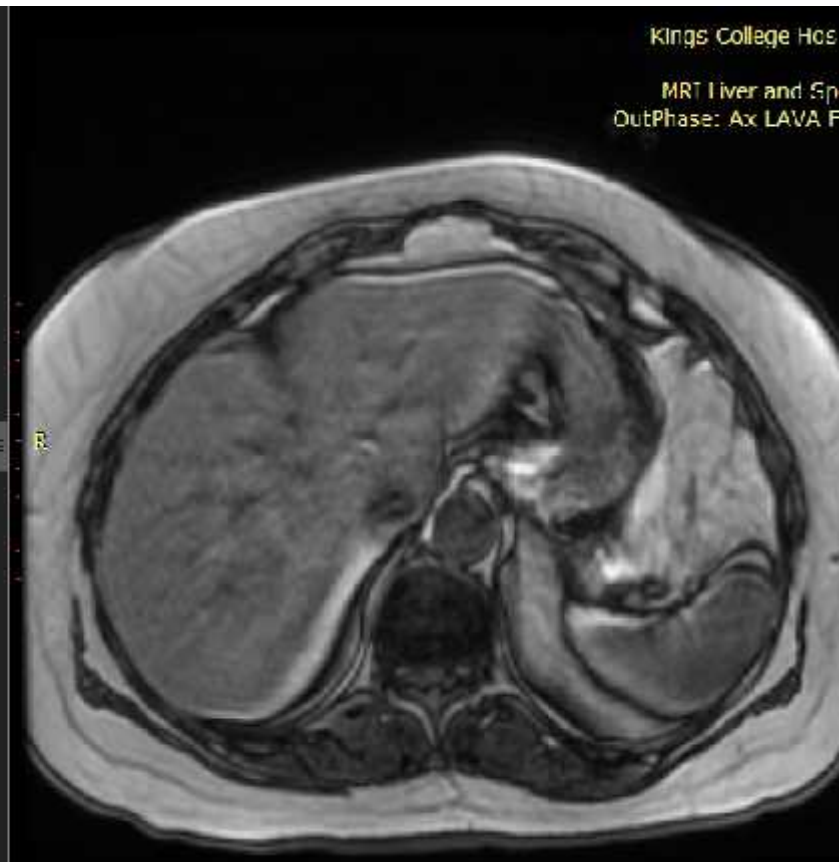
$$\eta = \frac{|S_{IP} - S_{OP}|}{(2 \times S_{IP})} \quad \text{IP = in-phase signal, OP = out-of-phase signal}$$

MRI liver: same patient post-Endobarrier

In Phase

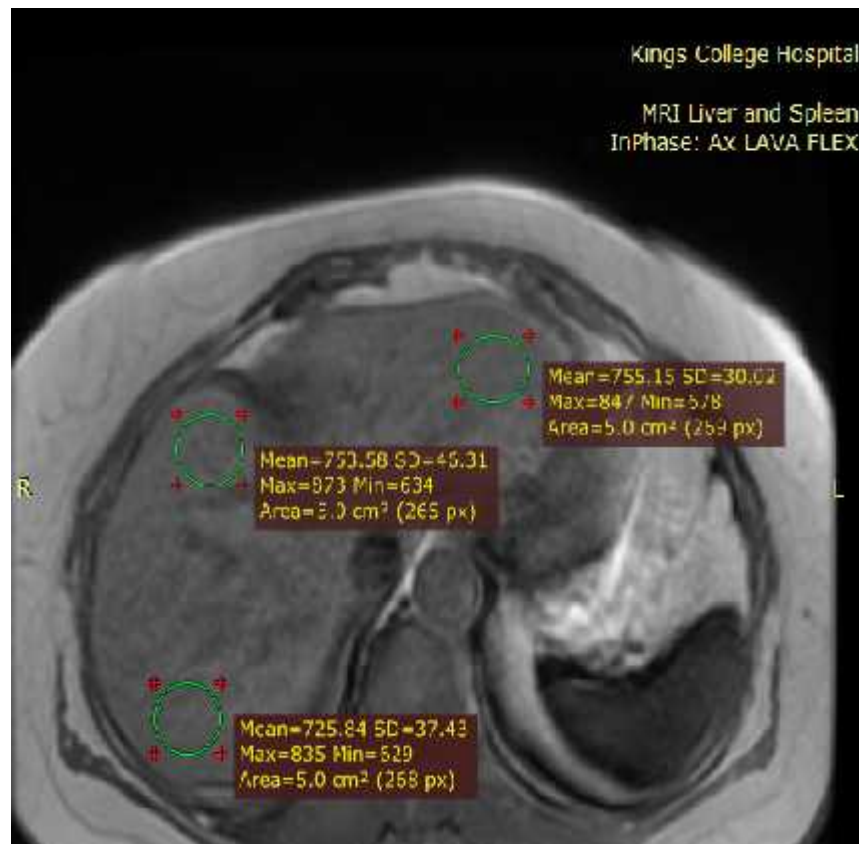


Out of Phase

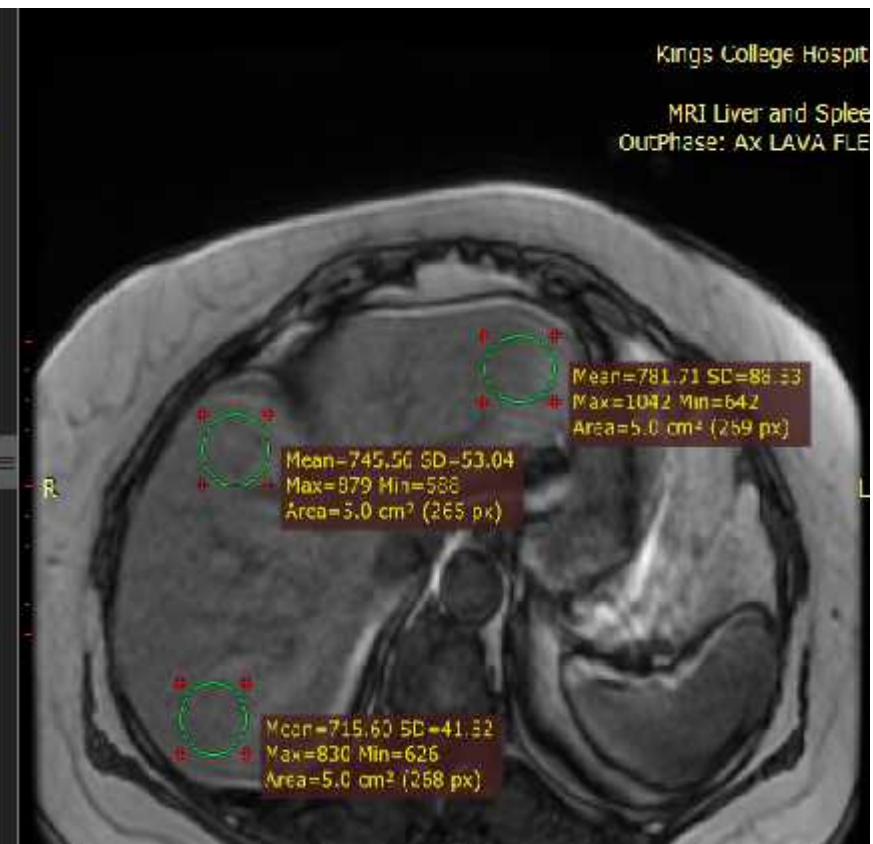


MRI liver: same patient post-Endobarrier liver fat fraction 0.5%

In Phase



Out of Phase



Preliminary MRI liver data

- n5/8
- 3 assessors, blinded
- Mean (95% CI) pre-endobarrier hepatic fat fraction was 16.2% (3.2, 29.1%), falling to 3.5% (-3.5,10.5%) at 4 months post-endobarrier
- This represents a reduction of 12.7% (2.3,23.1), **P=0.028** (paired t test)

Safety & Complications

- Independent data monitoring committee

Expected:

- Adverse events: gastrointestinal symptoms, hypoglycaemia
- SAEs: GI bleeding, migration, obstruction (<5%)

To date:

- 1 failed implant
- 5 early removals:
 - 3 due to GI symptoms without obstruction (2-8 months)
 - 1 due to GI bleed (2 months)
 - 1 due to obstruction (7 months)
- 1 liver abscess at 6 weeks

Summary

- Liraglutide audit - 75.0% 'failure' rate at 6-months
- This RCT is targeted towards these patients
- Combined E+L has a superior effect in reducing HbA1c and weight in those failing GLP-1RA treatment
- E without L produces a comparable weight reduction without improving glycaemic control

Conclusion

- Adding duodenal exclusion to suboptimally performing GLP-1RA therapy has clinical advantage to converting to duodenal exclusion
- Endobarrier is effective at reducing hepatic triacylglycerol content

Acknowledgements

All study participants



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Association of British Clinical Diabetologists

NIHR/ Wellcome Trust King's Clinical Research Facility

There are **4 spaces** left (recruitment ends in 2 weeks):
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