Low Calorie Diets in Obesity and Type 2 Diabetes – DiRECT, DROPLET and the NHS Pilot Programme

Professor Roy Taylor, Newcastle University
Dr Nerys Astbury, University of Oxford
Dr Chirag Bakhai, NHS England and NHS Improvement
The Randomised Diabetes Remission Clinical Trial - DiRECT

Roy Taylor
Professor of Medicine and Metabolism, Newcastle University
DiRECT – a study in routine NHS General Practice

Duration of T2DM less than 6 years; on oral agents and/or diet

49 Practices

INTERVENTION
15kg weight loss then maintain
149 people

CONTROL
Best management by guidelines
149 people

0 12 months 24 months
Remissions at 12 and 24 months

% in remission

Lean et al, Lancet Diab & Endo 2019; 7: 344
Remissions by 24-month weight loss: entire study population

- <5kg: 5% remission
- 5-10kg: 29% remission
- 10-15kg: 60% remission
- ≥15kg: 70% remission

24-months ≥10kg loss
64% are in remission

Lean et al Lancet Diab & Endo 2019; 7: 344
“Diet” for weight loss

Simple
Practical
Spouse/partner on board
Duration limited and planned

Compensatory eating renders exercise counterproductive during weight loss
Rescue Plans for Relapse Management

1: Regain >2kg - 1 meal/day replaced with TDR

2: Regain >4kg - TDR offered
Effects of achieving HbA1c <48mmol/l over 2 years

Serious adverse events

- HbA1c <48
  - 1 non-fatal MI
  - No cancers

- HbA1c >48
  - 1 Fatal MI
  - 2 CVA
  - 1 atrial fibrillation
  - 1 aortic aneurysm
  - 1 toe amputation
  - 5 cancers (2 colon, bladder, kidney, prostate)

Lean et al *Lancet Diab & Endo* 2019 online
Summary at 24-Months

- One third with early T2D achieve remission
- Two thirds achieve remission if $\geq 10$kg loss
- Achieving and maintaining weight loss are critical for success
- Weight loss at 24-months remains greater than most lifestyle interventions, despite modest regain
Essential components of future T2DM management

Information

Personal planning with family & friends

15kg wt loss in 3 months

Long term support via Primary Care
Doctor Referral of Overweight People to Low Energy total diet replacement Treatment (DROPLET): a randomised controlled trial

Dr Nerys Astbury

Nuffield Department of Primary Care Health Sciences
University of Oxford
What is a total diet replacement programme?

- A period of Total Diet Replacement (TDR) using low-energy formula diet products

  All foods are replaced with specially formulated low-energy food replacement products, such as soups, shakes and bars, which provide 800kcal–1200kcal/day and all essential nutrients, vitamins and minerals.

- Regular behavioural support
  Used alternative model of delivery to DiRECT
### Evidence before the DROPLET trial

**VLED vs BWMP:** -4.27 kg  
(95% CI: -7.41, -1.14); p < 0.00003

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VLCD programme</th>
<th>Control</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Rossner 1997 (VLCD 1)</td>
<td>-10.4</td>
<td>12.3</td>
<td>30</td>
<td>-6.6</td>
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<tr>
<td>Rossner 1997 (VLCD 2)</td>
<td>-9.1</td>
<td>10.8</td>
<td>32</td>
<td>-6.6</td>
</tr>
<tr>
<td>Ryttig 1997 B&amp;C</td>
<td>-11.2</td>
<td>11.85</td>
<td>54</td>
<td>-9.3</td>
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<tr>
<td>Stenius 2000</td>
<td>-11.1</td>
<td>5.35</td>
<td>19</td>
<td>2.3</td>
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<tr>
<td>Torgerson 1997</td>
<td>-11.3</td>
<td>11.9</td>
<td>58</td>
<td>-6.5</td>
</tr>
<tr>
<td>Wadden 1994</td>
<td>-14.2</td>
<td>11.2</td>
<td>28</td>
<td>-11.7</td>
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<tr>
<td>Wing 1991</td>
<td>-8.6</td>
<td>5.6</td>
<td>17</td>
<td>-5.7</td>
</tr>
<tr>
<td>Wing 1994</td>
<td>-12</td>
<td>10.8</td>
<td>45</td>
<td>-8.97</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>306</strong></td>
<td><strong>229</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 16.23; Chi² = 29.15, df = 8 (P = 0.00003); I² = 73%  
Test for overall effect: Z = 2.67 (P = 0.008)  
Test for subgroup differences: Not applicable

Participants: n = 278; BMI > 30
Excluded patients on insulin or with contraindications to TDR

Intervention: Total Diet Replacement (810 kcal/d) for 8 weeks, food reintroduction over 4 weeks, plus 12 weeks weight-loss maintenance plan

Comparator: Nurse-led behavioural weight management programme (usual care)

Primary outcome: weight loss at 1 y

Secondary outcomes: BP, lipids, HbA1c, QoL
Clinical Oversight

Practice nurses conducted initial onboarding & review at 4 weeks

GPs adjusted medication for hypertension and diabetes at the start of the programme and as needed thereafter

Clinicians were supplied with guidelines for this
Weight Loss over 1 year

TDR = -10.7 (9.6) kg
UC = -3.1 (7.0) kg

Adjusted difference: -7.2 (-9.4,-4.9) kg; p<0.0001
Percentage achieving ≥5% and ≥10% baseline weight loss

Odds ratio 5.3 (3.0; 9.2)

Odds ratio 4.9 (2.4:9.9). P<.0001

Astbury et al BMJ 2018;362:k3760
doi:10.1002/oby.22407
## 12 month outcomes by group

<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>Total Diet Replacement</th>
<th>Treatment Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>2.9 ± 15.2</td>
<td>-1.6 ± 16.4</td>
<td>-2.9 (-6.4; 0.6)</td>
<td>0.1072</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>0.3 ± 9.3</td>
<td>-4.2 ± 11.1</td>
<td>-3.1 (-5.5; -0.7)</td>
<td>0.0117</td>
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<tr>
<td>HbA1c (mmol/mol)</td>
<td>-1.0 ± 7.7</td>
<td>-3.2 ± 8.8</td>
<td>-2.2 (-4.4; 0.0)</td>
<td>0.0511</td>
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<tr>
<td>LDL Cholesterol (mmol/L)</td>
<td>-0.1 ± 0.7</td>
<td>-0.1 ± 0.6</td>
<td>0.0 (-0.2; 0.2)</td>
<td>0.8184</td>
</tr>
<tr>
<td>QRISK (%)</td>
<td>0.0 ± 2.1</td>
<td>-0.9 ± 2.6</td>
<td>-1.0 (-1.7; -0.3)</td>
<td>0.0061</td>
</tr>
<tr>
<td>EQ-5D (VAS)</td>
<td>9.2 ± 17.0</td>
<td>13.0 ± 18.7</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Adverse events

AEs recorded during the first three months of the programme and at six months for gallstone-related events only, to allow for diagnostic delay.

Any AEs reported in 52% and 30% of TDR and UC groups (a treatment excess of 1 in 5 cases)

Most common AEs with an excess in TDR groups were:
   Constipation;
   Fatigue;
   Headache;
   Dizziness;

AEs classed as moderate or greater occurred in 11% and 12% of participants in TDR and UC

One SAE which occurred after randomisation but before treatment initiated
Participants experiences

She was brilliant, actually. She was a very lovely lady. And she was very knowledgeable about her, you know, the products and things. So I got a great deal of confidence from her, to be honest. When she told me, and—Yes, it did. Yeah, she told me. So I think she—er—I'm not so sure she didn't show me a photograph when she was—before she started it. Yeah. It did help. … I think it always helps er experienced things rather than just er teaching them. Um, if— if I was struggling at any point, if I needed to speak to her about anything she gave me her number to call her. But you know, it's just to get to know “Susie Smith” as opposed to Susie the counsellor. Just, if anybody's ever thinking, “should I do it”, don’t, don’t question it, do it, it's well worth it. The health benefits, your, your self-confidence, it just builds everything, because your, you see, what it is you wanted to be. Changed me, changed my life.
Summary

• Referral to a commercial total diet replacement programme was a feasible, acceptable, safe, clinically and cost effective treatment for obesity in routine primary care.

• Weight losses average 10kg at 1 y, 45% patients losing >10% baseline weight

• Significant improvements in biomarkers of cardiovascular disease and diabetes

• Highly cost effective when offered as a referral to a commercial provider

• Positive experiences of participants and healthcare practitioners

• NHS pilot will provide opportunity to explore whether trial results can be translated into routine care
Low Calorie Diets in Type 2 Diabetes – the NHS Pilot Programme

Dr Chirag Bakhai
GP and Vice-Chair of Luton CCG
Primary Care Lead, East of England Diabetes Clinical Network
Primary Care Advisor to the NHS Diabetes Programme

NHS England and NHS Improvement
The NHS Long Term Plan commitment

Medical research has shown that some people with Type 2 diabetes can achieve remission through adoption of a low calorie diet. This allowed nearly half of patients to stop taking anti-diabetic drugs and still achieve non-diabetic range glucose levels. We will therefore test an NHS programme supporting low calorie diets (LCD) for obese people with Type 2 diabetes.
Purpose of the NHS LCD Pilot Programme

• Launch real-world pilots of Total Diet Replacement in people recently diagnosed with Type 2 Diabetes (within 6 years of diagnosis with BMI ≥ 27 kg/m² [ethnicity adjusted])
• Weight loss and achievement of remission
• Reduce glycaemia and improve cardiometabolic risk factors
• Further build the evidence base for clinical and cost-effectiveness in the real world
• Evaluate the effectiveness of TDR in more diverse population groups
• Explore and evaluate alternative delivery approaches for the behavioural support
Moving from the RCT to the ‘real world’

• Guided by an Expert Advisory Group

• Seeking to implement TDR, similar to DiRECT and DROPLET, at scale in real-world settings

• Eligibility criteria aligned to the evidence-base but adapted pragmatically for real-world

• Aiming for optimal feasibility in Primary Care – three elements:
  • TDR and behavioural support
  • monitoring response to intervention and checking for adverse events
  • medication adjustments and responding to clinical needs

• Commercial process to select a provider for each pilot site

NHS England and NHS Improvement
Programme overview

- TDR products in line with European regulations
- No direct cost to participants
- Referral to the programme by primary care
- Three phases to the intervention:
  - Total Diet Replacement: 12 weeks
  - Food re-introduction: 4-6 weeks
  - Weight maintenance: Until 12 months
- Relapse protocol if participant regains weight after TDR phase

NHS England and NHS Improvement
Testing three delivery approaches

• 1:1 Face to Face support
• Group Face to Face support
• Digital / remote support

• Which approaches are most feasible to implement at scale?
• How effective are they at achieving remission / weight loss?
• How does cost-effectiveness compare?

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Requirements of Primary Care

• Identify possible patients who could benefit
• Clinically screen for suitability

• Explain programme and obtain informed consent to refer
• Discuss and agree medication adjustments to take place on Day 1

• Make further medication adjustments as required
• Respond appropriately to concurrent / adverse events
• Check bloods at 6 months and 12 months
Pilot sites

- Expressions of interest were submitted by sites in September
- Sites selected by NHS Regional Teams
- 7-10 STPs – one delivery model in each
- 5000-8000 places in total
- Pilots will run over 3 years
- Sites will be publically announced in next few weeks

NHS England and NHS Improvement
Evaluation

• Given proposed scale, likely to expand international evidence base

• Evaluation specification has been developed

• Process with Department of Health and Social Care and National Institute of Health Research to identify programme evaluator

NHS England and NHS Improvement
Timeline to Pilot Launch

**Locality specific detail developed**
Short prospectus / information to go alongside the procurement documentation

**Pilot sites develop project mobilisation plans and local pathways**
Clinical governance and monitoring protocols to be developed nationally
Nov 19 – Mar 20

**Pilot sites confirmed**
Oct 2019

**Agree delivery model to be tested in each locality**
Oct/Nov 2019

**Invitation to Tender open**
Mid-Nov to mid-Dec 2019

**Provider contracts issued**
February 2020

**Services go live April 2020**

Pilot sites working with providers to develop implementation plans
Questions?

NHS England and NHS Improvement