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1 Diabetic Medicine (3000 words full text, 30 references, 250 abstract)

2 **Type 2 diabetes remission: economic evaluation of the**
3 **DiRECT/Counterweight-Plus weight management programme**
4 **within a primary care randomised controlled trial**

5

6 **A short running title (75 characters):**

7 Cost-effectiveness of DiRECT weight management programme

8

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3 **Conflict of Interest disclosures:**

4 MEJL reports personal fees from Counterweight Ltd, paid to the University of Glasgow for
5 medical advisory consultancy, and advisory board, consultancy and speaking fees from Novo
6 Nordisk, Novartis, Astra Zenica, Eli Lilly, all outside the submitted work. AB reports personal
7 fees for consultancy from Novo Nordisk, Bristol-Myers Squibb, and GSK, outside the
8 submitted work. All other authors declare no competing interests.

9

10

11 **Novelty statement (bulleted, maximum 100 words):**

12 What is already known?

- 13 • Diabetes and its complications accounts for approximately 10% of health care budgets
14 worldwide.
- 15 • Counterweight-Plus weight management programme in DiRECT achieved 46%
16 remissions of Type 2 diabetes and improved cardiovascular risk factors at one year

17 What this study has found?

- 18 • One-year incremental cost for the intervention group was estimated at £982 (95%CI
19 £732, £1,258) per participant compared to the control arm.
- 20 • Providing the DiRECT/Counterweight-Plus intervention in primary care incurs a cost
21 (£2,359 per one-year diabetes remission) below the average annual direct cost of
22 managing a person with Type 2 diabetes (including complications), and has the
23 potential for long-term cost effectiveness

24 What are the clinical implications of the study?

- 25 • Providing a reasonable proportion of remissions can be maintained for a period of time,
26 with multiple medical gains expected, as well as immediate social benefits, there is a
27 case for shifting resources within diabetes care budgets to offer support for people with
28 diabetes to attempt remission as early as possible after diagnosis.

29

30

31 **Funding sources**

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2 13/0004691), with support in kind (Counterweight-Plus formula diet sachets) provided by
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16 participation.

17

18 **Ethical approval**

19 The DiRECT was approved by West 3 Ethics Committee in January 2014, with additional
20 approvals by the National Health Service health boards in Scotland and clinical
21 commissioning groups in Tyneside. Informed consent was obtained from all participants.

1 **Abstract**

2

3 **Background:** The Counterweight-Plus weight management programme achieved 46%
4 remissions of type 2 diabetes at one year in the DiRECT trial. We estimated the
5 implementation costs of the Counterweight-Plus programme and its one-year cost-
6 effectiveness in terms of diabetes remission, compared with usual care, from the UK NHS
7 perspective.

8 **Methods:** Within-trial total costs included the programme set-up and running cost (practitioner
9 appointment visits, low formula diet sachets, and training), oral anti-diabetes and
10 antihypertensive medications, and healthcare contacts. Total costs were calculated for
11 aggregated resource use for each participant and 95% confidence intervals were based on
12 1,000 non-parametric bootstrap iterations.

13 **Findings:** One-year programme cost under trial conditions was estimated at £1,137 per
14 participant (95%CI £1,071, £1,205). The intervention led to a significant cost-saving of £120
15 (95%CI £78, £163) for the oral anti-diabetes drugs and a £14 (95%CI £7.9, £22) saving for
16 antihypertensive medications compared to the control. Deducting the cost-savings of all
17 healthcare contacts from the intervention cost resulted an incremental cost of £982 (95%CI
18 £732, £1,258). Cost per one-year diabetes remission was £2,359 (95%CI £1,668, £3,250).

19 **Interpretation:** Remission of type 2 diabetes within one-year can be achieved at a cost lower
20 than the annual cost of diabetes (including complications). Providing a reasonable proportion
21 of remissions can be maintained for a period of time, with multiple medical gains expected, as
22 well as immediate social benefits, there is a case for shifting resources within diabetes care
23 budgets to offer support for people with type 2 diabetes to attempt remission.

24

25 **Keywords:** Cost effectiveness, Cost-benefit, Type 2 Diabetes, Caloric Restriction, Weight
26 Loss

1 Introduction

2 Approximately one in 12 adults worldwide have type 2 diabetes [1]. Care for people with
3 diabetes accounts for 24% of total healthcare spending in the USA, with more than half directly
4 attributable to diabetes (approximately USD\$9,600 per diagnosed person per year) [2]. These
5 figures are expected to rise rapidly with increasing prevalence of type 2 diabetes and the
6 introduction of new more expensive treatment options. Diabetes accounted for approximately
7 10% of the total UK NHS budget (£8.8 billion in 2010/2011), with 80% attributed to diabetes
8 complications. This is anticipated to rise to 17% (£22 billion) by 2035, if traditional approaches
9 to diabetes management continue [3]. Indirect costs (economic output lost), were even greater,
10 at £13 billion, largely through working years lost (including early mortality), and the burden of
11 informal care required for people with diabetes aged over 70 years. In Germany, annual direct
12 healthcare cost was increased 1.8-fold with diabetes (€3,352 vs €1,849), and indirect costs
13 elevated two-fold (€4,103 vs €1,981) compared to those without diabetes [4].

14 Type 2 diabetes is being diagnosed younger as populations become more overweight, and
15 expensive complications are much more likely with a younger diagnosis [5]. A US study
16 estimated lifetime medical spending at US\$35,900 for people who were diagnosed with
17 diabetes at age 65 years but US\$124,600 with diagnosis aged 40 years [6]. This suggests that
18 periods of diabetes remission may be particularly valuable for younger people with diabetes,
19 avoiding enormous expenditure.

20 Current guidelines for type 2 diabetes management focus heavily on drug treatments to lower
21 blood glucose and counter elevated cardiovascular risks. These management strategies,
22 however, are not aimed at remission of diabetes, which progresses, so morbidity and mortality
23 remain high despite the application of clinical guidelines [7]. Bariatric surgery can consistently
24 convert 60-80% of people with type 2 diabetes to a non-diabetic state for 2-5 years, through
25 weight loss >10-15kg [8]. Surgical treatments present their own risks and long-term
26 complications, and reach only 1% of the eligible population [9], and are less preferred by
27 people [10], so other options are needed. Several studies have found weight loss of this order
28 from non-surgical calorie restriction and structured weight-loss maintenance can normalize
29 hepatic fat, blood glucose and insulin, and may extend life expectancy for people with type 2
30 diabetes [11-13].

31 The Diabetes Remission Clinical Trial (DiRECT) assesses the extent to which effective weight
32 management, delivered in the primary care setting, can lead to sustained remission of type 2
33 diabetes [14,15]. DiRECT is an open-label, cluster-randomised trial in 49 primary care
34 practices, which represented the characteristics of people with diabetes and poorer social
35 settings where type 2 diabetes is most frequent in Scotland and the Tyneside region of

1 England. Eligibility criteria included age 20-65 years, type 2 diabetes diagnosed within the
2 previous six years, body-mass index (BMI) 27-45 kg/m², and most recent HbA1c >48mmol/mol
3 (6.5%) (or >43 mmol/mol (6.1%) if taking diabetes medication). Between July 2014 and Aug
4 2016, 298 participants were randomised equally to control (usual care) and intervention
5 groups. Both groups continued to receive optimal routine care under current clinical guidelines.
6 Participants in the intervention arm followed the Counterweight-Plus weight management
7 programme, to achieve and maintain substantial weight loss, aiming for >15kg weight loss.
8 The programme, delivered in the primary care setting by trained dietitians or practice nurses,
9 contained three phases: 'total diet replacement' during which participants consumed only a
10 low energy formula diet (soups and shakes, 825–853 kcal/day) for 12 weeks, which could be
11 extended up to 20 weeks to accommodate holidays or other periods of slow progress, followed
12 by a structured food reintroduction phase of 2-8 weeks, and then longer-term weight loss
13 maintenance. Following weight loss, 'rescue packages' of the formula diet may be provided
14 if >2kg weight was regained or diabetes returned. All oral anti-diabetes and antihypertensive
15 medications were ceased, on safety grounds, when participants began the programme. These
16 were reintroduced under standard protocols following national clinical guidelines, where
17 indicated by regular monitoring of blood glucose and blood pressure. Otherwise, participants
18 in both groups continued to receive diabetes care under current national guidelines and
19 standards. At one year, DiRECT showed remission of diabetes (HbA1c < 48 mmol/mol (6.5%))
20 was achieved in 46% of intervention and 4% of control participants (p<0.0001) [15]. We have
21 previously briefly reported the intervention cost and cost per diabetes remission [16] and now
22 report the methods used in detail, especially the Counterweight-Plus programme cost
23 elements, and the complete results of the one-year within-trial cost-effectiveness analysis.

24

25 **Methods**

26 This analysis adopted the perspective of the UK National Health Service (NHS). Cost per
27 additional diabetes remission at one year (2016/2017 prices) is calculated from the resource
28 use and the proportion of diabetic remissions observed from the Counterweight-Plus and
29 usual-care arms in DiRECT, based on the intention to treat (ITT) principle.

30

31 **DiRECT intervention set-up cost**

32 Fixed costs of providing the Counterweight-Plus intervention include 'set-up' costs for training
33 practitioners (nurse or dietitian). Each practitioner received structured training by experienced

1 Counterweight-Plus research dietitians. This totalled 16 hours of face-to-face sessions (one
2 initial eight-hour session plus one four-hour session for weight loss maintenance and a further
3 four-hour consolidation session). Training is required for one practitioner per participating
4 practice, though several practitioners may undergo training in groups. Costs associated with
5 the training included practitioners' attendance time and instructors' costs, based on a £300
6 Counterweight-Plus fee (paid per practitioner), that also includes provision of dedicated
7 training materials, and annual licence fee which covers Counterweight-Plus programme
8 support and access to a medical advisor. After training practitioners, Counterweight-Plus
9 research dietitians provide mentoring support for them when they see their first few
10 intervention participants, with standard competency checks and fidelity testing. This service is
11 included in the £300 Counterweight-Plus fee.

12 We costed practitioner time using standard UK unit cost sources (Personal Social Service
13 Research Unit (PSSRU)). Training costs were annualised, assuming each trained practitioner
14 remains in place for five years.

15

16 **DIRECT intervention running cost**

17 Resource use for running the Counterweight-Plus weight management intervention included
18 the formula diet (total diet replacement sachets), review appointments with a practitioner, and
19 supporting workbooks. The number of sachets issued to each participant and duration of each
20 appointment were collected prospectively throughout the study.

21 Sachets of low energy formula-diet (reconstituted with water as soups and shakes, 4 sachets
22 daily) are designed to supply all essential micronutrients. Sachets were intended to replace all
23 food during total diet replacement. During the food reintroduction phase, food-based diet
24 gradually replaced the low energy sachets. Occasional further use of sachets, however, was
25 permitted during the weight loss maintenance stage. Participants attended fortnightly review
26 appointments during total diet replacement and food reintroduction stages, and monthly
27 appointments during weight loss maintenance. Actual consumption of sachets and
28 attendances for healthcare appointments were included in the cost analysis; these varied
29 across participants, depending, for example, on adherence, holidays, time to weight loss, and
30 need for 'rescue plans'. The workbooks were provided to participants at the start of each of
31 the phases but were included in full in the cost analysis for each enrolled participant
32 irrespective of potential drop-out [14]. Details of the programme have been described
33 elsewhere [14,15].

34

1 **Health care contacts and medication use**

2 Data on all contacts with medical professionals in primary and secondary care were obtained
3 directly from the GP practice records. This ensured the completeness and accuracy of the
4 resource use data, including for those who ceased to engage with the intervention. This
5 method did not depend on self-reporting, and thus avoiding recall bias. Each primary or
6 community care record was indicated as being related to diabetes or otherwise. Unit costs for
7 health care resource use, including medical contacts and hospitalisations, were obtained from
8 published national sources (PSSRU, NHS reference costs, or Information Services Division
9 (ISD) Scotland) for the 2016-2017 financial year (Appendix 1).

10 Use of oral anti-diabetes and antihypertensive medicines was suspended on initiation of the
11 programme and reinstated as necessary according to NHS clinical guidelines, however,
12 people who achieve and sustain remission, may continue without these medications. Use of
13 these medications was costed according to individual participants' medication records in each
14 participating GP practice. Data included dose, frequency, start and end dates of each
15 medication. Prescriptions for all concomitant medications (i.e., other than the oral anti-
16 diabetes and antihypertensive medications) were compared between arms but were not
17 included in our cost estimates. Unit cost for individual doses of each medication was calculated
18 based on the British National Formulary online database (accessed June 2018).

19

20 **Statistical analysis**

21 Statistical analysis was conducted according to the intention to treat (ITT) principle with all
22 randomised participants included in the analysis. Patient characteristics have been previously
23 reported elsewhere [15]. Resource use data were incomplete for one participant in each arm
24 (< 1%) due to relocation. For the one relocated participant in the control arm, we assumed
25 that she/he continued oral anti-diabetes or antihypertensive drugs throughout the period. The
26 relocated intervention group participant attended only one intervention visit, so we also
27 assumed continued usage in that case. We assigned each of these participants zero
28 healthcare contacts. Mean cost was calculated by averaging the aggregated resource use
29 costs (Counterweight-Plus intervention, primary and secondary care, oral anti-diabetes and
30 antihypertensive medication) over all participants within each group. Standard errors of all
31 analyses were adjusted for clustering at GP practice level. An incremental cost effectiveness
32 ratio was calculated as the difference in the groups' total costs divided by the difference in
33 diabetes remission rates at one-year. 95% confidence intervals were based on 1,000 non-
34 parametric bootstrap iterations (samples with replacement from the observed data). All
35 analyses were undertaken in STATA/MP 14.2 (StataCorp, TX, USA).

1 **Results**

2 **Intervention cost**

3 The total cost per intervention participant of delivering the Counterweight-Plus programme
4 was £1,137 (95% CI: £1,071, £1,205) (Table 1). The mean duration of total diet replacement,
5 food reintroduction and weight loss maintenance was 3.5, 2.3 and 3.5 months respectively,
6 including all participants who ceased the intervention. Each participant consumed a mean of
7 3.6, 0.9 and 0.5 sachets per day and attended 2.2, 1.6 and 1.2 appointments per month for
8 total diet replacement, food reintroduction and weight loss maintenance respectively (Figure
9 1). In total, each participant was issued a mean of 495 sachets (costed at £708), which
10 accounted for over half of total intervention costs. A total of 15.6 (95% CI: 14.7, 16.5)
11 practitioner visits (costed at £362) were observed over the first year, and these accounted for
12 approximately one third of total intervention costs.

13

14 **Routine resource use and cost over one-year**

15 Table 2 shows the healthcare contacts of participants over the 12-month period. There was
16 little difference between the arms, as might be expected, though participants in the intervention
17 arm had fewer GP visits related to diabetes (mean difference 0.5; 95% CI: 0.2, 0.7), and fewer
18 practice nurse visits unrelated to diabetes (0.5; 95% CI: 0.1, 1.0). The aggregate number of
19 days using individual oral anti-diabetes and antihypertensive drugs, however, differed greatly
20 between arms with the intervention arm having a total of 332 fewer days per participant on
21 oral anti-diabetes medications and 240 fewer days on antihypertensive drugs.

22 Table 3 applies unit costs to the resource use. Overall, the intervention group's costs for
23 routine healthcare contacts were £155 (95% CI: -£74, £394) lower than the control group's.
24 Statistically significant mean differences were observed for oral anti-diabetes drugs of £120
25 (95% CI: £78, £163) per participant, and for antihypertensive drugs of £14 (95% CI: £7.9, £22).
26 Aggregating the intervention costs and routine resource use costs together, the difference in
27 total costs over one-year between the groups was therefore due almost entirely to the
28 intervention delivery cost, with some offset provided through medication cost savings.

29

30 **Cost-effectiveness for remission of diabetes**

31 Over the one-year period, the mean cost per participant was £1,827 (95% CI £1,652, £2,021)
32 in the intervention group and £846 (95% CI £685, £1,038) in the control group (Table 4),
33 leading to an incremental cost difference of £982 (95% CI £732, £1,258) per participant.

1 Combined with the incremental remission rate (42%; 95% CI 33%, 50%), the incremental cost
2 per diabetes remission over the first year was £2,359 (95% CI £1,668, £3,250).

3 **Discussion**

4 We have analysed the observed resource use over one year, under the DiRECT trial
5 conditions, to estimate the DiRECT/Counterweight-Plus intervention cost and its cost-
6 effectiveness (incremental cost per remission achieved). The average cost of intervention
7 delivery was £1,137 per participant randomised to the intervention arm. There were observed
8 reductions in several routine (non-intervention) cost elements such that the net intervention
9 cost per participant was £982. The intervention delivery costs may be reduced when rolled out
10 in routine practice. For example, the training costs per participant, with an average of five
11 participants per practice in the trial (33 practitioners managing 149 participants), will be lower
12 as each trained practitioner will manage many more people. Lower costs of formula diet
13 sachets per participant in the programme would be expected in routine practice if lower unit
14 costs could be negotiated for large contracts. As patients following the Counterweight-Plus
15 programme do not require normal food during total diet replacement, and less than usual
16 during the food re-introduction and maintenance stages, there will be some decreased spend
17 for patients. A case might be made to introduce out-of-pocket payment for the formula diet
18 sachets. This could apply after a specific period, be part payment, or for ongoing use such as
19 rescue plans or for one sachet per day for weight loss maintenance. For people in some socio-
20 economic groups there may be value in exploring means tested payments to avoid widening
21 the inequality gap in this area of care. Such options would need careful consideration and
22 ongoing audit to ensure no impact on effectiveness.

23 The delivery cost of the DiRECT/Counterweight-Plus programme compares favourably with
24 other diabetes remission interventions. There are no directly comparable studies of weight
25 management with diabetes remission as the primary outcome. The US Look AHEAD trial in
26 type 2 diabetes involved an exercise training and weight loss intervention which cost almost
27 twice as much the DiRECT intervention (USD \$2,865 per participant, 2012 value), but DiRECT
28 achieved greater weight losses and a four-fold greater remission rate at 1 year (DiRECT 46%
29 vs. Look AHEAD 12%) [17,18]. Bariatric surgery usually produces much greater weight losses
30 and remissions of type 2 diabetes, however, surgery carries risks of mild to serious long-term
31 complications, with frequent vitamin and mineral deficiencies and symptoms such as
32 hypoglycaemia and hypovolemic dumping, and it is expensive (e.g., at £6,346 [19] for
33 laparoscopic gastric bypass, £7,224 (€8,105 [20]) for vertical banded gastroplasty), with most
34 costs incurred during the initial hospitalisation [21].

1 Limited offsetting cost-savings were observed in the initial 12-months (including significantly
2 lower prescription costs). The benefits from weight loss and remission may persist into future
3 years during which the relatively high initial intervention costs do not apply. The two-year
4 analysis will inform this. The numbers of participants prescribed any concomitant medication
5 during the study (i.e., excluding oral anti-diabetes, diuretic and antihypertensive drugs) were
6 comparable between the arms. Given this, the low cost of most items, and the likelihood that
7 any aggregate differences would tend to favour the intervention arm through the broader
8 benefits related to weight loss, we excluded the concomitant medications from the present
9 analysis. However the proportion of participants taking no prescription drugs increased in the
10 intervention arm at 12 months in DiRECT [15], pointing to further possible cost advantages for
11 the intervention in the longer term.

12

13 **Strengths and Limitations**

14 This analysis is based on one-year outcomes, and detailed data collection, during a rigorously
15 conducted randomised trial. DiRECT was the first study in a primary care setting to set
16 remission of type 2 diabetes as a primary outcome. The intervention was well received by
17 participants, with significantly improved quality of life at one year, and healthcare contacts
18 outside the trial were reduced (e.g. GP visits as shown in the results). The participants were
19 very typical of people currently living with type 2 diabetes, up to 6 years after diagnosis. A high
20 proportion were from socially deprived circumstances, where type 2 diabetes is most prevalent
21 and difficult to manage [22]. The study design ensured that cost and outcome data were
22 available from primary care records in nearly all the participants (296/298 for costs and
23 298/298 for remission rates) for ITT analysis, even if they had ceased to engage with the
24 programme. The control group received standard treatment under guidelines which are
25 broadly similar internationally. Our results are thus likely to be robust and generalizable.

26 The costs of the intervention, and of routine care, are similar in many other studies [23,24].
27 For example, the standard care arm among people with prediabetes in the UK Let's Prevent
28 trial had an annual mean non-inpatient health service cost of £437 and medication cost of
29 £124 [24], which is similar to the control arm resource use in our study (£520 for non-inpatient
30 health care services, and £168 for primary medications as shown in Table 3). As such the
31 present economic analysis is likely to be widely transferable to diabetes care elsewhere, at
32 least within countries with similar healthcare systems. However, the population studied was
33 almost entirely European, and up to six years after diagnosis: we cannot be certain whether
34 the results are applicable to people from other racial or ethnic origins where type 2 diabetes
35 has different characteristics, or with diabetes for over six years. Asian populations have a

1 higher prevalence of diabetes than their European counterparts for the same BMI [25]. Also,
2 many Asian people with diabetes develop both early β cell dysfunction and insulin resistance,
3 so many require earlier insulin treatment [26]. There is therefore need for research to evaluate
4 intensive weight management in Asian populations and to develop appropriate methods for
5 developing countries, where type 2 diabetes and its treatment costs are rising dramatically.

6 **Future long-term cost-effectiveness analysis**

7 Over a period of one year, it would be unrealistic to expect to identify resource savings relating
8 to the long-term consequences of diabetes, such as neuropathy, renal failure and vision loss,
9 and DiRECT was not powered for these outcomes. Nevertheless, given the clear benefit of
10 lower HbA1c in reducing complications [27], diabetes remission rates such as those seen in
11 DiRECT at one-year are potentially transformative both for participants' health, quality of life,
12 and longevity, and for the burden to healthcare systems such as the NHS. Participants'
13 abilities to maintain weight loss and healthy lifestyles, and avoid reversion to a diabetic state
14 will be critical but are under-researched, and will require appropriate research and
15 development investment for programme improvement. There is ample evidence that
16 substantial weight loss and a period of remission consistently improves multiple cardio-
17 metabolic risk factors [28,29], and that weight management interventions may extend life
18 expectancy [12]. On-going follow up in DiRECT will contribute to modelling of long-term health
19 gains, resource savings following initial remission, and inform long-term cost-effectiveness
20 modelling and healthcare planning. Recent studies using different methodologies have
21 indicated reduced life expectancy with type 2 diabetes of 6 - 7 years for those who are
22 diagnosed with diabetes at the age of 50 years (similar to DiRECT population) [7,30,31].
23 Irrespective of future resource use that may be avoided, such estimates imply costs per
24 quality-adjusted life-year (QALY) ratios comfortably within the cost-effectiveness threshold of
25 £20,000 - £30,000 per QALY gained applied to healthcare interventions in the UK.

26 **Conclusions**

27 Providing the DiRECT/Counterweight-Plus intervention in primary care incurs a cost lower
28 than the average annual direct cost of managing a person with type 2 diabetes (including
29 complications at later stage), and has the potential for long-term cost effectiveness, based on
30 the data up to one year. The programme involves early intervention costs that may generate
31 substantial future healthcare resource savings if remissions and reduced drug prescriptions
32 are maintained by sufficient numbers of participants. DiRECT is on-going, and further data will
33 support future cost-effectiveness analyses incorporating long-term outcomes including quality-
34 adjusted life-years. However, given the likelihood that a period of remission will reduce

- 1 disabling long-term diabetes complications, as well as improving quality of life, the case
- 2 already appears strong for shifting resources within diabetes care budgets to offer the support
- 3 for people with diabetes to attempt remission.

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Tables and figures

Table 1 Intervention resource use components and cost (per participant) (n=149) over the first 12 months of the DiRECT trial

Intervention cost components						Total	
1a. Intervention set-up cost		Units	Unit cost				
	Counterweight-Plus specialist training, support and mentoring	33 practitioners	£300 per practitioner			£9,900	
	Practice nurses and dietitians' time	16 hours per practitioner	£42 per hour ^c			£22,176	
	Total set-up cost					£32,076	
	Total set-up cost annualised over five years ^a					£7,104	
Total intervention set-up cost per participant						£48^e	
1b. Intervention running resource use and costs at each stage of the Counterweight-Plus programme		Total diet replacement	Food reintroduction	Weight Maintenance	Rescue package – Total diet replacement	Rescue package – food reintroduction	Total (95% CI)
Intervention running resource use		Mean (SD) (n=149^b)					
	Number of practice nurse or dietitian visits	7.7 (2.9)	3.7 (1.9)	3.5 (2.7)	0.3 (0.7)	0.4 (1.0)	15.6 (14.7, 16.5)
	Number of Counterweight-Plus sachets issued	383 (156)	62 (50)	30 (48)	10 (27)	10 (31)	495 (461, 530)
Intervention running cost		Mean (SD) (n=149^b) (£)					
	Practice nurse/dietitian visits ^c	172 (63)	88 (47)	84 (63)	7.7 (19)	10 (24)	£362 (337, 384)
	Sachets ^c	547 (223)	89 (71)	42 (68)	14 (39)	15 (44)	£708 (659, 757)
	Counterweight-Plus booklets						£20 (-)
Total intervention running cost per participant						£1,089 (1,023, 1,158)	
Total cost per participant (n=149)						£1,137 (1,071, 1,205)	

a. Annualising the total cost over five years using the formula, equivalent annual cost (E): $=K/[(1-1/(1+r)^n)/r]$. K=£32,076, r=3.5%, n=5, gives an annual specialist training and support cost of £48 per participant.

b. Includes six randomised participants who did not initiate the intervention.

c. Unit cost £42/hour was obtained from the PSSRU unit cost of medical and social care 2016/2017; sachet costs £20 per 14 sachets.

d. 95% CI was obtained from 1000 iterations of bootstrap.

e. This is the training cost for 33 practitioners managing 149 participants (a ratio of 1:4.5), as implemented in the trial.

Table 2 NHS resource use quantity per participant 12 months trial period

Resource use items ^a	Mean (SD)		Mean difference (95% CI ^c)
	Intervention (n=149 ^b)	Control (n=149 ^b)	
Primary and community care visits related to diabetes			
GP	0.44 (0.82)	0.89 (1.24)	-0.45 (-0.69, -0.20)
Practice nurse	1.73 (1.41)	2.03 (1.52)	-0.30 (-0.64, 0.03)
Health care assistant	0.26 (0.64)	0.32 (0.72)	-0.07 (-0.23, 0.09)
Community care	0.41 (0.67)	0.43 (0.87)	-0.02 (-0.21, 0.15)
Primary care visits not related to diabetes			
GP	3.91 (4.71)	4.05 (4.70)	-0.14 (-1.24, 0.95)
Practice nurse	0.94 (1.53)	1.46 (2.74)	-0.52 (-1.03, -0.07)
Health care assistant	0.16 (0.48)	0.28 (1.54)	-0.11 (-0.41, 0.09)
Community care	0.28 (0.90)	0.28 (1.75)	-0.00 (-0.38, 0.27)
Outpatient visits	1.31 (1.90)	1.81 (2.72)	-0.50 (-1.02, 0.03)
Hospitalisation length of stay (day)	0.21 (0.98)	0.17 (0.72)	0.03 (-0.16, 0.24)
Medication days (sum of individual drug days) ^d			
Oral anti-diabetes drugs	104 (197)	436 (312)	-332 (-397, -267)
Antihypertensive drugs	148 (218)	387 (389)	-240 (-314, -166)

- a. The resource use included all the health care contacts the participants had over the one-year period except for the intervention visits, including the routine annual checks for diabetes such as retina screening for both arms.
- b. Included one participant in each arm who moved away from the trial participating practice. Their healthcare resource use was assumed to be 0 after they moved away, and their medication use was assumed to continue since they moved away.
- c. 95% CI for the mean differences were obtained from bootstrap.
- d. The number of 'individual-drug-days' was generated by adding together the number of days on each individual drug taken by participants during the one-year period. If the participant has more than one oral anti-diabetes medication administered during the one-year period, then the days were added up together, even when the drugs have overlapping period.

Table 3 NHS cost (£) per participant (n=149 for each arm) over the 12 months trial period

Cost (per participant)	Mean cost (SD) (£)		Mean difference (Intervention – Control) (£) (95% CI ^b)
	Intervention (n=149 ^a)	Control (n=149 ^a)	
3a. Resource use of health care contacts			
Primary and community care visits related to diabetes			
GP	17 (31)	34 (47)	-17 (-26, -7.6)
Practice nurse	19 (15)	22 (16)	-3.3 (-7.0, 0.3)
Health care assistant	1.0 (2.6)	1.3 (2.9)	-0.3 (-0.9, 0.4)
Community care	16 (28)	18 (43)	-2.2 (-11, 5.6)
Primary and community care visits not related to diabetes			
GP	149 (179)	154 (178)	-5.4 (-47, 36)
Practice nurse	10 (17)	16 (30)	-5.6 (-11, -0.8)
Health care assistant	0.6 (1.9)	1.1 (6.2)	-0.5 (-1.6, 0.4)
Community care	13 (45)	13 (92)	-0.2 (-20, 14)
Outpatient visits	244 (476)	261 (407)	-17 (-111, 83)
Hospitalisation	187 (796)	157 (713)	30 (-142, 201)
<u>Total cost of resource use of health care contacts</u>	<u>656 (1,047)</u>	<u>677 (1,028)</u>	<u>-21 (-249, 215)</u>
3b. Medications			
Anti-diabetes drugs	29 (86)	149 (228)	-120 (-163, -78)
Antihypertensive drugs	5.3 (9.1)	19 (43)	-14 (-22, -7.9)
<u>Total cost of oral anti-diabetes and antihypertensive drugs</u>	<u>34 (87)</u>	<u>168 (229)</u>	<u>-134 (-177, -93)</u>
<i>Total cost of resource use (incl. medications, regardless of relation to diabetes)</i>	<i>691 (1,058)</i>	<i>846 (1,066)</i>	<i>-155 (-394, 74)</i>
3c. Intervention cost			
<u>Total intervention cost (see Table 1)</u>	<u>1,137 (421)</u>	<u>0 (-)</u>	<u>1,137 (1,071, 1,205)</u>
<u>GRAND TOTAL cost per participant</u>	<u>1,827 (1,145)</u>	<u>846 (1,066)</u>	<u>982 (732, 1,258)</u>

a. Included one participant in each arm who moved away from the trial participating practice. Their healthcare resource use was assumed to be 0 after they moved away, and their medication use was assumed to continue since they moved away.

b. 95% CI values for the mean differences were obtained from the 1,000 iteration bootstrap.

Table 4 Cost-effectiveness results of DiRECT intervention over 1 year within trial time horizon

	Diabetes Remission (%) (95% CI ^a)	Mean cost (£) (95% CI ^a)
Intervention	45.6 (37.9, 53.6)	1,827 (1,652, 2,021)
Control	4.0 (1.3, 7.5)	846 (685, 1,038)
Difference	41.6 (33.0, 50.4)	982 (732, 1,258)
Cost per diabetes remission (95% CI)		2,359 (1,668, 3,250)

a. the 95% CI for the incremental cost and incremental number of remissions were both obtained from the 1,000-iteration bootstrap.

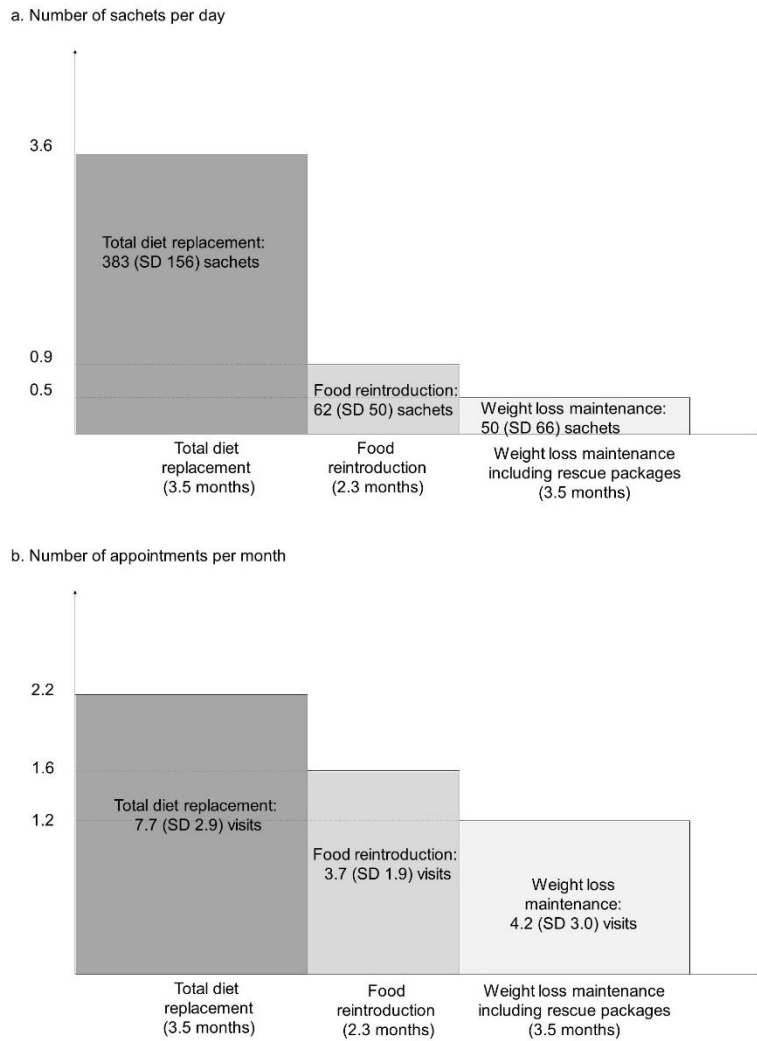


Figure 1 Mean number of sachets (a) and mean number of appointments per month (b) offered to participants during each stage of the DiRECT intervention within year 1 (n = 149, including the participants who discontinued from the trial).

Appendix 1 Unit costs for community and outpatient health-care resource use

Resource use item (unit used in the source)	Unit Cost	Source
NHS community based resource use		
GP (per contact)	£38.00	PSSRU 2016/17 pg. 162. Per patient contact lasting 9-22 minutes, with qualifications
Practice Nurse (per hour)	£42.00 (£10.85 per contact)	PSSRU 2016/17 pg. 160. Nursing average cost per hour, with qualifications. Duration of contact per patient is 15.5 minutes (PSSRU 2014/15, pg.174, based on the 2006/07 UK general practice survey)
Healthcare assistant (per hour)	£24 (£4 per contact)	PSSRU 2016/17 pg.159. Nurses Band 3. Average duration per contact is estimated to be 10min.
Podiatrist (per contact)	£41	NHS reference cost – Community health services – Podiatrist Tier 1, General podiatry P09A.
Pharmacist (per hour)	£43 (£10.75 per contact)	PSSRU 2016/17 pg. 153-155. Community Scientific and professional staff Pharmacist Band 6. Length of contact assumed to be 15min.
Dietitians (per contact)	£85	NHS reference cost 2016/17 community health service.A03 dietitian £85 per contact.
Physiotherapist (per contact)	£53	NHS reference cost, AHP allied health professionals A08A1, physiotherapist, adult, one to one.
Clinical psychologist/counselor (per hour)	£53	PSSRU 2016/17 pg. 153-155. Community Scientific and professional staff band 7 (£53 per hour) clinical psychologist/counsellor. Length per contact assumed to be 1hr.
Occupational therapist (per contact)	£77	NHS reference cost community health service. Occupational therapist, adult, one to one.
District nurse (per visit)	£37	NHS reference cost – community health services. N02AF District Nurse, Adult, Face to face.
Haemodialysis	£137.03	NHS reference cost 2016/17 Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, 19 years and over
A&E services		
Urgent and emergency Calls answered (NHS 111, or 999)	£7	NHS Reference costs 2016/17 highlights, analysis and introduction to the data. Table 6. Costs by currency for ambulance services between 2014/15 and 2016/17. Unit cost for calls. (pg.9)
Hear and treat or refer (ambulance trust clinician resolves the call or	£37	NHS Reference costs 2016/17 highlights, analysis and introduction to the data. Table 6. Costs by currency for ambulance services between 2014/15 and 2016/17. Unit cost for hear and treat or refer. (pg.9)

refer over the phone)		
Ambulance service (see and treat or refer)	£181	NHS Reference costs 2016/17 highlights, analysis and introduction to the data. Table 6. Costs by currency for ambulance services between 2014/15 and 2016/17. Unit cost for see and treat or refer. (pg.9)
Ambulance (see and treat and convey)	£248	NHS Reference costs 2016/17 highlights, analysis and introduction to the data. Table 6. Costs by currency for ambulance services between 2014/15 and 2016/17. Unit cost for see and treat and convey (pg.9)
A&E attendance (per attendance)	£148	NHS Reference costs 2016/17 highlights, analysis and introduction to the data. Table 2. Unit costs by point of delivery, 2014/15 and 2016/17 (£). Unit cost for A&E attendance (pg.5)
Outpatient appointment by specialty (per attendance)		
Average outpatient appointment cost	£168	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Gynaecology	£169	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Gynaecology (nurse led)	£58	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Gastroenterology	£226	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Gastroenterology (nurse led)	£134	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Cardiology	£143	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Dermatology	£157	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Geriatric assessment	£190	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Ear, Nose & Throat (ENT)	£114	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Ophthalmology	£154	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Ophthalmology (nurse led)	£76	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
General medicine	£255	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c

General surgery (excluding vascular surgery)	£147	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Clinical genetics	£553	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Haematology	£370	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
General psychiatry	£233	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Orthopaedic	£119	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Neurology	£214	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Neurosurgery	£149	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Obstetrics	£181	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Clinical oncology	£250	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Oral surgery & medicine	£111	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Pain relief	£203	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Respiratory medicine	£199	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Rheumatology	£214	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Urology	£154	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Vascular surgery	£154	ISD Scotland 2016/17 Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c
Radiology	£65-59	ISD Scotland 2016/17 R120 Radiology services. Outpatients specialty cost. R044X – outpatient consultant clinics, by specialty, by board. Net cost per attendance ^c .
Midwife service	£80-98	NHS reference cost 2016/17. Total outpatient attendances 560 midwifery service.
Clinical microbiology	£119-40	NHS reference cost 2016/17. Total outpatient attendances 322 clinical microbiology.

Endocrinology	£158.34 (average) £161.83 (consultant led) £110.60 (non consultant led)	NHS reference cost 2016/17. Total outpatient attendances 302 endocrinology.
Podiatry	£46.64	NHS reference cost 2016/17. Total outpatient attendances 653 podiatry.
Clinical immunology	£263.67	NHS reference cost 2016/17. Total outpatient attendances 316 Clinical immunology.
Orthotics	£119.07	NHS reference cost 2016/17. Total outpatient attendances. 658 Orthotics
Physiotherapy	£48.81	NHS reference cost 2016/17. Total outpatient attendances. 650 physiotherapy
Out of hours GP service (per contact)	£71.07 ^a	National Audit Office. Out of Hours GP Services in England. London: Department of Health and NHS England; 2014 (https://www.nao.org.uk/wp-content/uploads/2014/09/Out-of-hours-GP-services-in-England1.pdf) pg 15-16. a national average cost, for opted-out services of £68.30 in 2013-14.
Out of hours NHS telephone service	£37.00	NHS reference cost (hear and treat or refer)
Diabetic retina screening	£37.14 ^b	Scanlon PH et al. 2009/10 NHS reference cost - £33
Walk in services	£41.64 ^b	PSSRU 2009/10 pg. 119 A&E SERVICES (Weighted average of attendances) – walk in services leading to admitted (not admitted) £37(37)
Diagnostic services		
Other radiology (includes 'conventional' X rays)	£72.83 ^b	ISD Scotland 2009/2010. R120X radiology services by board. Other radiology (includes 'conventional' X rays) net cost per examination: £64.71
Ultrasonic	£57.40 ^b	ISD Scotland 2009/2010. R120X radiology services by board. Ultrasonic net cost per examination: £51.00
Magnetic Resonance Imaging	£243.55 ^b	ISD Scotland 2009/2010. R120X radiology services by board. Magnetic Resonance Imaging, net cost per examination: £216.40
CT scan	£124.35 ^b	ISD Scotland 2009/2010. R120X radiology services by board. CT scan net cost per examination: £110.49
ECG (electrocardiogram monitoring)	£52	NHS reference cost 2016/17 Directly accessed diagnostic services. EY51Z Electrocardiogram monitoring or stress testing.

a. HCHS inflation factor 1.04062 (2013/14 Pay and prices index (PPI) 290.5 / 2016/17 PPI 302.3)

b. HCHS inflation factor 1.12547 (2009/10 Pay and prices index (PPI) 268.6 / 2016/17 PPI 302.3)

c. ISD R044X cost notes: these costs are mainly for consultation or very minor procedures, but may include patients who receive more complex (and expensive) treatments.

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