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Title: The DiRECT principles: giving Type 2 diabetes remission programmes the best chance of success

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In 2017 the 12-month primary outcome results of the Diabetes UK-funded Diabetes Remission Clinical Trial (DiRECT) were published, providing randomised controlled trial evidence to challenge the conventional view of Type 2 diabetes as a permanent and progressive condition. They showed, for the first time, that a three-phase integrated weight management programme, delivered within routine primary care, achieved remission of Type 2 diabetes in almost half of participants. Almost 9/10 achieved remissions if they could lose 15 Kg or more [1]. The participants were very representative of those normally managed in UK primary care, within 6 years of diagnosis and not yet with serious complications or requiring insulin.

Further results, published in 2019, showed that 70% of remissions could be sustained for 24 months, provided an average weight loss of 10 Kg was maintained: 36% of all people offered the intervention were in remission, defined by DiRECT as an HbA_{1c} below 48 mmol/mol (6.5%) and off all anti-diabetes drug therapy [2].

These results have captured the attention of people with diabetes, healthcare professionals and healthcare providers internationally. A pilot Type 2 diabetes remission programme, inspired by DiRECT, is currently under development by NHS England [3], and NHS Scotland is moving ahead at pace with remission programmes embedded within its Prevention, Early Detection and Early Intervention of Type 2 Diabetes framework [4]. Plans are already well established for well-designed diabetes remission services, and further research into remission and beta cell recovery, in countries across the world. However, other treatments are being offered, aimed at the remission of Type 2 diabetes, and making claims of efficacy based on the results of DiRECT, which may not in fact use the same evidence-based intervention or even its core elements, hence the need for a standard set of principles.

The DiRECT Principles

To support the development and delivery of effective interventions, Diabetes UK, together with the Principal Investigators of DiRECT from the University of Glasgow and Newcastle University have developed the 'DiRECT Principles'. These four principles (Table 1) set out the core elements of the successful DiRECT intervention, to guide development of future health interventions. A specific intervention programme, Counterweight-Plus [6], was used in DiRECT. If the underlying principles are adopted in future programmes, this would have the best chance of achieving the outcomes seen in DiRECT.

These are promising times for people with Type 2 diabetes. We are moving from an era of simply managing Type 2 diabetes, with its stigma and the likelihood that complications will develop in time, into one where, with effective weight-management, it can become a warning but a condition of the past.

The DiRECT intervention improved all cardiovascular risk factors, enhanced quality of life, and was highly cost-effective compared to conventional treatment [7]. To best serve people with Type 2 diabetes, we need to maintain the rigour of the approach seen in DiRECT, while acknowledging the possible need for adaptations for delivery in different real-world settings and populations. The DiRECT principles will be updated periodically, as new evidence emerges from the DiRECT trial and associated studies.

With this in mind, we urge healthcare providers to be cautious when a programme is described as being based on DiRECT, and to adopt the principles laid out in this paper. This will ensure that any person with Type 2 diabetes offered a diabetes remission programme may have the best possible chance of success.

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Table 1

The 'DiRECT Principles': criteria required for a type 2 diabetes management programme intended or advertised to help achieve remission of diabetes.

1. An initial assessment using defined criteria for suitability of the individual to the programme.

There were four key inclusion criteria within the trial, as listed below:

- Age 20-65 years
- Diagnosed with Type 2 diabetes within previous 6 years
- HbA1c of greater than 48 mmol/mol (6.5%), or for individuals receiving anti-diabetes medication, greater than 43 mmol/mol (6.0%).
- Body Mass Index (BMI) of 27-45 kg/m².

For further details, including exclusion criteria, please refer to the DiRECT Lancet publication¹.

2. An integrated programme with a focus on long-term behaviour change and strategies for relapse management, which should be introduced at the start of the programme. To include:

- I. A period of Total Diet Replacement using a nutritionally complete diet. It should be noted that the specific calorie count may be dependent on the baseline weight of the individual, with the participants in the DiRECT study generally having less than 850 kcal per day.
 - a. Documentation that the proposed approach constitutes a nutritionally complete approach.
 - b. Confirmation of availability of healthcare professional consultation - at least weekly for 4 weeks, then monthly with on-demand access to advice.
- II. A period of supervised stepped food/meal reintroduction, to establish a regular and sustainable eating pattern.
 - a. Confirmation of at least fortnightly visit frequency plus telephone or other support on-demand.
- III. Supervised weight loss maintenance (supported by a trained healthcare professional and written resources) to minimise weight regain for at least 24 months.
 - a. Confirmation of training status of personnel.
 - b. Confirmation of visit frequency of monthly, up until 24 months, and subsequently quarterly.
- IV. A clear, documented relapse management protocol with the following elements:
 - a. Recognition of the importance of early intervention for weight regain of >2 Kg;
 - b. Protocol for use of either further period of low calorie liquid diet or major decrease in advised energy intake;
 - c. Schedule for increased visit frequency.

3. Protocols for management of anti-diabetes and antihypertensive medications.

- All antihypertensive, diuretic and anti-diabetes drugs were stopped on the day Total Diet Replacement commenced. This is a safety measure, because blood pressure is likely to fall on the diet, and blood glucose levels fall rapidly on the diet.
- Clear protocols were established for the reintroduction of medications. For full details, refer to the appendices of the DiRECT Protocol paper [5].

- A full review of the DiRECT blood pressure data is underway and may identify clinical exceptions. Further guidance about management of antihypertensive drugs during intensive weight management will be provided as new evidence emerges.

4. Prospective data collection and audit for continuous programme improvement

- Clear description of data items to be collected which must include weight, waist circumference, HbA1c, plasma lipids and ALT + gamma GT;
- Specification of data storage;
- Specification of biannual data analysis with publication on website of the organisation.