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N.B. The published paper has an error on page 27, line 13. The word 'lower' is missing where it should read 'The satisfaction scores (lower at 44 months than it had been at 12 months….)'.

Title: Long-term biomedical and psychosocial outcomes following DAFNE (Dose Adjustment For Normal Eating) structured education to promote intensive insulin therapy in adults with sub-optimally controlled Type 1 diabetes

Author: The DAFNE Study Group*

* J Speight PhD[1], SA Amiel MD[2], C Bradley PhD[3], S Heller DM[4], L Oliver BSc(Hons) RD[5], S Roberts MSc[5], H Rogers MSc[2], C Taylor DipN[4], G Thompson BSc(Hons)[6]

[1] AHP Research, Brunel Science Park, Uxbridge, UK

[2] Diabetes Research Group, King's College London School of Medicine, London, UK

[3] Department of Psychology, Royal Holloway University of London, Egham, UK

[4] Division of Clinical Sciences, Northern General Hospital, Sheffield, UK

[5] Northumbria Diabetes Service, Northumbria Healthcare NHS Foundation Trust, North Shields, UK

[6] National DAFNE Service, Northumbria Healthcare NHS Foundation Trust, North Shields, UK

Please address correspondence to:
Dr Jane Speight
Email: jane.speight@ahpresearch.com
Tel. 01895 273599

For access to questionnaires used, please visit www.healthpsychologyresearch.com

Running title: Long-term follow-up of DAFNE trial cohort

Word count: 3,447 words (max 5,000) excluding references, plus 2 tables and 4 figures

Structured Abstract

Aims: To explore long-term outcomes of participation in a Dose Adjustment For Normal Eating (DAFNE) training course, which provided one-off exposure to structured education in intensive insulin therapy to people with established Type 1 diabetes.

Methods: A cohort design follow-up of original trial participants at a mean of 44 months (range: 37-51 months) in hospital diabetes clinics in three English health districts. 104 (74%) original participants provided biomedical data; 88 (63%) completed questionnaires (including the ADDQoL, measuring impact of diabetes on quality of life (QoL).

Results: At 44 months, mean improvement in HbA_{1c} from baseline was 0.36% (9.32±1.1% to 8.96±1.2%, $p<0.01$) remaining significant but deteriorated from 12 months ($p<0.05$). Improvements in QoL seen at 12 months were sustained at 44 (e.g. impact of diabetes on dietary freedom: -1.78±2.33 at 44 months vs -4.27±2.94, baseline, $p<0.0001$; vs 1.80±2.32 at 12 months, ns). Similar results were obtained using last observation carried forward for patients not supplying follow-up data.

Conclusions: The impact of a single DAFNE course on glycaemic control remains apparent in the long term, although further interventions will be required to achieve recommended HbA1c. In contrast, improvements in QoL and other patient reported outcomes are well maintained over approximately 4 years.

Word count: 200 (200 max)

Keywords: DAFNE; structured education; flexible intensive insulin therapy; Type 1 diabetes; quality of life; treatment satisfaction.

Abbreviations

ADDQoL = Audit of Diabetes-Dependent Quality of Life

ANOVA = analysis of variance

BMI = body mass index

DAFNE = Dose Adjustment For Normal Eating

DCCT = Diabetes Control and Complications Trial

DTSQ = Diabetes Treatment Satisfaction Questionnaire

HbA_{1c} = Haemaglobin A1c

HDL = High density lipoprotein

QoL= quality of life

STTP = structured teaching and treatment programme

Introduction

The value of a skills-based structured education programme originating in Germany [1], which trains people with Type 1 diabetes to use insulin flexibly to achieve dietary freedom and other lifestyle benefits, has been demonstrated in several studies [2-7]. The diabetes Structured Teaching and Treatment Programme (STTP) used in Germany and other parts of the world has shown sustained improvement in glycaemic control and reduced rates of severe hypoglycaemia. In a group of adults with established Type 1 diabetes and sub-optimal glycaemic control, the UK version of the STTP demonstrated a clinically significant improvement in HbA_{1c} without any increase in severe hypoglycaemia [8].

The UK programme (known as Dose Adjustment For Normal Eating (DAFNE)) was the first to assess formally the impact of the training on quality of life (QoL) and other psychological outcomes in a randomised waiting list controlled trial. The negative impact of diabetes on QoL was reduced significantly at six months and this was sustained at one year [8]. Furthermore, there was no significant overall change in cardiovascular risk factors, demonstrating that excessive over-eating and/or unhealthy eating patterns were not inevitable following increased dietary freedom. Thus, the DAFNE trial provided evidence that training in flexible intensive insulin therapy offers short-term benefits for both biomedical and psychological outcomes. Long-term improvements in biomedical outcomes have been demonstrated for the STTP [1,9,10] upon which DAFNE is based, but have not previously been established in the UK and there have, until recently [10], been no data on the long-term impact of any of these programmes on QoL.

Since the original DAFNE trial, the care of people with Type 1 diabetes in the UK has changed considerably. The introduction of the National Service Framework [11] engendered a culture supportive of patient empowerment and skills-based training. Consequently, DAFNE has been adopted across the UK and a database of over 10,000 DAFNE graduates established. Post-DAFNE, graduates are now better supported in both secondary and primary care.

We followed-up the original trial cohort approximately 4 years after they completed their original DAFNE course, to determine the extent to which improvements in biomedical and psychological outcomes observed 6 and 12-months post DAFNE training, with no formal opportunities for reinforcement of training, have been sustained in the long term.

Subject, Materials and Methods

Participants

For the original DAFNE trial, we recruited patients attending hospital diabetes clinics in Sheffield, Northumbria and South London. Patients were randomised to attend a DAFNE course immediately or to attend after a 6 month delay. A total of 141 patients attended a DAFNE course, with 140 completing baseline and 6-month assessments, and 136 providing biomedical data 12-months post-randomisation (see Figure 1 and further details published elsewhere [8]).

Immediately following the end of the DAFNE trial, participants returned to routine care at each of the three centres. In one of the centres (Sheffield), annual attendance in groups has been offered to DAFNE graduates since 2003 to enable them to revise their DAFNE skills. In the other two centres, reinforcement in self-management skills has been less formal and has usually been provided individually upon request. Subsequently, and after gaining approval from relevant ethics committees, each of the DAFNE graduates was approached by letter to give written informed consent to be included in a follow-up study.

Primary endpoints

For the long-term follow-up, glycated haemoglobin (HbA_{1c}) measurements were performed centrally using a high performance liquid chromatography, diabetes control and complications trial (DCCT) aligned method (Eurogenic Tosh G7). The top of the reference range for people without diabetes was 6.1%. The Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaire [12,13] was used to assess the impact of diabetes on quality of life. The ADDQoL provides a rating of the impact of diabetes (weighted by importance) for 18 potentially applicable domains of life, including dietary freedom (item 16). The “average weighted impact” is a composite score of all applicable weighted domains, indicating the individualised impact of diabetes on quality of life. Scores for single domains and the “average weighted impact” range from -9 (maximum negative impact of diabetes) to +9 (maximum positive impact of diabetes). The questionnaire also includes a single item measuring “present quality of life”, with scores ranging from -3 (extremely bad) to +3 (excellent).

Secondary endpoints

Satisfaction with treatment was measured using a short-form of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [14], which includes 3 individual items measuring “satisfaction to continue” with present form of treatment, “perceived frequency of hyperglycaemia”, and “perceived frequency of hypoglycaemia”. Each item is scored 0-6,

with higher scores indicating greater satisfaction or greater perceived frequency of hyper/hypoglycaemia. Weight was measured using electronic scales. Blood pressure was measured by using a standard mercury sphygmomanometer, with phase 5 denoting diastolic pressure. Each of the three local laboratories used standard methods to measure serum cholesterol, triglycerides, and high density lipoprotein (HDL) cholesterol.

Statistical analyses

Prior to the statistical analyses conducted to evaluate outcomes at long-term follow-up, the following exploratory analyses were conducted using demographic, biomedical and psychosocial outcomes (at baseline and at 6 and 12months post-randomisation):

- differences between DAFNE centres at 44-months were explored using Kruskal-Wallis statistics for continuous data and χ^2 for categorical data
- differences between follow-up participants and non-participants (for baseline data and 12 month data) were explored using Mann-Whitney U statistics for continuous data and χ^2 statistics for categorical data.

Data were checked for normality (using standardised Z(skew) values) and skewed variables were transformed (using square root, log and inverse transformations) where appropriate. At each timepoint, continuous data are expressed as mean (standard deviation), while categorical data are presented as N(%).

For the primary outcomes (i.e. HbA_{1c} and ADDQoL variables), differences were analysed using mixed model (4x2 design) ANOVA, performed with time (0, 6, 12 and 44 months) as the within-subjects variable and treatment group (Immediate or Delayed) as the between-subjects independent variable. For each analysis, missing data were excluded case-wise. These analyses were supported by post-hoc:

- paired t-tests (baseline versus 44 months, 12 versus 44 months) for the full cohort
- unpaired t-tests for differences between “immediate DAFNE” and “delayed DAFNE” at 44 months.

Secondary outcomes (i.e. 3-item DTSQ, weight (kg), BMI, total cholesterol, HDL cholesterol and triglycerides) were analysed using paired t-tests (baseline versus 44 months, 12 versus 44 months) and unpaired t-tests at 44 months.

To investigate the generalisability of the findings (i.e. to determine whether those who returned long-term data had more positive outcomes than those who did not), data were also analysed using last observation carried forward (LOCF).

Results

Participant flow and follow-up

One of the original 140 trial participants who did not provide written consent and one who had switched to using an insulin pump were excluded from this analysis, leaving 138 patients for inclusion. Of these, 104 (74.3%) provided both written consent and follow-up biomedical data between 37 and 51 months (mean follow-up 44 months). Long-term psychological data were provided by 88 participants (62.9% of those whose data were analysed during the DAFNE trial, 84.6% of those providing follow-up biomedical data) (see Figure 1).

Participants' mean age was 44±9 years (range = 26-65 years), and the mean duration of diabetes was 20±10 years (range= 5-47 years). Of the 104 participants, 52 (50%) were women and 51 (49%) had originally attended "immediate DAFNE training".

Exploratory analyses

At 44 months, there were only two differences noted between centres: HbA_{1c} and weight (see Table 1a). Similarly, there were few differences (in terms of baseline characteristics or 12 month outcomes) between those who had provided follow-up biomedical and psychological data and those who did not (Table 1b). Tables 1a and 1b show only the variables for which there were statistically significant differences between groups.

Primary and secondary endpoints

Table 2 shows the data for primary and secondary outcomes. Unless stated otherwise in the text below, there were no significant differences between "immediate" and "delayed" DAFNE treatment groups at 44 months. Analyses using LOCF data (not shown) did not differ significantly from those presented here.

HbA_{1c} remained significantly improved from prior to the trial (9.32±1.1 to 8.96±1.2, t=-2.92, $p<0.01$), an overall improvement from baseline of 0.36% (95% CI = 0.07 to 0.58). However, there had been deterioration between HbA_{1c} soon after DAFNE training (6 and 12 months later) and 44 months (from 8.75±1.2 to 8.96±1.2, t=2.14, $p<0.05$). There were no significant differences between "immediate" and "delayed" DAFNE treatment groups at 44 months (see Figure 2).

For each of the QoL outcomes, the significant improvements observed following DAFNE training (i.e. at 12 months) were maintained at 44-month follow-up. There was no significant

deterioration between 12-month and 44-month follow-up, nor were there any between group differences at 44 months. Figure 3 shows the impact of diabetes on each of the 18 domains of life of the ADDQoL as well as the "average weighted impact" of diabetes on QoL. Significant improvements were observed in 10 of the 18 domains as well as in the overall average weighted impact score. The improvements were maintained between baseline and 44 months for eight of those 10 domains; initial improvements were not maintained at 44-month follow-up in only two of the 10 domains: "worries about the future" and "finances". Figure 4 shows that a more general improvement in "present QoL" during the DAFNE trial (baseline to 12 months) was maintained at four years.

Despite a statistically significant decrease in "satisfaction to continue with present treatment" from 12 to 44 months, the long-term mean of 5.49±0.73 represented a highly significant improvement in satisfaction from baseline (3.65±1.24). There was a significant decrease in "perceived frequency of hyperglycaemia" (from baseline to 44 months) with no difference between 12 and 44 months. There was no significant difference in "perceived frequency of hypoglycaemia" from baseline to 44 months or from 12 to 44 months. However, it was observed that this was the only outcome to show a difference between the "immediate" and "delayed" DAFNE groups at 44 months, with "delayed DAFNE" reporting greater frequency of hypoglycaemia (2.31±1.41) than "immediate DAFNE" (1.64±1.15) ($t=-2.42$, $p<0.05$)). We found a significant mean increase in weight (1.5kg) between baseline and 44 months ($t=-2.86$, $p<0.01$), most of which (1.15kg) was incurred between 12 and 44 months ($t=-2.58$, $p<0.05$). There was a significant improvement in HDL cholesterol from baseline (1.55±0.46) to 44 months (1.67±0.53). There were no significant differences in other cardiovascular risk factors (i.e. total cholesterol, triglycerides).

Discussion

Our data show that the impact of a single DAFNE course on glycaemic control is still apparent in the long term. Improvements in QoL and other patient reported outcomes are well maintained over approximately 4 years in the 62% of patients who completed questionnaires at long-term follow up. As with any complex intervention, it is difficult to know which aspects have contributed to its effects. Critics of the DAFNE trial suggested that a waiting-list-control was insufficient to demonstrate that the effects were due to the DAFNE curriculum and not to some more general factor (e.g. increased clinician contact) [15]. In a long-duration cohort study, it would be reasonable to consider that outcomes might be influenced by factors other than the prolonged effect of a single 5-day training course almost four years earlier. However, a feature of the original DAFNE trial was lack of provision of DAFNE-specific follow up, with all patients returning to routine clinical services. We suggest that the specific combination of improvements in both biomedical and patient reported outcomes was unlikely to be achieved by intensive support or empowerment alone [8]. The treatment satisfaction scores (lower at 44 months than it had been at 12 months albeit remaining significantly higher than at baseline) suggested that the DAFNE graduates were disappointed by the reduction of biomedical benefits. QoL benefits on the other hand (including but not limited to dietary freedom) were well maintained, indicating that DAFNE graduates continued to reap other benefits from the education programme.

This study is limited by the fact that we were unable to obtain follow-up data at 44 months for the whole cohort. Exploratory analyses suggest that those who participated in the long-term follow-up were more ‘satisfied to continue’ with their treatment at 12 months and had better glycaemic control at baseline. Nevertheless, satisfaction to continue treatment was still high in those who did not provide data at long-term follow-up and inclusion of their data at 12 months did not prevent the improvement in satisfaction from baseline to 12 months reaching significance. ADDQoL scores showed no difference at baseline or 12 months between those who provided follow-up data at 44 months and those who did not and we can feel confident that QoL benefits were not determining willingness to provide data at long-term follow up. Care is needed, however, in generalising from these findings. It is possible that the patient-reported outcomes obtained in those 62% who provided data at long-term follow-up would have been less positive in those who did not provide long-term data.

Notwithstanding, our data indicate that a single structured 5-day training course (designed to maintain glucose control while enabling dietary freedom) teaching self-management skills to

people with established Type 1 diabetes has benefits for both glycaemia and QoL in the long term. During the DAFNE trial, improvements in HbA_{1c} detected at 6 months (in "immediate DAFNE") had drifted slightly at 12-month follow-up. This pattern continued for the whole cohort at 44-month follow-up, albeit that, between baseline and 44-month follow-up, the mean improvement in glycaemic control (Δ=0.36%) remained significant. The achieved mean HbA_{1c} at 44 months, though significantly improved from baseline, is considerably higher than required by current targets [16,17]. We note also that the long-term HbA_{1c} results of the STTP on which DAFNE is based are somewhat more encouraging than the UK HbA_{1c} data presented here. Bott and colleagues demonstrated that improvements in glycaemic control were sustained for up to 3 years (reduced from 8.3% at baseline to 7.5% (1 year), 7.5% (2 years), and 7.6% (3 years) and partially sustained (7.9%) for up to 6 years [5]. Our long-term results show a decrease in HbA_{1c} of 0.36% over an average of 44 months, which is comparable to the 6 year outcomes described by Bott et al, though it is unclear whether the German participants experienced a gradual decline from 3-6 years or a sharp fall after 3 years. We have no clear explanation for this difference but would note that the UK patients had higher baseline HbA_{1c} and included people of very long diabetes duration. In addition, in the UK, there was no formal reinforcement of DAFNE principles and this may have contributed to the upward drift in HbA_{1c}.

It is our hypothesis (from combined current experience of over 10,000 DAFNE graduates in the UK) that those who are able to maintain improved HbA_{1c} levels in the longer term are those who not only adhere strictly to the principles of carbohydrate (CHO) counting but also monitor and reflect on the effects of CHO, insulin and blood glucose levels – either of which may be influential in their own right or be a function of motivation and other psychosocial processes. Behaviour change (and its maintenance) is a complex issue [18]. While we believe that the positive impact on treatment satisfaction of some treatment regimens may well be an issue affecting people's willingness and ability to achieve optimal self-management in the short-term [13], maintenance of that change in the long term appears to involve other factors that require further exploration. The partially maintained improvement in HbA_{1c} (Δ=0.36%) and treatment satisfaction suggests a need for further intervention (e.g. refresher courses to boost skills maintenance, or goal setting to focus participants' newly acquired skills on improving certain aspects of their diabetes management). Such psychosocial methods have been used previously to enhance outcomes for certain patient groups in the German programme [19], but are only now being explored in routine and research DAFNE settings. Furthermore, exploration and recording of participant's personal goals and motivations may be helpful in understanding why some individuals have better outcomes than others [20]. DAFNE may have placed more emphasis upon the opportunity

for greater dietary freedom than the early German programmes, whose authors gave only brief acknowledgement of possible lifestyle benefits in the small print of the methods section of their published paper: *"they should gain a certain 'liberalisation' of lifestyle with respect to exercise and eating schedules"* [1, p471]. The more limited glycaemic improvements in the UK may be the result of individuals focusing more on the lifestyle benefits without equal attention to the processes (such as CHO counting, monitoring, recording and reflection) that are likely to be important in ensuring the glycaemic benefits. Despite DAFNE's emphasis on flexibility of lifestyle and dietary freedom, it is noteworthy that biochemical CVD risk factors did not deteriorate after participation in the course. There was a small increase in the average weight of the DAFNE graduates, but this may be no more than the expected age-related gain [21].

For each of the primary psychological outcomes (i.e. the impact of diabetes on "dietary freedom", the "average weighted impact" of diabetes on quality of life and "present quality of life"), the significant improvements observed following DAFNE training were maintained fully between 12-month and 44-month follow-up. This suggests that participants still appreciate DAFNE's wide-ranging QoL benefits even if clinically significant glycaemic benefits are not fully maintained. There was some deterioration in "satisfaction to continue", although the mean score (5.49) at 44-month follow-up was extremely high and remained significantly higher than baseline levels (3.65). It is well-documented that subsequent administration of the DTSQ is prone to ceiling effects when participants have previously been highly satisfied with treatment [22]. Although participants were not highly satisfied at baseline, they were at 12 months with ceiling effects potentially limiting the opportunity to report further improvement at long-term follow-up. The deterioration in satisfaction at 44-month follow-up should be considered in this context and also in view of the fact that this is a single-item measure of treatment satisfaction, which is unlikely to be as reliable as the full six-item treatment satisfaction scale. The single-item was used in the DAFNE rollout in the interests of reducing the questionnaire burden on participants. A change version of the DTSQ (DTSQc) has been developed which overcomes the ceiling effects that can affect scores on the original status version of the DTSQ (DTSQs) [23].

In contrast to other trials of intensification of insulin therapy [24], the proportion of participants who experienced at least one episode of severe hypoglycaemia in the preceding six months did not increase during the DAFNE trial, despite the reduction in $HbA_{1c.}$ Following the DAFNE trial, the wording of the clinician-completed case report form was changed (from "number of episodes in the past 6 months" to "number of episodes since last DAFNE review") and direct comparisons were no longer possible. However, it is likely,

particularly given the only partially maintained improvements in glycaemic control, that there was no significant change in rates of severe hypoglycaemia during these four years in this relatively small group of patients. This is supported by lack of change in responses to the DTSQ item 'perceived frequency of hypoglycaemia' (see Table 3) during and following the trial. The parent course (STTP) on which DAFNE is based was unique (at the time) in demonstrating a fall in rates of severe hypoglycaemia alongside falling HbA_{1c}. Preliminary reports of audit data of the clinical programme of DAFNE in the UK following the trial suggest that, in a larger sample (n>450), the UK DAFNE programme reproduces this [25]. Exclusion of patients with complete hypoglycaemia unawareness from the original DAFNE trial may have reduced its ability to detect a fall in severe hypoglycaemia rates by excluding the patients at highest risk.

Conclusion

We have shown, in a cohort of adults with established Type 1 diabetes and sub-optimal glycaemic control, that a single 5-day course in flexible, intensive insulin therapy offers major long-term benefits for QoL outcomes and treatment-satisfaction and more modest long-term benefits for glycaemic control. To maximise both the short- and long-term benefits for glycaemic control, there is a need to modify the DAFNE programme, which might include additional input (e.g. structured follow-up as well as attention to factors likely to contribute to successful behaviour change and maintenance).

Following publication of the original DAFNE trial results, Howard Wolpert and Barbara Anderson commented, "these findings should prompt some rethinking about how health providers frame the benefits of multiple daily injections and insulin pumps. Focusing on the immediate lifestyle benefits can be critical to overcoming patients' ambivalence about change and promoting engagement in self-care" [26]. Our most recent findings indicate that patients do, indeed, value the QoL benefits that DAFNE offers but also that further efforts are needed to ensure that improvements in glycaemic control are not only maximised in the short term but maintained in the long term.

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Contributorship

The following were members of the DAFNE Study Group: Stephanie Amiel, Clare Bradley, Simon Heller, Peter James, Lindsay Oliver, Helen Rogers, Sue Roberts, Jane Speight, Carolin Taylor, Gillian Thompson. The following were members of the writing committee: Stephanie Amiel, Clare Bradley, Simon Heller and Jane Speight. All contributors have reviewed the final manuscript and confirm its content.
Guarantor: Jane Speight.

Declaration of competing interests

Clare Bradley is copyright owner of the ADDQoL and DTSQ (used in DAFNE) and is a director and majority shareholder of Health Psychology Research Ltd, which licenses these questionnaires.

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Table 1a Differences between centres at 44 months. Values are mean (SD) unless stated otherwise

	London (n=35)	Northumbria (n=40)	Sheffield (n=29)	Statistical values
HbA_{1c}	8.4 (0.9)	9.3 (1.1)	9.3 (1.5)	H(2)=13.4, p<0.05
Weight (kg)	73.4 (13.2)	85.2 (16.3)	80.1 (19.6)	H(2)=9.8, p<0.05

H(2)=Kruskal-Wallis

Table 1b Differences between those providing long-term follow-up data (biomedical and psychological) and those who did not. Values are mean (SD) unless stated otherwise

Follow-up biomedical data	No follow-up (n=33)	Follow-up (n=104)	Statistical values
Centre (n) - London - Northumbria - Sheffield	 9 6 18	 35 40 29	χ^2=35.5, p<0.0001
Sex (n) - Men - Women	 10 23	 52 52	χ^2=35.5, p<0.0001
Satisfaction at 12 months[1]	5.3 (1.3)	5.8 (0.5)	t=2.8, p<0.01
Total cholesterol at 12 months	4.5 (1.2)	5.0 (0.8)	t=-3.0, p<0.01
Follow-up psychological data	No follow-up (n=47)	Follow-up (n=88)	Statistical values
HbA_{1c} at baseline	9.7 (1.2)	9.2 (1.1)	t=-2.4, p<0.05
Satisfaction at 12 months[1]	5.5 (1.1)	5.8 (1.4)	t=2.1, p<0.05

Note: those who provided no biomedical data at follow-up also provided no psychological data

[1] Single DTSQ item "Satisfaction to continue" scored from 0 to 6; a higher score indicates greater satisfaction.

Table 2 Primary and secondary outcomes in original DAFNE trial cohort at baseline, 12 and 44 months post-DAFNE

Primary outcomes	Cohort at Baseline Mean (SD)	Cohort at 12 months Mean (SD)	Cohort at 44 months Mean (SD)	Statistical values (t)	
				Baseline to 44mths	12mths to 44mths
HbA_{1c}	9.32 (1.15)	8.75 (1.23)	8.96 (1.22)	-2.92**	2.14*
ADDQoL: Weighted impact of diabetes on dietary freedom (item 16)[1]	-4.27 (2.94)	-1.80 (2.32)	-1.78 (2.33)	7.33***	-0.10
ADDQoL: Average weighted impact of diabetes on quality of life[1]	-1.89 (1.44)	-1.22 (1.08)	-1.26 (1.28)	5.31***	0.99
ADDQoL: Present quality of life[2]	1.04 (0.89)	1.41 (0.98)	1.40 (0.88)	-2.54*	0.88
Secondary outcomes					
DTSQ: Satisfaction to continue[3]	3.65 (1.24)	5.80 (0.45)	5.49 (0.73)	13.68***	-4.04***
DTSQ: Perceived frequency of hyperglycaemia[4]	3.45 (1.49)	2.69 (1.39)	2.86 (1.43)	2.91**	-0.32
DTSQ: Perceived frequency of hypoglycaemia[4]	2.20 (1.30)	2.14 (1.14)	1.97 (1.32)	1.27	1.34
Weight (kg)	78.30 (15.20)	78.65 (15.74)	79.80 (16.98)	-2.86**	-2.58*
Total cholesterol (mmol/l)	5.05 (0.85)	5.03 (0.78)	5.15 (0.93)	-1.05	-1.30
HDL cholesterol (mmol/l)	1.55 (0.46)	1.53 (0.38)	1.67 (0.53)	-2.49*	-2.11*
Triglycerides (mmol/l)	1.47 (0.91)	1.40 (0.78)	1.36 (0.72)	0.85	-0.04

* p<0.05, ** p<0.01, *** p<0.001
[1] Scored from -9 (maximum negative impact) to +9 (maximum positive impact).
[2] Scored from -3 (extremely bad) to +3 (excellent); 0=neither good nor bad, 1=good, 2=very good.
[3] Scored from 0 to 6; a higher score indicates greater satisfaction.
[4] Scored from 0 to 6; a higher score indicates greater perceived frequency of hyperglycaemia or hypoglycaemia.
HDL = high density lipoprotein
Natural data are reported but some variables were transformed before parametric analysis was performed.

Figure 1 **Flow of participants through original DAFNE trial (baseline, 6 and 12 months) to long-term follow-up (44 months)**

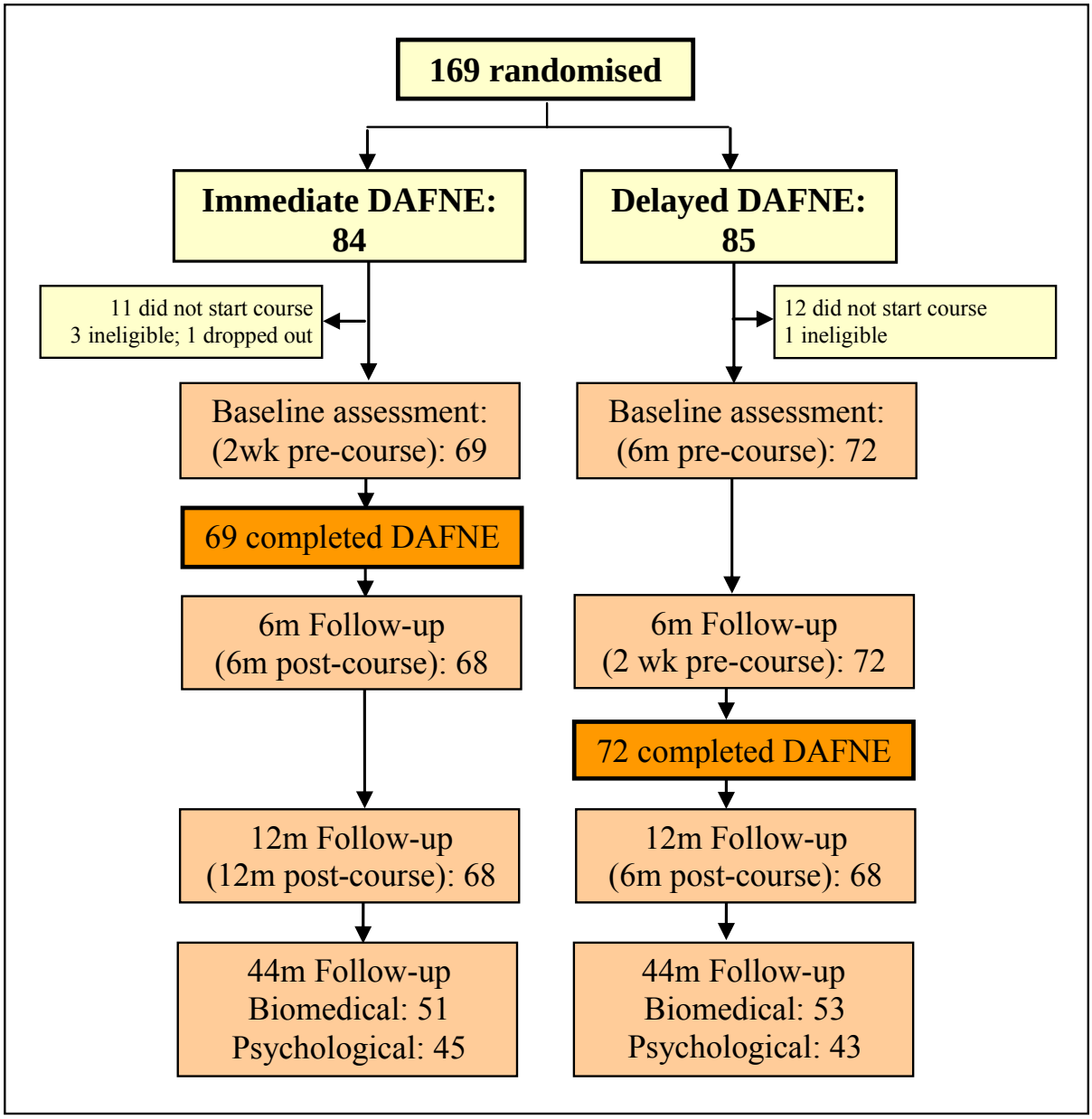
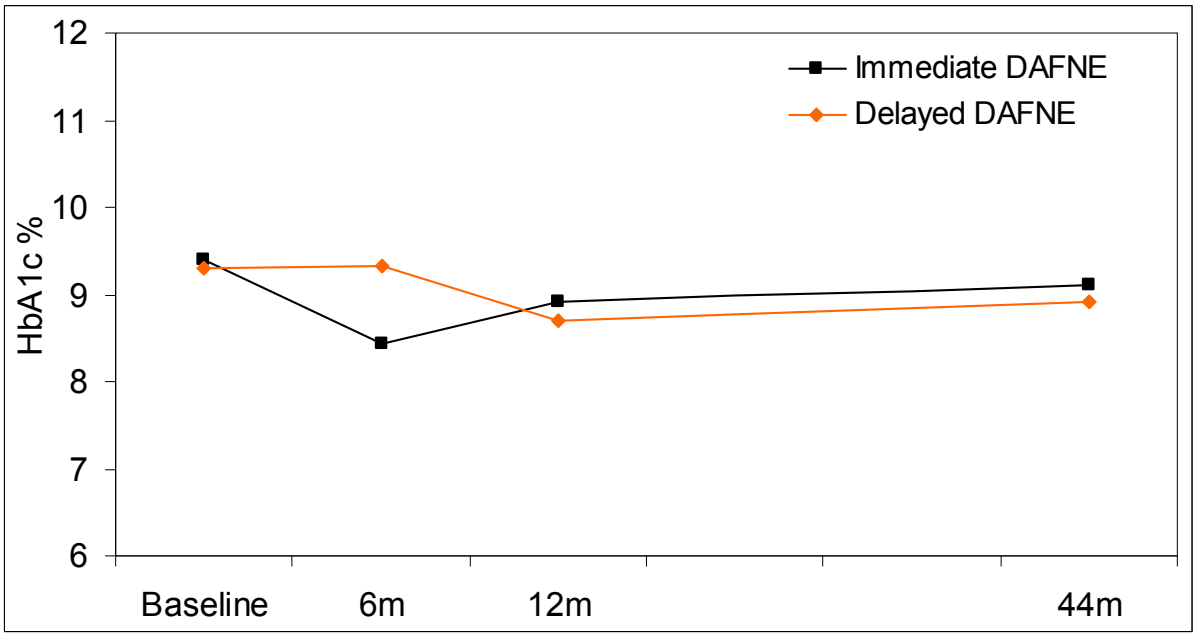
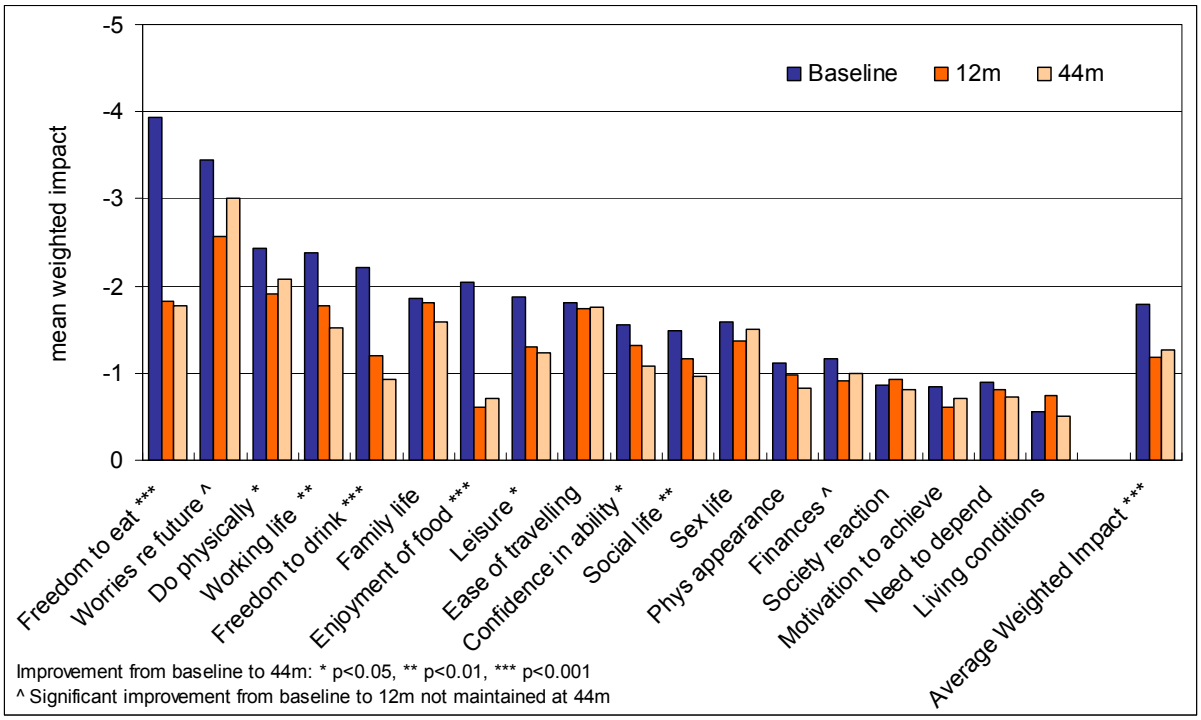


Figure 2 Glycaemic control as measured by glycated haemoglobin (HbA_{1c})



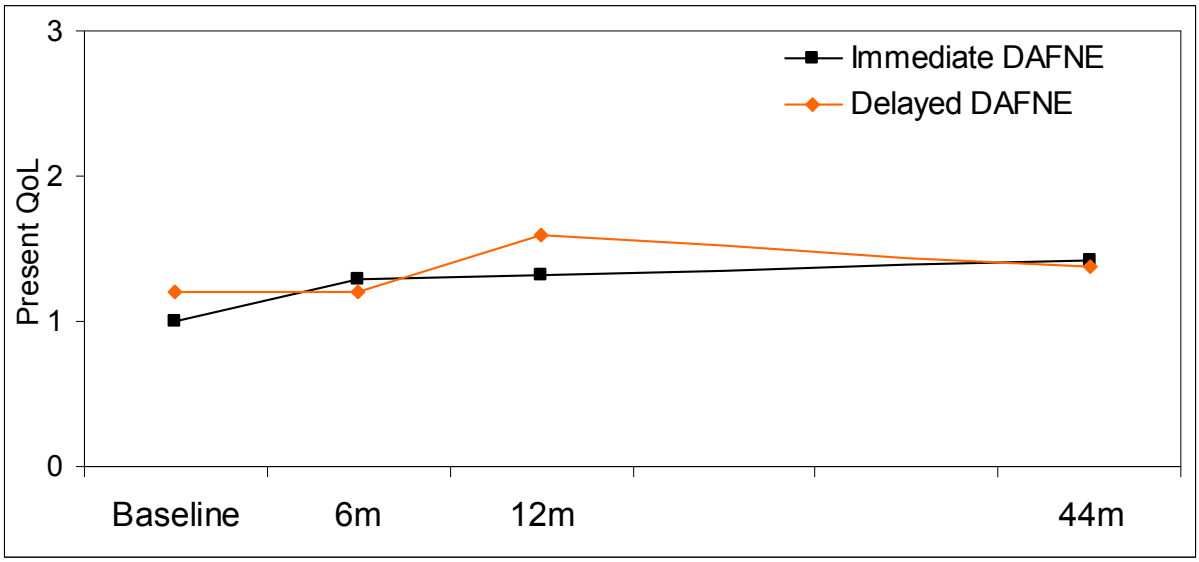
Timeline represents months post-randomisation

Figure 3 **Mean reported impact of diabetes on domains of life at baseline, 12 and 44 months**



Mean weighted impact: scores can range from -9 (maximum negative impact of diabetes) to +9 (maximum positive impact of diabetes)
Timeline represents months post-randomisation

Figure 4 Mean reported impact of diabetes on 'present quality of life'



Present QoL: scores can range from -3 (extremely bad) to +3 (excellent)

Timeline represents months post-randomisation