Supplementary material 3 – Protocol for DAFNE*plus* Economic Evaluation

Aims and perspective

We will complete an economic evaluation as part of the study so that we are able to understand the cost-effectiveness of DAFNE*plus* compared to the standard DAFNE programme. The economic evaluation will follow guidance set by the National Institute for Health and Clinical Excellence for its Technology Appraisal process [1]. The analysis will take an NHS and personal social services perspective, measure health effects in quality adjusted life years (QALYs), discount future outcomes at 3.5% per annum and consider effects and costs over a lifetime time horizon. The primary analysis will be use long-term cost-effectiveness modelling, a secondary analysis will be an economic evaluation alongside the clinical trial (EEACT). The analysis population for all health economic analyses will consist of all participants in the DAFNEplus trial. A full Health Economic and Decision Modelling Analysis Plan (HEDMAP) will be written and circulated to the Trial Management Group and Programme Steering Committee before being signed-off.

Long-term cost-effectiveness modelling

In the long-term modelling exercise, the resulting evidence base will be incorporated into an updated Sheffield T1D Diabetes Policy Model [2]. This model has been used extensively in the evaluation of education and psychological interventions for people with T1D[3–6]. The time horizon of this analysis will be over each simulated individual's lifetime. As such, the long-term modelling will be considered as the primary health economic analysis. Demographic variables and some key resource use data (e.g. insulin use, contacts with NHS professionals) will be obtained from the trial data. The Sheffield T1D Diabetes Policy Model will be updated to use statistical models that estimate the clinical effects of DAFNE*plus* compared to DAFNE on HbA1c, the incidence of severe hypoglycaemia and the incidence of DKA. Two long-term modelling analyses will be conducted, the first will use the data collected by the one-year time point and will be submitted as part of the report to the NIHR on the DAFNE*plus* programme grant. This analysis will be updated after the two-year data collection is complete to incorporate the statistical analysis of the two-year follow up data. These statistical analyses of the clinical effects of DAFNE*plus* compared to DAFNE will be pre-specified in either the statistical analysis plan or the HEDMAP. The reporting of this evaluation will follow the Palmer *et al*[7] checklist for the reporting of model inputs to diabetes health economic studies.

Economic evaluation alongside the clinical trial

For the EEACT, we conduct the analysis in line with Ramsey *et al's* [8] recommendations for cost-effectiveness analysis alongside clinical trials. Specifically, we will collect data alongside the trial on intervention costs, associated healthcare resource use and a preference based utility measure: the EQ-5D-5L measure [9]. The intervention costing process will include training of educators, resource use, and adherence to structured follow up appointments, professional staff time and the technology component. A standard self-reported resource use questionnaire, used

previously in the DAFNE*plus* pilot (as well as the 5x1 DAFNE [10] and the REPOSE trials [11]), will ascertain NHS usage in terms of GP, community, outpatient, A&E and inpatients, as well as occurrence of DKA and hypoglycaemic events by level of severity. Unit costs will be taken from standard sources (NHS Reference Costs, British National Formulary, PSSRU). The standard self-reported resource use questionnaire and the EQ-5D-5L will be collected at baseline, 6 months and 12 months. Course costs (administrative and clinical) will be estimated using a bespoke questionnaire for completion by site staff. Our primary analysis will use the EQ-5D-5L valuation study to generate utility scores at baseline, course completion, 6 months and 12 months for each study participant [12]. There are on-going discussions about the valuation of the EQ-5D-5L, and NICE recently produced a position statement recommending that EQ-5D-5L data should be valued using mapping to the EQ-5D-3L and not the bespoke EQ-5D-5L value set [13,14]. Therefore our primary analysis will follow the most recent NICE guidance at the time of analysis, with the other valuation method been used in a sensitivity analysis. QALYs for each participant will be estimated by calculating the area under the curve defined by EQ-5D utility score, mortality and length of follow-up. The base case analysis will use the complete case data. In a scenario analysis, the missing data will be imputed. The time horizon of this analysis will be limited to the one-year time horizon of the trial. This evaluation will be considered as the secondary health economic analysis for two reasons: 1) The effects and costs of DAFNE*plus* may be incurred beyond the one-year trial time horizon (due to expected differences in the time to onset of diabetes related complications and potential maintenance of treatment effects beyond the trial period); and, 2) the DAFNEplus trial is not powered to detect differences in the incidence of long-term diabetes complications, as such the estimates of differences in the cost and QALYs between the two trial arms may be misleading.

Outcome measures and uncertainty analyses

In both the EEACT and the long term modelling the main outcome of interest will be the comparison of the incremental cost-effectiveness ratio (ICER) of DAFNE*plus* compared to DAFNE. The ICER will be compared to a maximum acceptable ICER of £20,000 per QALY gained, as this is the lower limit of the ICER range used by NICE to determine if an intervention is cost-effective [1]. Uncertainty in the ICER will be determined using: scenario analyses, subgroup analyses (pre-specified with the wider DAFNE*plus* team), probabilistic sensitivity analysis and expected value of information calculations. In particular, uncertainty in the cost-effectiveness of DAFNE*plus* as used in a wider rollout (compared to as utilised in the trial) and in subgroups of participants with a HbA1c less than 7.5% and greater than or equal to 7.5% will be explored in our scenario analyses.

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