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Cost-effectiveness of multicomponent interventions in type 2 diabetes mellitus in a cluster randomised controlled trial: the INDICA study

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ABSTRACT

Objective To analyse the cost-effectiveness of multicomponent interventions designed to improve outcomes in type 2 diabetes mellitus (T2DM) in primary care in the Canary Islands, Spain, within the INDICA randomised clinical trial, from the public health system perspective.

Design An economic evaluation was conducted for the within-trial period (2 years) comparing the four arms of the INDICA study.

Setting Primary care in the Canary Islands, Spain.

Participants 2334 patients with T2DM without complications were included.

Interventions Interventions for patients (PTI), for primary care professionals (PFI), for both (combined intervention arm for patients and professionals, CBI) and usual care (UC) as a control group.

Outcomes The main outcome was the incremental cost per quality-adjusted life-years (QALY). Only the intervention and the healthcare costs were included.

Analysis Multilevel models were used to estimate results, and to measure the size and significance of incremental changes. Missed values were treated by means of multiple imputations procedure.

Results There were no differences between arms in terms of costs (p=0.093), while some differences were observed in terms of QALYs after 2 years of follow-up (p=0.028). PFI and CBI arms were dominated by the other two arms, PTI and UC. The differences between the PTI and the UC arms were very small in terms of QALYs, but significant in terms of healthcare costs (p=0.045). The total cost of the PTI arm (€2571, 95% CI €2317 to €2826) was lower than the cost in the UC arm (€2750, 95% CI €2506 to €2995), but this difference did not reach statistical significance. Base case estimates of the incremental cost per QALY indicate that the PTI strategy was the cost-effective option.

Conclusions The INDICA intervention designed for patients with T2DM and families is likely to be cost-effective from the public healthcare perspective. A cost-effectiveness model should explore this in the long term.

Trial registration number NCT01657227.

Strengths and limitations of this study

- This paper presents an individual-based cost-effectiveness analysis of the INDICA study, a large randomised clinical trial.
- This paper analyses the cost-effectiveness of knowledge transfer and behaviour modification interventions from the public healthcare perspective in the Canary Islands, Spain.
- The outcome was quality-adjusted life-years, estimated using the EQ-5D-5L, and the costs were obtained from the local healthcare providers.
- We present the results of the whole sample, 2334 individuals, and the results of the subgroup of patients with glycated haemoglobin >7%.
- From the point of view of the economic evaluation, the main limitation is the relatively short duration of the trial, 2 years.

INTRODUCTION

Diabetes is a prevalent chronic disease with a major global impact. A worldwide prevalence of 8.5% in adults, 7.3% in Europe,[1] and a direct annual cost to the world higher than US$825 billion[2 3] has been estimated. The prevalence of type 2 diabetes mellitus (T2DM) in the population aged 15 and over in the Canary Islands is 7.74%,[4] which is slightly higher than the Spanish average (6.99%).[5] Moreover, the Canary Islands show a higher mortality and a higher incidence of complications than the rest of Spain.[6 7] This situation has prompted the implementation of secondary prevention strategies that, nevertheless, should be evaluated before and after their implementation.[8]

Given these circumstances, the INDICA study was designed with the aim of evaluating evidence-based interventions. Several reviews

were undertaken and various relevant systematic reviews and guidelines were identified.[9–11] Some trials, such those conducted by Trento *et al*[12] were inspirational. Despite the increasing healthcare expenditure[13] and availability of services[14] and guidelines,[15] the adherence to recommended actions of T2DM self-management and lifestyle changes is limited.[16] Furthermore, healthcare professionals and family members play an important role in supporting patients with T2DM. There is also evidence on the effectiveness of the information and communication technologies (ICT) to transfer the knowledge of diseases and support patients and professionals in their decisions.[10 17–20] Based on all this evidence, the INDICA interventions were designed, implemented and evaluated. As both effectiveness and cost-effectiveness are criteria for health technologies reimbursement in Spain,[21] and bearing in mind that the efficiency of complex interventions is not easily transferable,[22] an economic evaluation was conducted alongside a clinical trial.

The INDICA study is a randomised controlled trial (RCT) that evaluates the effectiveness and cost-effectiveness of three different ICT-based multicomponent interventions to support decision making in patients with T2DM and primary healthcare professionals in the Canary Islands.[23 24] Results on the effectiveness of the interventions are reported elsewhere.[25 26] In this paper, we present the cost-effectiveness analyses.

METHODS

Trial design

The INDICA study is an open, community-based, multicentre, controlled clinical trial with random cluster allocation to one of four arms, one of them a control group. We estimated the cost-effectiveness for the 'within-trial' period (2 years) where incremental cost per quality-adjusted life-year (QALY) was the main outcome.[23 24]

Ethical approval and consent to participate

All participants provided written informed consent. The study fulfilled the regulatory requirements, Good Clinical Practice standards, Declaration of Helsinki, and received the approval of the Scientific and Ethics Committees of two hospitals (University Hospital of Canarias (ID: 2012_44) and University Hospital Nuestra SEñora de la Candelaria (ID: EPA-07/10)). General guidelines for economic evaluation and clinical trials were followed.[27–29] The methods were reported in the published protocol.[23]

Interventions

The intervention for patients and family members (PTI) included a diabetes-coaching programme using a combination of educational workshops with automated and personalised phone messages and a web-based platform. The intervention for primary care healthcare professionals (physicians and nurses) (PFI) included workshops to update clinical management, a decision support tool nested into the electronic clinical record system; and periodic feedback reports on patient outcomes. In the combined intervention arm for patients and professionals (CBI), both received the reported interventions. The control group received usual care (UC), that is, neither patients nor professionals received any educational intervention or supporting activities beyond the usual healthcare provided by Servicio Canario de la Salud (SCS), an organisation that is part of the National Health System and provides public healthcare in the Canary Islands (Spain).

Subjects

Patient inclusion criteria were T2DM diagnosed at least 1 year prior to study enrolment, 18–65 years of age, formal consent to participate in the study, and regular use of a mobile phone. Patients with serious comorbidities, insufficient (Spanish) language skills, physical disability limiting participation in group education activities or concurrent participation in another clinical study were excluded.

Setting, recruitment and randomisation

The study was conducted in the primary care setting in the Canary Islands, Spain. In the more populated islands (Tenerife and Gran Canaria) three different strata were created according to the geographic areas. In the less populated islands (La Palma and Lanzarote) each island was divided into four zones. Randomisation was applied at different levels: Primary Care Health Practices (PHCP), Family Care Units (FCU) and patients. First, in each strata of Tenerife and Gran Canaria, four PHCP (clusters) were randomly recruited, providing 12 PHCP in total. The two other islands, La Palma and Lanzarote, provided four PHCP each (one in each area). Block permutation was used to assign PHCPs to study arms, with PHCP as the sampling unit. In every island and each strata, all arms were equally distributed. Second, six FCU, composed of a family physician and a nurse, were randomly selected from all those consenting to participate in each PHCP. And thirdly, the electronic clinical records (ECR) of patients at each participating FCU were screened and 15 patients were randomly selected from all patients fulfilling the inclusion criteria and consenting to participate. Cluster allocation avoids contamination bias among participants, also facilitating logistics in group interventions. PHCP (in Tenerife and Gran Canaria), FCU and patient randomisation were performed by simple generation from a list of random numbers. FCUs were blinded to the intervention assignment until the last patient was recruited.

Patient and public involvement

Patients were actively involved in design of the trial. Two associations of patients with T2DM in the Canary Islands were included from the beginning of the study as part of the research team, with an active participation in the design of the interventions and selection of the outcomes measured. In the same way, primary care professionals and clinical management staff participated in preparation

of the protocol. The patients and professionals included in the study could express their satisfaction with the interventions through a questionnaire, as well as through focus groups and in-depth interviews that will be the subject of another study. Finally, we established a commitment with patients and healthcare professionals to share the results with them in an easy-to-understand way.

Healthcare utilisation and costs

Direct costs were evaluated from the public healthcare service perspective (SCS). Hence the following resources and services were included: costs related to the development and implementation of each intervention (including materials and development of ICTs) and the use of healthcare in all arms (including UC arm), which included the costs of contacts with primary care services, hospital admissions, outpatient visits, emergency visits, tests and medications. Those resources not very commonly accessed (visits to neurologists, physiotherapy or Doppler echocardiography, eg) were excluded from the analysis. Resource use was collected from questionnaires completed by patients, ECR and administrative data. Unit costs were obtained from different sources, that is, public sources, administrative accounts and specific suppliers (see online supplemental appendix 1 tables A1 and A2 for further details). The costs of medicines were obtained from the database of dispensed medicines charged to the public healthcare sector and included: antihypertensive drugs (ACE inhibitors, angiotensin receptor antagonists, calcium-channel blockers, diuretics and beta blockers), lipid-lowering agents, antithrombotic drugs, amitriptyline, duloxetine, pregabalin and tramadol. Unit costs were adjusted for inflation when needed. Costs are reported in Euros from 2017.

Quality-adjusted life years

Patients completed at baseline and every 6 months the EQ-5D-5L, a generic health-related quality of life questionnaire[30] that evaluates five domains: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each domain is scored at one of five levels, yielding a descriptive system that can be combined into a five-digit number that reports the patient's state of health. Each EQ-5D-5L health state can be converted to a single summary index by applying a formula that attaches weights to each of the levels in each dimension. A number of formulae, or value sets are available for different countries, based on the valuation of EQ-5D health states from general population samples. In this study, the value set estimated for Spain by Ramos-Goñi *et al* was used.[31] After applying these weights, or utilities, an EQ-5D-5L index score of 1 represents full health, a score of 0 is equivalent to death and negative scores represent health states perceived as worse than death by population. Patient-specific utility profiles over the 2-year follow-up were estimated assuming a straight line relation between each patient score at each follow-up point. The QALYs from baseline to month 24 were calculated as the area under the curve.[28]

Sample size calculation

The sample size calculation was based on the primary endpoint of the effectiveness study, that is, the mean change in glycated haemoglobin (HbA1c) from baseline to month 24. A total of 2330 patients was estimated (482 patients per arm).

Statistical methods

QALYs and costs were estimated using multilevel models.[28] The first level included patients characteristics, and the second level variables correspond to PHCPs. QALYs were adjusted by time elapsed since diagnosis and baseline utility as covariates.[32] Costs were adjusted by age, sex and baseline utility. To estimate use of resources a negative-binomial regression model, adjusted by time since diagnosis and baseline resource use, was used. The final model for each dependent variable included the covariates that modified the treatment effect of the estimates by at least 10%. As suggested in the Consolidated Standards of Reporting Trials statement, decisions about covariates will not be based on the p value.[33 34]

Patient characteristics were compared at baseline with a χ^2 test for the variable sex and using a multilevel model for age, duration of diabetes, HbA1c and EQ-5D-5L Index. Only the arm was included as independent variable.

Intergroup differences were considered statistically significant if $p<0.05$. For multiple comparisons, the p value was adjusted with Bonferroni correction.

Missing values were treated by means of multiple imputation procedures,[35] with results based on 100 imputed datasets. The missing data patterns were published as Multimedia Appendix in Ramallo-Fariña *et al*.[26] The model of imputation used for variables involved in the cost-effectiveness evaluation can be found in online supplemental appendix 2. Analysis was performed on an intention-to-treat basis.

Incremental cost-effectiveness ratio (ICER), that is, the differences between costs divided by the differences in QALYs, was calculated when one alternative was more (less) effective and more (less) costly than another, once the dominated alternatives were excluded. The results were re-estimated using alternative values for some parameters (costs) in a deterministic one-way sensitivity analysis (±20% of unit costs). Finally, a post hoc subgroup analysis was conducted with only subjects with HbA1c above the treatment target, that is, baseline HbA1c >7%. For reference, €25 000 per QALY was considered the cost-effectiveness threshold as this is the latest value estimated following robust methods in Spain.[36] All analyses were conducted using STATA V.15.0 (StataCorp).

RESULTS

Between February 2013 and October 2016, 32 PHCP and 2334 patients (mean age: 55.7±SD: 7.1 years;

Table 1 Baseline characteristics of the participants in the study

	PTI arm (n=537)	PFI arm (n=654)	CBI arm (n=557)	UC arm (n=586)	P value
Age (years) (mean±SD)	55.9±7.0	56.2±7.0	55.5±7.1	55.2±7.3	0.216
Sex: male (%)	52.9*	44.0	47.4	48.8	0.024
Duration of diabetes (years) (mean±SD)	8.4±6.8	8.2±6.1	8.9±6.3	8.6±6.8	0.471
Glycated haemoglobin (%) (mean±SD)	7.3±1.5	7.2±1.4	7.4±1.5	7.3±1.5	0.224
<7%	48.0	53.7	43.3	51.9	
7%–8%	27.2	25.2	29.6	24.1	
8%–9%	12.3	11.5	14.7	11.4	
≥9%	12.5	9.6	12.4	12.6	
EQ-5D-5L Index (mean±SD)	0.86±0.19	0.88±0.16	0.86±0.19	0.85±0.20	0.796

Sex: $\chi 2$ test.
Age, duration of diabetes, glycated haemoglobin and EQ-5D-5L index: multilevel model with arm as independent variables, without adjusting by covariates.
*Statistically significant differences between arms PTI and PFI (p=0.002).
CBI, combined intervention for patients and professionals; PFI, intervention only for healthcare professionals at primary care; PTI, intervention only for patients and family members; UC, usual care (control group).

51.9% women) were recruited and included in the RCT. There were no statistically significant differences among the groups in terms of their baseline characteristics, except for sex between the PTI and PFI arm (p=0.002) (table 1). The flowchart of included patients by arm in each follow-up can be seen in Ramallo-Fariña *et al*.[26]

Quality-adjusted life-years

Statistically significant differences in QALYs were found at month 18 (p=0.030) and 24 (p=0.028). The differences are found between the CBI arm and the UC arm (1.24 vs 1.29 at 18 months; 1.63 vs 1.72 at 24 months), favouring the UC arm; and between the CBI arm and PTI arm (1.24 vs 1.29 at 18 months; 1.63 vs 1.71 at 24 months), with CBI showing the lowest values (table 2). Representations of the profile of utilities for patients in each arm for the 2 year period can be found in online supplemental appendix 1 figure A1.

Use of resources and healthcare costs

Statistically significant differences were found between arms for the following resources: hospital admissions (p=0.025), laboratory procedures (p<0.001), visits to primary care (doctors and nurses) (p<0.001) and non-hospital emergency room visits (p=0.002) (see online supplemental appendix 1 table A3). In regard to healthcare costs, we found differences between arms in hospital admissions (p=0.019), laboratory procedures (p=0.044), and visits to primary care (p=0.002), but no differences were found in the aggregated healthcare cost (excluding INDICA interventions costs). The highest mean healthcare cost was found in the UC arm (€2750, 95% CI €2506 to €2995), followed by the CBI arm (€2698, 95% CI €2449 to €2948), the PFI arm (€2664, 95% CI €2432 to €2896) and, lastly, the PTI arm (€2391, 95% CI €2137 to €2646) (table 2). The only significant difference was found in the healthcare cost between the PTI and the UC arms (p=0.045).

Cost of INDICA interventions and total costs

The costs of INDICA interventions over the 2 years of implementation are reported in online supplemental appendix 1 table A2. The mean intervention costs for patients was higher than the cost for professionals (€180 vs €130). The total cost, that is the result of adding the INDICA intervention costs and the healthcare costs, was found to be highest in the CBI arm (€3025, 95% CI €2776 to €3274), followed by the PFI arm (€2794, 95% CI €2562 to €3026), the UC arm (€2750, 95% CI €2506 to €2995), and, finally, the PTI arm (€2571, 95% CI €2317 to €2826) (table 2). Although no differences in total cost were identified among arms (p=0.093), statistically significant differences were found between two specific arms, the PTI arm and the CBI arm (p=0.013).

Cost-effectiveness analysis: base case

Table 3 shows the incremental cost, the incremental effect and the ICER. The PFI and the CBI arms were dominated by other alternatives, so they cannot be considered cost-effective. Between the other two arms, PTI and UC arms, the difference in effects and costs were found to be small and non-statistically significant (p=0.319). The ICER is estimated at €38 486 per QALY. This ratio should be interpreted with care since the intervention evaluated (PTI arm) is (slightly) less effective but also less expensive than the control (UC arm) and the differences in total costs and QALYs were not found to be statistically significant.

Cost-effectiveness analysis: sensitivity analysis

The results of the sensitivity analysis are very similar to the base case (see online supplemental appendix 1 table A4). The PFI and CBI arms are in all cases dominated by the other two arms, while the PTI arm is less expensive than the UC arm. There are only significant differences in costs between arms when a lower cost of hospital stay

Table 2 Adjusted means (95% CI) of QALYs and healthcare costs per arm (€), multilevel model

QALYs per period					
Period	**PTI arm**	**PFI arm**	**CBI arm**	**UC arm**	**P value**
0–6 months	0.43 (0.42 to 0.44)	0.43 (0.42 to 0.44)	0.42 (0.41 to 0.43)	0.43 (0.42 to 0.44)	0.352
0–12 months	0.86 (0.84 to 0.88)*	0.85 (0.84 to 0.87)	0.83 (0.81 to 0.85)†	0.86 (0.85 to 0.88)	0.087
0–18 months	1.29 (1.26 to 1.32)*	1.27 (1.25 to 1.3)	1.24 (1.21 to 1.27)†	1.29 (1.27 to 1.32)	0.030
0–24 months	1.71 (1.67 to 1.75)*	1.69 (1.65 to 1.73)	1.63 (1.59 to 1.68)†	1.72 (1.68 to 1.76)	0.028
Healthcare costs in 2 years					
Resource	**PTI arm**	**PFI arm**	**CBI arm**	**UC arm**	**P value**
Hospital stays	462.06 (287.6 to 636.52)‡	554.31 (398.15 to 710.47)	400.58 (230.24 to 570.91)†	757.72 (590.70 to 924.74)	0.019
Laboratory tests	46.12 (40.68 to 51.56)*§	56.35 (51.36 to 61.34)	54.15 (48.62 to 59.69)	51.47 (46.33 to 56.61)	0.044
Retinography	117.78 (91.24 to 144.32)	127.57 (101.83 to 153.32)	117.18 (90.44 to 143.91)	115.69 (89.67 to 141.72)	0.920
Primary care visits	293.13 (205.04 to 381.21)*	293.13 (297.35 to 472.18)¶	481.99 (393.78 to 570.21)†	263.11 (175.4 to 350.92)	0.002
Specialist visits	37.49 (26.74 to 48.24)	46.94 (37.22 to 56.66)	43.88 (33.07 to 54.70)	44.38 (34.21 to 54.54)	0.634
Emergency room visits	275.89 (191.09 to 360.69)	264.88 (183.39 to 346.37)	337.16 (251.86 to 422.46)	251.90 (169.24 to 334.56)	0.505
Medication	1156.96 (1016.23 to 1297.7)	1222.31 (1090.12 to 1354.5)	1242.16 (1102.59 to 1381.72)	1269.47 (1132.53 to 1406.42)	0.715
Healthcare cost (without INDICA interventions related costs)	2391.22 (2136.87 to 2645.58)‡	2663.6 (2431.57 to 2895.63)	2698.25 (2448.72 to 2947.78)	2750.44 (2506.19 to 2994.69)	0.191
INDICA interventions related costs	180.26	130.28	326.76	0	–
Total cost	2571.53 (2317.17 to 2825.88)*	2793.91 (2561.86 to 3025.95)	3025.12 (2775.55 to 3274)	2750.44 (2506.18 to 2994.71)	0.093

Healthcare costs: multilevel model, adjusted by age, sex and baseline utility.
QALYs: multilevel model, adjusted by time elapsed since diagnosis and baseline utility.
*Statistically significant differences between PTI and CBI
†Statistically significant differences between CBI and UC
‡Statistically significant differences between PTI and UC
§Statistically significant differences between PTI and PFI
¶Statistically significant differences between PFI and UC
CBI, combined intervention for patients and professionals; CI, Confidence interval; PFI, intervention only for healthcare professionals in primary care; PTI, intervention only for patients and family members; QALY, quality-adjusted life-years; UC, usual care (control group).

(p=0.039) or a higher cost of the intervention on professionals (p=0.036) is assumed.

Analysis of subgroups: patients with baseline HbA1c >7%

The subgroup of patients with baseline HbA1c >7% revealed some benefits of interventions. The PTI arm had the highest effect in terms of QALYs and is dominant over all the other arms after the multilevel model adjustment (table 4). In terms of costs, statistically significant differences were observed only in visits to primary care professionals (p=0.003) (see online supplemental appendix 1 table A5). The highest average healthcare cost per patient, not including the cost of INDICA interventions,

Table 3 Cost, effectiveness and ICER

Arm	Mean total cost (€) (95% CI)	Mean QALYs (95% CI)	Incremental cost and incremental QALYs (95% CI)
CBI	3025.01 (2775.55 to 3274.69)	1.63 (1.59 to 1.68)	Dominated
PFI	2793.88 (2561.86 to 3025.95)	1.69 (1.65 to 1.73)	Dominated
PTI	2571.48 (2317.17 to 2825.88)	1.71 (1.67 to 1.75)	-178.95996 € (–499.61 to 141.69) -0.00465 QALYs (–0.036 to 0.027)
UC	2750.44 (2506.18 to 2994.71)	1.72 (1.68 to 1.76)	
ICER between PTI and UC			38486.0129 €/QALY

CBI, combined intervention for patients and professionals; CI, Confidence interval; ICER, incremental cost-effectiveness ratio; PFI, intervention only for healthcare professionals in primary care; PTI, Intervention only for patients and family members; QALY, quality-adjusted life-years; UC, usual care (control group).

Table 4 Cost and effectiveness in subgroup with baseline HbA1c >7%

Arm	Mean total cost (€) (95% CI)	Mean QALYs (95% CI)	Cost-effectiveness
CBI	3516.44 (3207.58 to 3825.31)	1.62 (1.59 to 1.67)	Dominated
UC	3492.08 (3092.06 to 3892.1)	1.70 (1.66 to 1.73)	Dominated
PFI	3310.96 (2981.6 to 3640.32)	1.71 (1.68 to 1.75)	Dominated
PTI	3117.46 (2763.4 to 3471.53)	1.72 (1.69 to 1.75)	Dominant

CBI, combined intervention for patients and professionals; CI, Confidence interval; HbA1c, glycated haemoglobin; PFI, intervention only for healthcare professionals in primary care; PTI, intervention only for patients and family members; QALY, quality-adjusted life-years; UC, usual care (control group).

was found in the UC arm (€3492, 95% CI €3092 to €3892), followed by the CBI arm (€3189, 95% CI €2881 to €3498), the PFI arm (€3181, 95% CI €2851 to €3510) and, lastly, the PTI arm (€2937, 95% CI €2583 to €3291). These costs were higher than those observed for the entire sample. The only statistically significant difference was found between the average cost of the PTI arm and the average cost of the UC arm, as was the case for the total sample. No differences between arms were found in total cost in patients with baseline HbA1c>7% (p=0.399). The highest total cost per patient was estimated for the CBI arm (€3516, 95% CI €3208 to €3825), followed by the UC arm (€3492, 95% CI €3092 to €3892), the PFI arm (€3311, 95% CI €2982 to €3640) and, lastly, the PTI arm (€3117, 95% CI €2763 to €3471) (see table 4).

The estimate of costs and QALYs was similar for all imputed, non-imputed and completed data. The same arms stayed as dominant and the same conclusion with regard to ICER was upheld.

DISCUSSION

This paper presents the results of an economic evaluation conducted alongside a RCT, the INDICA Study (n=2334), in the Canary Islands, Spain, and from the healthcare perspective. The alternatives evaluated were ICT-based PTI and for professionals in primary care, developed to improve self-management and health outcomes in people with T2DM and prevent serious comorbidity or advanced complications of the disease.

The lowest mean cost was found in the PTI arm, that is, the group where patients received a diabetes-coaching programme combining group education workshops, personalised phone messages and a web-based platform. At the other end, as expected, the cost of the CBI arm, where both PTI and for professionals were included, was higher than in any other arm. The main costs driver was the healthcare costs, lower in the PTI arm than in any other arm and higher in the control group than in any intervention arm. To be precise, the differences between arms were partly explained due to differences in the use of resources and costs of visits to primary care, lab tests and hospital admissions. Regarding the effectiveness of the interventions, although the ICT-based interventions developed for the INDICA trial improved HbA1c and other clinical measures after 24 months of follow-up,[26] these results were not translated into large differences in terms of QALYs between arms. Taking into account costs and QALYs, the CBI and the PFI arms were dominated, that is, were less effective and more costly than other alternatives. Meanwhile, the PTI arm was found to be slightly less effective and less costly than the control group (non-significant differences). The sensitivity analysis confirmed this result. Furthermore, we estimated that the incremental cost per QALY of the UC strategy compared with the PTI arm was above the cost-effectiveness threshold in Spain (€25 000 per QALY),[36] indicating that the PTI intervention is likely to be a cost-effective option.[37] This ICER must be cautiously interpreted given that CIs for both costs and QALYs show uncertainty around the estimates. To complement the results, we conducted a subgroup analysis (not included in the trial protocol) that revealed that in the sample of patients with uncontrolled T2DM (baseline HbA1c >7%) the PTI arm was dominant over all the other arms. This suggests that the INDICA intervention designed for patients and their families is likely to be more cost-effective, especially in patients with poorly controlled blood glucose levels. Transferability to real clinical practice of cost-effective interventions could be even more efficient as their application can be extended to thousands of patients with T2DM, with minimal cost increases.

The INDICA study was designed to be ambitious, inspired by several systematic reviews.[9 10] More recent reviews confirmed the pertinence of studies as INDICA. Lian *et al* conducted a systematic review of cost-effectiveness studies on self-management education programmes for T2DM.[38] This review found two interesting results. First, the number of studies of sufficiently good quality was low, only five cost-effectiveness studies alongside clinical trials. The longest follow-up was 12 months and the largest sample size was 1570. Consequently, from the point of view of these two methodological characteristics, the INDICA study is superior. The second conclusion from Lian *et al* is that the cost of these interventions is not very high and likely to be cost-effective in the long-term. In fact, the only study they identified that found that the intervention was not cost-effective was conditioned by the short-term analysis and could benefit from a long term modelling analysis.[38 39] More recently, Siegel *et al* found strong evidence that multicomponent interventions (involving behaviour change and education and pharmacological therapy) compared with UC are cost-saving or cost-effective (range of the ICERs from cost-saving to US$58 587 per QALY; median: US$2315 per QALY, based on six studies).[40] Interestingly, they also found uncertain evidence about the cost-effectiveness of a computerised decision support system linked to ECR.

Finally, the generalisability of the INDICA findings and the transferability of its results to other settings are not straightforward. Interventions were designed and implemented considering the level of health and digital literacy of the population in the Canary Islands, that is quite similar to the average in Spain (and above the EU mean), and the organisation of the primary healthcare provision by the public system in the region.[41 42] Although not all regions in Spain offer the same support to patients with diabetes, primary healthcare is quite homogeneous throughout the country[43] so the interventions could be implemented with few modifications in regions other than the Canary Islands. Therefore, we could conclude that the intervention and the cost-effectiveness results could be transferable to other regions in Spain, but the transferability to other countries would need a thorough analysis of the care for T2DM in other foreign settings.

Strengths and limitations

The strengths of the INDICA Study as a trial include the pragmatic nature, its large sample size, the duration of follow-up when compared with other trials and, especially, the high rate of patient retention at the last control visit in month 24. There is prior evidence supporting the effectiveness of similar interventions in the reduction of HbA1c in the short term[18 44 45] but not in the long term.[46] The INDICA study revealed differences in clinical outcomes between the intervention arms and the control group that remained statistically and clinically significant at the end of 24 months despite the gradual reduction of effectiveness over time.[26] These findings highlight the importance of conducting trials with long follow-up and sufficient statistical power to evaluate interventions of limited effect sizes but of potential efficacy. In addition, this study applied careful randomisation methods and hierarchical modelling techniques to minimise potential bias due to sample selection or due to baseline differences across subjects. Further explanations can be found in the main article with the clinical results of the INDICA study.[26]

As an economic evaluation, the most important strength comes from the quality and quantity of data on resource use. Medication was collected from the information system for the electronic drugs prescriptions, a very reliable register that includes data on prescription and collection of drugs from community pharmacists. But most data were collected from the patients in common face-to-face meetings to avoid recall bias, and checked against the ECR for those considered critical as healthcare visits and hospital admissions. These meetings also facilitated the high rate of completed EQ-5D-5L questionnaires.

The main limitations of this study are as follows. First, there was some degree of missing data addressed by the robust imputation technique. Multiple Imputation methods were used instead of the technique specified in the protocol, since this is the best option for our missing data patterns.[47] Related to this limitation, due to the complexity of our models, which included multilevel analyses and imputed data, it was not possible to apply bootstrapping techniques that could effectively characterise the uncertainty around the ICER point estimates. This also prevented estimate of the cost-effectiveness acceptability curve. Instead, we presented the CIs for costs and QALYs separately and conducted comprehensive deterministic sensitivity analyses.

Second, we conducted the costs analysis in the framework of the clinical trial. Intervention costs might differ in real life as implementation all over the Canary Islands would require the escalation of resources in a fragmented territory as it is an archipelago if other criteria such as access equity have to be taken into consideration. Nonetheless, the sensitivity analysis applied to costs confirmed the main result as reported in this study.

Third, we found some unexpected results that were further explored. For instance, the small effect observed in the PFI and CBI arms in comparison to PTI was potentially explained by the high staff turnover noted among primary care professionals around the time the study was ongoing. Similarly, the unexpected results with regard to the outcomes measured in the UC arm might be accounted for by the intensive trial follow-up that all the arms experienced (ie, answering questions about diet, physical activity and self-care six times in 2 years, plus blood tests and other examinations) that could be seen as a kind of intervention.[44 45 48 49] Therefore, the intensity of the follow-up in the study might have also impacted patient behaviour in the UC arm, to the point of reducing the differences in effects at the end of the 2-year period.

Finally, the lack of important differences in QALYs is potentially due to two main reasons. First, it is difficult to observe large changes when most patients included in the study were already well controlled at baseline (49.4% of the whole sample had an HbA1c <7%).[44] Second, the time horizon is too short to observe changes in diabetes-related complications that are the main cause of variations in quality of life.[50] We will aim to overcome these limitations by implementing the INDICA-DOS study, a follow-up of patients included in the INDICA study that aims to collect outcomes and healthcare costs in the longer term. This information will be useful to complement the within-trial economic evaluation presented in this paper with a lifetime Markov model.[23 24]

Conclusions

In summary, the multicomponent intervention designed by INDICA for patients with T2DM and their families is likely to be a cost-effective option, and particularly so in patients with not so well controlled TD2M (baseline HbA1c >7%). This kind of intervention is likely to be effective, cost-effective and, if focused on those with the highest needs, its impact on the public health budget would be limited.

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Contributors LGP, YRF, LVT, LRR, AMW and PGSA contributed to the study design. YRF, LVT, HGP, BSH and MAGB contributed to the statistical analyses. LGP, YRF, LVT, HGP, MC and PGSA were part of the manuscript's writing committee. All authors reviewed, commented and approved the final manuscript. LGP is the guarantor.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by University Hospital of Canarias (ID: 2012_44) and University Hospital Nuestra Señora de la Candelaria (ID: EPA-07/10). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. The datasets generated and/or analysed during the current study, including deidentified participant data are available from the corresponding author on reasonable request in the next 10 years. The study protocol is available at https://implementationscience.biomedcentral.com/articles/10.1186/s13012-015-0233-1.

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Appendix 1. Supplementary data: Inputs and outputs

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Table A1. Health care resources included in the analysis and their unit costs

	Unit cost (€)	Source
Hospital stay (*)	5171.77	Assumption based on Crespo et al. 2013
Lab test by general practitioner	15	Assumption based on eSalud
Lab test by specialist	20	Assumption based on eSalud
Retinography	100	Assumption base on several sources
Visit to general practitioner	28.78	Public tariff, Servicio Canario de la Salud (2017)
Visit to nurse at primary care	26.62	Public tariff, Servicio Canario de la Salud (2017)
Visit to endocrinologist	110	Assumption based on public tariff, Servicio Canario de la Salud (2017)
Visit to accident & emergency	227.78	Public tariff, Servicio Canario de la Salud (2017)
Medication	Unit costs varied depending on the medication. The source was the database of dispensed medicines in community pharmacy offices.	

(*) As the mean stay of INDICA patients was 9 days, the unit cost reported by Crespo et al. (Av Diabetol. 2013) is considered adequate for the estimation of hospital stay costs.

Sources:

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Table A2. Cost of INDICA interventions (€)

Resource	Patients	Professionals	Both
Time dedicated to developing the materials used by the study nurses (educators)	20163	(-)	20163
Time spent by other professionals on reviewing the materials	1523	(-)	1523
Training in empowerment received by the nurses	229	(-)	229
Training in emotional management received by the nurses	414	(-)	414
Time for educational workshops to patients and their relatives by nurses	27824	(-)	27824
Laptops	3620	(-)	3620
Printed materials for group education	780	(-)	780
Transport by nurses to visit centres	5004	(-)	5004
Diaries for patients	7910	(-)	7910
Video recording of educational workshops given by nurses	1091	(-)	1091
Website with educational materials for the patients	12120	(-)	12120
SMSs sent to patients	16119	(-)	16119
Time dedicated to developing the materials: review of studies and design of INDICA guideline for GPs	(-)	44460	44460
Edition and printing of INDICA guideline	(-)	1292	1292
Development and maintenance of computerized decision support system	(-)	26477	26477
Development of feedback system	(-)	7284	7284
Folders for professionals in primary care	(-)	1452	1452
Catering for training workshops for professionals in primary care	(-)	1741	1741
Training workshops of professionals in primary care (introduction to INDICA guideline and shared decision making)	(-)	2500	2500
Total cost (€)	96798	85206	182004
Number of patients	537	654	557
Mean cost per patient (€)	180.26	130.28	326.76

Figure A1. EQ-5D-5L Index profile per arm

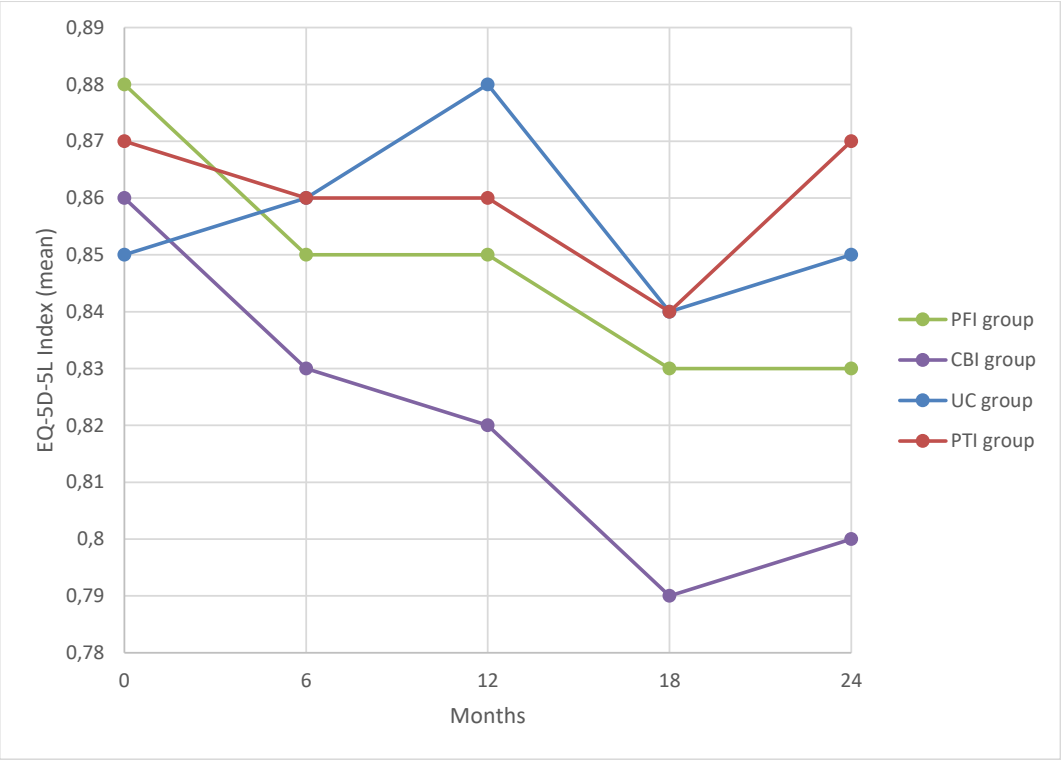

Table A3. Adjusted mean (95%CI) of use of resources for all follow-up per arm. Negative-binomial regression model

Resource	PTI arm	PFI arm	CBI arm	UC arm	p-value
Hospital stays	0.09 (0.06 to 0.12)[a]	0.10 (0.07 to 0.13)	0.08 (0.04 to 0.11)[b]	0.15 (0.12 to 0.18)	**0.025**
Lab tests by general practitioner	2.04 (1.88 to 2.19)[d e]	2.60 (2.47 to 2.74)[c]	2.51 (2.34 to 2.68)[b]	2.12 (1.98 to 2.27)	**<0.001**
Lab tests by specialist	0.77 (0.62 to 0.92)	0.85 (0.71 to 0.98)	0.85 (0.70 to 1.0)	0.95 (0.91 to 1.09)	0.373
Retinography	1.20 (1.08 to 1.32)	1.29 (1.18 to 1.38)	1.18 (1.07 to 1.31)	1.15 (1.04 to 1.25)	0.323
Visits to general practitioner	5.96 (5.56 to 6.36)[a d e]	8.08 (7.53 to 8.59)[c f]	9.73 (9.3 to 10.67)[b]	5.35 (4.93 to 5.71)	**<0.001**
Visits to nurse at primary care	4.59 (4.07 to 5.11)[d e]	5.71 (5.24 to 6.17)[c f]	7.31 (6.78 to 7.86)[b]	4.66 (4.17 to 5.15)	**<0.001**
Visits to endocrinologist	0.39 (0.30 to 0.48)	0.46 (0.37 to 0.53)	0.45 (0.36 to 0.55)	0.43 (0.35 to 0.52)	0.693
Visit to accident & emergency (outpatient centre)	0.95 (0.77 to 1.13)[a]	0.86 (0.70 to 1.02)[e]	1.13 (0.94 to 1.31)[b]	0.78 (0.62 to 0.94)	**0.002**
Visit to accident & emergency (hospital)	0.33 (0.25 to 0.40)	0.29 (0.23 to 0.35)	0.36 (0.28 to 0.43)	0.33 (0.27 to 0.4)	0.577

Negative-binomial regression model, adjusted by time since diagnosis and baseline resource use.

Statistically significant differences between arms: a, UC and PTI; b, UC and CBI; c, UC and PFI; d, CBI and PTI; e, PFI and PTI; f, CBI and PFI.

CBI, Combined intervention for patients and professionals; PFI, Intervention only for health care professionals in primary care; PTI, Intervention only for patients and family members; UC, usual care (control group).

Table A4. Results of the one-way sensitivity analysis

		Costs (€) Mean (95%CI)					PTI *vs* UC		
Resource	**Unit cost (€)**	**PFI arm***	**CBI arm***	**PTI arm**	**UC arm**	**p-value**	**Incremental cost**	**Incremental QALYs**	**ICER (€/QALY)**
Hospital stay	4137.42	2683 (2467.21 to 2898.79)	2942.75 (2711.91 to 3173.59)[b]	2479.59 (2244.96 to 2714.21)[a]	2598.18 (2372.31 to 2824.04)	**0.039**	-118.591	-0.00465	25503.44
	6206.12	2904.48 (2653.62 to 3155.33)	3107.11 (2836.14 to 3378.07)	2663.45 (2386.66 to 2940.24)	2903.04 (2637.74 to 3168.34)	0.164	-239.585	-0.00465	51523.66
Lab test by general practitioner	12	2786.09 (2553.97 to 3018.2)	3017.6 (2767.97 to 3267.22)	2565.41 (2311.0 to 2819.81)	2744.06 (2499.73 to 2988.39)	0.095	-178.652	-0.00465	38419.78
	18	2801.73 (2569.75 to 3033.71)	3032.65 (2783.13 to 3282.16)	2577.65 (2323.34 to 2831.96)	2756.83 (2512.63 to 3001.02)	0.091	-179.18	-0.00465	38533.33
Lab test by specialist	16	2790.46 (2558.83 to 3022.09)	3021.86 (2772.71 to 3271.02)	2568.42 (2314.48 to 2822.35)	2746.59 (2502.74 to 2990.44)	0.092	-178.177	-0.00465	38317.63
	24	2797.35 (2564.89 to 3029.82)	3028.38 (2778.4 to 3278.37)	2574.64 (2319.86 to 2829.41)	2754.29 (2509.61 to 2998.97)	0.094	-179.655	-0.00465	38635.48
Retinography	80	2768.43 (2535.88 to 3000.98)	3001.36 (2751.29 to 3251.42)	2547.57 (2292.82 to 2802.32)	2727.31 (2482.53 to 2972.09)	0.094	-179.739	-0.00465	38653.55
	120	2819.39 (2587.74 to 3051.05)	3048.87 (2799.68 to 3298.06)	2595.49 (2341.42 to 2849.56)	2773.56 (2529.7 to 3017.42)	0.092	-178.065	-0.00465	38293.55

Visit to general practitioner	23.02	2746.8 (2521.19 to 2972.4)	2969.39 (2726.11 to 3212.67)	2536.77 (2288.5 to 2785.04)	2721.83 (2483.8 to 2959.85)	0.108	-185.058	-0.00465	39797.42
	34.54	2841.06 (2602.23 to 3079.88)	3080.72 (2824.54 to 3336.91)	2606.31 (2345.54 to 2867.07)	2779.03 (2528.20 to 3029.86)	0.080	-172.724	-0.00465	37144.95
Visit to nurse at primary care	21.30	2763.69 (2536.76 to 2990.61)	2984.26 (2739.65 to 3228.88)	2547.69 (2298.15 to 2797.22)	2727.94 (2488.62 to 2967.25)	0.104	-180.25	-0.00465	38763.44
	31.94	2824.11 (2586.79 to 3061.42)	3065.95 (2811.27 to 3320.62)	2595.39 (2336.06 to 2854.72)	2772.96 (2523.6 to 3022.33)	0.083	-177.572	-0.00465	38187.53
Visit to endocrinologist	88	2788.28 (2556.42 to 3020.13)	3019.83 (2770.46 to 3269.21)	2567.04 (2312.93 to 2821.15)	2745.12 (2501.06 to 2989.17)	0.093	-178.079	-0.00465	38296.56
	132	2808.92 (2576.33 to 3041.52)	3039.22 (2789.11 to 3289.34)	2583.5 (2328.46 to 2838.54)	2764.64 (2519.79 to 3009.5)	0.092	-181.146	-0.00465	38956.13
Visit to accident & emergency	182.22	2580 (2338.76 to 2821.25)	2743.24 (2486.37 to 3000.11)	2351.87 (2090.91 to 2612.83)	2561.98 (2309.3 to 2814.65)	0.216	-210.105	-0.00465	45183.87
	273.34	2607.18 (2363.74 to 2850.61)	2775.65 (2516.38 to 3034.93)	2381.07 (2117.76 to 2644.38)	2592.02 (2337.16 to 2846.89)	0.218	-210.951	-0.00465	45365.81
Cost of INDICA interventions (PTI and CBI	144.21-261.41	2793.91 (2561.86 to 3025.95)	2959.77 (2710.20 to 3209.34)	2535.48 (2281.12 to 2789.83)	2750.44 (2506.18 to 2994.71)	0.132	-214.966	-0.00465	46229.25

arm)	216.31-392.11	2793.91 (2561.86 to 3025.95)	3090.47 (2840.9 to 3340.04)	2607.58 (2353.22 to 2861.93)	2750.44 (2506.18 to 2994.71)	0.055	-142.866	-0.00465	30723.87
Cost of INDICA interventions (PFI and CBI arm)	104.22-261.41	2767.85 (2535.8 to 2999.89)	2959.77 (2710.2 to 3209.34)	2571.53 (2317.17 to 2825.88)	2750.44 (2506.18 to 2994.71)	0.201	-178.917	-0.00465	38476.77
	156.34-392.11	2819.97 (2587.92 3052.01)	3090.47 (2840.9 to 3340.04)[b]	2571.53 (2317.17 to 2825.88)[a]	2750.44 (2506.18 to 2994.71)	**0.036**	-248.442	-0.00465	53428.39

*Arm dominated
Statistically significant differences between arms: [a] PTI and CBI; [b], CBI and UC.

Table A5. Adjusted mean (95%CI) of healthcare costs per arm (€) in the subgroup with baseline HbA1c >7%. Multilevel model

Resource	PTI arm	PFI arm	CBI arm	UC arm	p-value
Hospital stays	586.27 (332.43 to 840.11)	619.88 (376.98 to 862.78)	465.11 (256.62 to 673.61)[b]	911.46 (604.52 to 1218.40)	0.104
Laboratory tests	46.64 (40.21 to 53.08)[e]	58.26 (52.78 to 63.75)	53.95 (49.02 to 58.89)	54.29 (48.33 to 60.25)	0.142
Retinography	124.54 (107.46 to 141.62)	128.22 (113.34 to 143.09)	125.20 (109.30 to 141.09)	118.99 (103.39 to 134.59)	0.987
Primary care visits	297.26 (269.30 to 325.22)[d]	385.42 (350.11 to 420.73)	506.72 (456.81 to 556.63)[b]	287.97 (256.28 to 319.66)	**0.003**
Specialist visits	40.90 (30.32 to 51.48)	57.91 (43.27 to 72.54)	54.19 (40.99 to 67.39)	58.58 (44.71 to 72.46)	0.371
Accident & emergency visits	269.82 (191.10 to 348.53)	275.62 (203.01 to 348.24)	348.99 (283.14 to 414.84)	278.52 (209.94 to 347.10)	0.738
Medication	1571.772 (1400.85 to 1742.69)	1655.37 (1457.79 to 1852.94)	1635.11 (1469.55 to 1800.67)	1770.71 (1591.67 to 1948.75)	0.811
Healthcare cost (without INDICA interventions related costs)	2937.20 (2583.14 to 3291.27)[a]	3180.68 (2851.32 to 3510.04)	3189.32 (2880.50 to 3498.13)	3492.08 (3092.06 to 3892.10)	0.264
INDICA interventions related costs	180.26	130.28	326.76	0	
Total cost	3117.46 (2763.40 to 3471.53)	3310.96 (2981.6 to 3640.32)	3516.44 (3207.58 to 3825)	3492.08 (3092.06 to 3892.1)	0.399

Multilevel model, adjusted by age, sex and baseline utility.

Statistically significant differences between arms: a, UC and PTI; b, UC and CBI; d, CBI and PTI; e, PFI and PTI.

CBI, Combined intervention for patients and professionals; PFI, Intervention only for health care professionals at primary care; PTI, Intervention only for patients and family members; UC, usual care (control group).

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Appendix 2. Description of mechanism for imputation of missed data.

Multiple imputation was performed by means of *mi impute chained* using the software Stata 15.0. Imputations were performed in a differentiated way for each of the four treatment groups. The following variables were considered regular and used as predictors to perform imputations: age of onset of the study, sex, baseline smoker status and baseline diabetes treatment. A total of 79 variables were imputed. Each variable was imputed in chronological order: baseline first and afterwards 3, 6, 12, 18 and 24 months. As a general rule, the latest available information of the variable to impute was used. When information from other variables was used the information from the same time moment was used. The imputation was not performed using secondary variables as random effects without fixed effects being used. A total of 90 imputations was performed for every missed data. For some imputations, predictor variables were omitted due to convergence problems.

The following table shows the order of imputation of the variables, the variables used in the imputation, the prediction model and the number of lost data for this variable.

	Imputed variable	**Variables used in the imputation**	**Imputation Model**	**N missed**
1	Mobility EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Duration of Diabetes	mlogit	21
2	Mobility EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L baseline	mlogit	573
3	Mobility EQ-5D-5L, 12 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 6 months	mlogit	670
4	Mobility EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 12 months	mlogit	745
5	Mobility EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 18 months	mlogit	671
6	Self-care EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L baseline	mlogit	27
7	Self-care EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 6 months	mlogit	577
8	Self-care EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Duration of Diabetes, Mobility EQ-5D-5L 18 months	mlogit	743
9	Usual activities EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L baseline	mlogit	25
10	Usual activities EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 6 months	mlogit	578
11	Usual activities EQ-5D-5L, 12 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 12 months	mlogit	671
12	Usual activities EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 18 months	mlogit	750
13	Usual activities EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline	mlogit	677
14	Pain/Discomfort EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L baseline	mlogit	22
15	Pain/Discomfort EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L baseline	mlogit	575

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
16	Pain/Discomfort EQ-5D-5L, 12 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 6 months	mlogit	670
17	Pain/Discomfort EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 12 months	mlogit	743
18	Pain/Discomfort EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 18 months	mlogit	672
19	Anxiety/Depression EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L Baseline, Usual activities EQ-5D-5L Baseline, Pain/Discomfort EQ-5D-5L baseline	mlogit	32
20	Anxiety/Depression EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 6 months, Usual activities EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L baseline	mlogit	575
21	Anxiety/Depression EQ-5D-5L, 12 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 6 months	mlogit	670
22	Anxiety/Depression EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 18 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, Anxiety/Depression EQ-5D-5L 12 months	mlogit	745
23	Anxiety/Depression EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 24 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 18 months	mlogit	671
24	VAS EQ-5D-5L, baseline	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline	poisson	47
25	VAS EQ-5D-5L, 6 months	Age, Sex, Diabetes treatment baseline, Mobility EQ-5D-5L 6 months, Self-care EQ-5D-5L 6 months, Usual activities EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L 6 months, VAS EQ-5D-5L baseline	poisson	584
26	VAS EQ-5D-5L, 12 months	Age, Smoking status baseline, Mobility EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, VAS EQ-5D-5L 6 months	poisson	686
27	VAS EQ-5D-5L, 18 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Mobility EQ-5D-5L 18 months, Self-care EQ-5D-5L 18 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, Anxiety/Depression EQ-5D-5L 18 months, VAS EQ-5D-5L 12 months	poisson	746
28	VAS EQ-5D-5L, 24 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Mobility EQ-5D-5L 24 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 18 months	poisson	679
29	Lab tests by general practitioner, baseline	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L baseline, VAS EQ-5D-5L baseline	poisson	70
30	Lab tests by general practitioner, 3 months	Age, Sex, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L 6 months, VAS		490

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
		EQ-5D-5L 6 months, Lab tests by general practitioner baseline		
31	Lab tests by general practitioner, 6 months	Age, Sex, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months, Lab tests by general practitioner 3 months	poisson	593
32	Lab tests by general practitioner, 12 months	Age, Comorbidity 12 months, Pain/Discomfort EQ-5D-5L 12 months, Lab tests by general practitioner 6 months	poisson	670
33	Lab tests by general practitioner, 18 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Pain/Discomfort EQ-5D-5L 18 months, VAS EQ-5D-5L 18 months, Lab tests by general practitioner 12 months	poisson	746
34	Lab tests by general practitioner, 24 months	Age, Sex, Comorbidity 24 months, Lab tests by general practitioner 18 months	poisson	676
35	Lab tests by specialist, baseline	Age, Diabetes treatment baseline, Comorbidity baseline	poisson	83
36	Lab tests by specialist, 3 months	Age, Sex, Comorbidity baseline, Lab tests by specialist baseline		539
37	Lab tests by specialist, 6 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Lab tests by specialist 3 months	poisson	597
38	Lab tests by specialist, 12 months	Sex, Smoking status baseline, Comorbidity 12 months, Lab tests by specialist 6 months	poisson	676
39	Lab tests by specialist, 18 months	Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Lab tests by specialist 12 months	poisson	748
40	Lab tests by specialist, 24 months	Age, Sex, Diabetes treatment baseline, Comorbidity 24 months, Lab tests by specialist 18 months	poisson	677
41	Retinography, baseline	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline	poisson	78
42	Retinography, 3 months	Sex, Smoking status baseline, Comorbidity baseline, Retinography baseline	poisson	497
43	Retinography, 6 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Retinography 3 months	poisson	593
44	Retinography, 12 months	Age, Smoking status baseline, Comorbidity 12 months	poisson	669
45	Retinography, 18 months	Age, Smoking status baseline, Comorbidity 12 months	poisson	745
46	Retinography, 24 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 24 months, Retinography 18 months	poisson	676
47	Visits to general practitioner, baseline	Age, Sex, Diabetes treatment baseline, Comorbidity baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline	poisson	147

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
48	Visits to general practitioner, 3 months	Age, Sex, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L Baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, Visits to general practitioner baseline	poisson	505
49	Visits to general practitioner, 6 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Usual activities EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months, Visits to general practitioner 3 months	poisson	615
50	Visits to general practitioner, 12 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, Visits to general practitioner 6 months	poisson	667
51	Visits to general practitioner, 18 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, Visits to general practitioner 12 months	poisson	746
52	Visits to general practitioner, 24 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 24 months, Mobility EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 24 months, Visits to general practitioner 18 months	poisson	672
53	Visits to nurse at primary care, baseline	Age, Sex, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline	poisson	202
54	Visits to nurse at primary care, 3 months	Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, VAS EQ-5D-5L baseline, Visits to nurse at primary care baseline	poisson	511
55	Visits to nurse at primary care, 6 months	Age, Sex, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Usual activities EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months, Visits to nurse at primary care 3 months	poisson	626
56	Visits to nurse at primary care, 12 months	Age, Sex, Smoking status baseline, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, VAS EQ-5D-5L 12 months, Visits to nurse at primary care 6 months	poisson	668
57	Visits to nurse at primary care, 18 months	Sex, Comorbidity 12 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, Anxiety/Depression EQ-5D-5L 18 months, Visits to nurse at primary care 12 months	poisson	747
58	Visits to nurse at primary care, 24 months	Age, Sex, Comorbidity 24 months, Mobility EQ-5D-5L 24 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 24 months, Visits to nurse at primary care 18 months	poisson	670

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
59	Visits to endocrinologist, baseline	Age, Sex, Smoking status baseline, Comorbidity baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, VAS EQ-5D-5L 12 months	poisson	227
60	Visits to endocrinologist, 3 months	Age, Sex, Comorbidity baseline, Mobility EQ-5D-5L baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, Visits to endocrinologist baseline	poisson	524
61	Visits to endocrinologist, 6 months	Age, Sex, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months, Visits to endocrinologist 3 months	poisson	630
62	Visits to endocrinologist, 12 months	Age, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Visits to endocrinologist 6 months	poisson	668
63	Visits to endocrinologist, 18 months	Sex, Comorbidity 12 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, VAS EQ-5D-5L 18 months, Visits to endocrinologist 12 months	poisson	744
64	Visits to endocrinologist, 24 months	Age, Sex, Smoking status baseline, Comorbidity 12 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 24 months, Visits to endocrinologist 18 months	poisson	671
65	Visit to accident & emergency (outpatient centre), baseline	Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Usual activities EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, VAS EQ-5D-5L baseline	poisson	229
66	Visit to accident & emergency (outpatient centre), 3 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, Visit to accident & emergency (outpatient centre) baseline	poisson	535
67	Visit to accident & emergency (outpatient centre), 6 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, Anxiety/Depression EQ-5D-5L 6 months, Visit to accident & emergency (outpatient centre) 3 months	poisson	632
68	Visit to accident & emergency (outpatient centre), 12 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, VAS EQ-5D-5L 12 months, Visit to accident & emergency (outpatient centre) 6 months	poisson	671
69	Visit to accident & emergency (outpatient centre), 18 months	Sex, Comorbidity 12 months, Mobility EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, Anxiety/Depression EQ-5D-5L 18 months, Visit to accident & emergency (outpatient centre) 12 months	poisson	748
70	Visit to accident & emergency (outpatient centre), 24 months	Age, Sex, Diabetes treatment baseline, Comorbidity 24 months, Usual activities EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Anxiety/Depression EQ-5D-5L 24 months, VAS EQ-5D-5L 24 months, Visit to accident & emergency (outpatient centre) 18 months	poisson	672

	Imputed variable	Variables used in the imputation	Imputation Model	N missed
71	Visit to accident & emergency (hospital), baseline	Comorbidity baseline, Mobility EQ-5D-5L baseline, Pain/Discomfort EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline	poisson	243
72	Visit to accident & emergency (hospital), 3 months	Comorbidity baseline, Mobility EQ-5D-5L baseline, Usual activities EQ-5D-5L baseline, Anxiety/Depression EQ-5D-5L baseline, VAS EQ-5D-5L baseline	poisson	532
73	Visit to accident & emergency (hospital), 6 months	Age, Comorbidity baseline, Mobility EQ-5D-5L 6 months, Pain/Discomfort EQ-5D-5L 6 months, VAS EQ-5D-5L 6 months	poisson	630
74	Visit to accident & emergency (hospital), 12 months	Age, Sex, Diabetes treatment baseline, Smoking status baseline, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, VAS EQ-5D-5L 12 months, Visit to accident & emergency (hospital) 6 months	poisson	670
75	Visit to accident & emergency (hospital), 18 months	Age, Sex, Comorbidity 12 months, Mobility EQ-5D-5L 18 months, Usual activities EQ-5D-5L 18 months, Pain/Discomfort EQ-5D-5L 18 months, VAS EQ-5D-5L 18 months	poisson	748
76	Visit to accident & emergency (hospital), 24 months	Sex, Diabetes treatment baseline, Comorbidity 24 months, Mobility EQ-5D-5L 24 months, Pain/Discomfort EQ-5D-5L 24 months, Visit to accident & emergency (hospital) 18 months	poisson	672
77	Hospital stays, Baseline	Age, Diabetes treatment baseline, Smoking status baseline, Comorbidity baseline, Pain/Discomfort EQ-5D-5L baseline, VAS EQ-5D-5L baseline, Visit to accident & emergency (hospital) baseline	poisson	11
78	Hospital stays, 12 months	Age, Comorbidity 12 months, Mobility EQ-5D-5L 12 months, Usual activities EQ-5D-5L 12 months, Pain/Discomfort EQ-5D-5L 12 months, Anxiety/Depression EQ-5D-5L 12 months, VAS EQ-5D-5L 12 months, Visit to accident & emergency (hospital) 12 months	poisson	664
79	Hospital stays, 24 months	Age, Mobility EQ-5D-5L 24 months	poisson	670
VAS, Visual Analogue Scale.				