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TITLE PAGE

Patient-reported outcome measures for knowledge transfer and behavior modification interventions in type 2 diabetes. The INDICA study: a multi-arm cluster randomized controlled trial

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ABSTRACT

Objective

This study assesses the effectiveness, from the patients´ perspective, of different interventions of knowledge transfer and behavior modification to improve type 2 diabetes mellitus (T2DM) outcomes in the long-term (24 months).

Methods

The INDICA study is an open, community-based pragmatic, multicenter, controlled trial with random allocation by clusters to usual care (UC) or two different interventions and their combination. The intervention for patients (PTI) included an educational group program, logs and a web-based platform for monitoring, and automated SMS. The intervention for professionals (PFI) included an educational program, a decision support tool embedded into the electronic clinical record, and periodic feedback about patients' results. A third group received a combined intervention (CBI). A total of 2,334 uncomplicated T2DM patients and 211 healthcare professionals were included of 32 Primary Care Centers in Canary Islands (Spain). The measurements included were cognitive-attitudinal, behavioral, affective and health related quality of life dimensions. Mixed models were performed.

Results

Compared to UC, the PTI group significantly improved knowledge and adherence to dietary recommendations. Significant improvements were also observed in quality of life, empowerment and distress. The PFI group improved in depression, anxiety self-empowerment and distress. The CBI group improved in knowledge, self-empowerment, and adherence to dietary recommendations. Significant improvements were also observed in the proportion of patients who quit smoking for PTI and CBI (41.2% in PTI and 42.2% in CBI vs. 21.4% in UC group).

Conclusions

Assessed interventions to improve patient reported outcomes measures (PROMS) in T2DM attain effectiveness for knowledge, empowerment, distress, diet adherence and tobacco cessation. PTI produced the most lasting benefits.

Trial Registration: ClinicalTrials.gov NCT01657227 (August 6, 2012) https://clinicaltrials.gov/ct2/show/NCT01657227

Keywords: Primary Care, Diabetes & Endocrinology, Quality in health Care, Health Informatics

Strengths and Limitation of this study

- The INDICA study provides randomized evidence on the effectiveness of complex interventions to improve outcomes in type 2 diabetes mellitus patients, with a longer follow up than previous studies.
- All relevant stakeholders in the community are involved in the INDICA study (patients and family caregivers and primary care professionals).
- The trial included a large sample of patients with type 2 diabetes regardless of their baseline HbA1c level, reinforcing the external validity of the results.
- The INDICA interventions with ICT-based components favor applicability and access, in a cost-effective manner, to a growing number of patients.
- A limitation in the use of PROMS is the absence of well-established empirically derived minimum clinically significant differences

INTRODUCTION

Many type 2 diabetes mellitus (T2DM) patients do not achieve the recommended treatment goals for glycemic control[1]. This might be due to inappropriate health care access and/or clinical management. However, research has also shown the role of health literacy and knowledge to empower patients[2]. Moreover, psychological and emotional aspects, such as diabetes distress, are also important issues for glycemic control[3].

A systematic review by Chen et al[4] states that interventions that aim to empower people with chronic illnesses are able to improve health status, outcome indicators of psychological and social aspects, and self-management. Patient-reported outcome measures (PROMs) are standardized, validated questionnaires completed by patients to mirror their perception of their health status, perceived level of impairment, disability and health-related quality of life[5]. Previous research has shown the value of PROMs to monitor these outcome measures in diabetes[6], which contribute to patient empowerment and patient-centered care[7].

The INDICA study is a pragmatic, cluster-randomized controlled trial with two years follow-up that assesses the effectiveness and cost-effectiveness of multicomponent interventions for knowledge transfer and behavior modification of patients, families, and healthcare professionals (physicians and nurses) in a large number of Primary Care Health Practices (PHCP). These interventions combine conventional group educational and training activities with different ICT-based interventions to guide the decisions of the main actors involved in the management of T2DM[8]. Descriptive information on the patients´ use of the different components of the intervention and the comparative clinical effectiveness among interventions can be seen in Ramallo-Fariña et al[9]. Their cost-effectiveness evaluation can be reviewed in García-Pérez et al[10].

The main objective of the INDICA study was to assess the effectiveness (HBA1c) and cost-effectiveness of different decision support interventions to modify the lifestyles of T2DM patients and improve their health outcomes[9,10]. This study examines the effect of a set of intertwined PROMs on cognitive-attitudinal (knowledge, empowerment), behavioral (i.e., adherence to the dietary recommendation, medication and tobacco use), affective (anxiety, depression, distress) and health related quality of life dimensions. These outcomes are commonly targeted for most diabetes interventions because of their

association with critical, longer-term outcomes, such as functional capacity[11], complications[12-14], mortality[15], health care costs[16], and quality of life[17].

METHODS

Trial design

The INDICA study is an open, community-based pragmatic, multicenter, controlled trial with random allocation by clusters to usual care or one of three multicomponent interventions of knowledge transfer and behavior modification. One intervention was aimed at patient and family members (PTI); another intervention was aimed at primary care healthcare professionals (physicians and nurses) (PFI) and the third intervention combined the other two (CBI). In the control group, both patients/families and physicians/nurses received the usual activities provided by the PHCP. The full study protocol has been published before[8].

Study Participants

The INDICA study included adults aged 18 to 65 years who had been diagnosed with T2DM at least one year before, did not have any diabetes-related complications, and used a mobile phone regularly[8]. Family Care Units (FCU) in each PCHP, comprised of a family physician and a nurse, were the recruitment unit. All PHCPs included had to have at least eight FCUs and the availability of appropriate facilities to provide educational group sessions. FCUs planning or awaiting placement changes among PHCP in the first six months after the project began were excluded.

Setting and recruitment

PHCPs were randomly selected in the islands of Tenerife, Gran Canaria, Lanzarote, and La Palma (Canary Islands, Spain). Moreover, FCUs were randomly selected from all consenting FCUs at each PHCP. The electronic clinical records (ECR) of all potentially eligible patients in selected FCUs were screened to verify inclusion and exclusion criteria.

Patient and public involvement

Patients were actively involved in the design of the trial. Two associations of patients with T2DM in the Canary Island 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 the elaboration 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 objective of another publication. Finally, we established a commitment with patients and healthcare professionals to share the results with them in an easy-to-understand way.

Random assignment

Randomization was applied at different levels. First, three different strata were created according to the geographic areas in the more populated islands (Tenerife and Gran Canaria). Second, four PHCP (clusters) were randomly allocated to every geographic stratum and block permutation was used to assign PHCPs to the study arms; the PHCP being the sampling unit. La Palma and Lanzarote (less populated islands) were geographically divided into four zones with only one eligible PHCP available in each zone randomly assigned to one of the study arms. In every island, all arms were equally distributed. Six FCUs were randomly selected, from all those consenting to participate in each PHCP. From all patients fulfilling inclusion criteria and consenting to participate in each PHCP, 15 were randomly selected per FCU. Exceptionally, more than six FCUs or more than 15 patients per FCU were selected, to guarantee recruitment of 90 patients in every PHCP. FCU and patient randomization were performed by simple generation from a list of random numbers.

Interventions

Patient interventions

Patients recruited to the PTI and CBI groups received a complex intervention of knowledge transfer and behavior modification, informed by conceptual frameworks of behavioral change[12]. The intervention combined: A) an eight-session, conventional, group educational program given by a nurse specialized in diabetes; B) monitoring of physical activity, diet, drug adherence, mood, blood pressure, and blood glucose readings by daily use of paper workbooks, complemented by weekly access to a website platform to upload paper workbook data; and C) continuous, personalized feedback by semi-automated mobile phone messages (SMS), modified according to the website information.

Interventions for primary care professionals

Primary care professionals recruited to the PFI and CBI groups received a complex intervention of knowledge transfer and decision support, informed by the determinants of behavior change suggested by Michie et al[18] for its design and implementation. The intervention included: A) an educational and interactive group program of two sessions to update clinical management information and promote patient-centered care; B) an automated decision aid tool, based on a CPG for T2DM embedded into the electronic clinical record; and C) monthly computerized graphic feedback, which displayed a set of processes and outcome indicators for all T2DM patients of the corresponding FCU compared to other FCU in their setting and the FCU with the best results. Both interventions were applied during the two years follow-up.

Duration of fieldwork

Fieldwork took place between February 2013 and October 2016. The first year and the following two years were devoted to recruitment of patients and healthcare providers, and intervention and follow-up, respectively. As interventions were maintained over time, intervention and follow-up periods overlapped.

Outcomes

Cognitive-attitudinal outcomes

To assess potential changes in patient knowledge about T2DM and its self-management, we developed a specific instrument created in the context of this project, named DIATEK, which consisted of 30 questions. Each item has four response options and only one correct answer. Items examined risk factors for disease development and deterioration, objective values for biochemical parameters; recommendations on nutrition, physical activity, drug use and self-management. The total score, obtained by adding all correct responses, and ranging from 0 to 30, was later rescaled from 0 to 10.

The Diabetes Empowerment Scale-Short Form (DES-SF)[19] is a validated questionnaire designed to evaluate psychosocial self-efficacy in diabetes. DES-SF is the short form of the original DES, which includes eight items (need for change, developing a plan, overcoming barriers, asking for support, supporting oneself, coping with emotion,

motivating oneself, and making diabetes care choices appropriate for one's priorities and circumstances) with responses on a five-point Likert scale and an overall range from eight to 40, according to increasing patient empowerment.

Behavioral outcomes

The Mediterranean Diet Adherence Screener (MEDAS)[20] is a validated questionnaire to assess dietary recommendation adherence, which consists of 14 targets for food consumption, rated with one point for each target attained. According to the final score, patients are classified as having low (0-6 points), moderate (7-10) or high adherence (11-14 points) to the Mediterranean diet.

The Morisky Medication Adherence Scale (MGLS)[21] assesses drug-treatment adherence, by means of a validated four-item self-report instrument and a final score ranging from 0 to 4. Patients are considered adherent, only if they obtain four points.

Smoking status was monitored from baseline and during follow-up, to check for potential cessation throughout the study.

Affective outcomes

The State Trait Anxiety Inventory (STAI-S)[22] is a validated patient-reporting questionnaire that includes two non-dependent scales; the applied state-anxiety scale (STAI State) and the trait-anxiety scale (STAI Trait). It assesses transient emotional state or condition as characterized by subjective feelings of tension and apprehension that can fluctuate in time and intensity. The STAI-S includes 20 items, with each item scored on a four-point Likert scale. Anxiety is defined by a cut-off point ≥ 30.

The Beck Depression Inventory II (BDI-II)[23] consists of 21 items scored on a four-point scale from 0 ("not at all") to 3 ("most of the time"). The items assess depression symptoms in the last two weeks. All item scores are added to a maximum score of 63. A BDI-II score of ≥ 14 indicates mild depressive symptoms.

The Diabetes Distress Scale (DDS2)[24] is a validated two-item diabetes distress-screening instrument that asks respondents to rate, on a six-point scale, the degree of distress caused by the two following items: (1) feeling overwhelmed by the demands of living with diabetes and (2) feeling that I am often failing with my diabetes regimen. High

Diabetes distress can be identified by an average score ≥ 3 or more, low distress by scores under two, and moderate distress by the scores in between.

Health- related quality of life and symptoms

The Audit of Diabetes-Dependent Quality of life (ADDQoL-19)[25] is a specific HRQoL questionnaire for diabetes. It assesses 19 domains, each with its impact and importance index to provide an integrated score for each domain. The sum of the score in each domain forms the global score (range: -9 to 3). The lower the score, the worse the quality of life.

The Michigan Neuropathy Screening Instrument (MNSI)[26] is an instrument that measures the incidence of distal diabetic peripheral polyneuropathy. It is composed of 15 self-administered items, in which the abnormal responses are added. A score of seven or more is considered abnormal.

Satisfaction

An ad-hoc self-completed questionnaire was developed to measure satisfaction with each component of the interventions in PTI and CBI groups. It was measured in the 24-month follow-up in patients who, having attended the group educational program, also used the web platform or received the semi-automated mobile phone messages. Satisfaction with each component was valued from 0 to 10 points, with 10 reflecting maximum satisfaction.

All information, including demographic data, overall and personal health history, diabetes health status, current medications, smoking status, and risk factors for complications, was obtained in a face to face interview at baseline and at 3, 6, 12, 18 and 24 months of follow-up. Similarly, all self-administered questionnaires (ADDQoL-19, BDI-II, DES-SF, DDS2, DIATEK, MEDAS, STAI-S, MGLS and MNSI), were distributed and collected at baseline, and at 12 and 24 months follow-up. ADDQol-19, MEDAS and MGLS were also applied at 6 and 18 months.

Statistical Analysis

Multilevel mixed models including the baseline value of dependent variables and time elapsed since diagnosis (in years) as covariates were implemented for all PROMs. First level variables are those corresponding to each measurement along follow-up (repeated time measurements). The second level includes patient variables and third level variables correspond to PHCP. The effect that identifies the intervention arm has been considered

fixed for the different PHCP, whilst the intercept has been considered random. The model also included an interaction term between arm and month, which allows for differences in the intervention effect between follow-up assessments[27]. The adjusted estimated mean was calculated for each follow up moment compared to baseline; and its statistical significance was calculated by means of the model already set out. The relative improvement for each follow-up was obtained as the ratio between the adjusted difference in mean between the intervention and control group and the mean of the control group. A logistic regression model was implemented to compare the proportion of patients who quit smoking at each follow-up, by intervention arm. The *P*-values of the multiple comparisons were corrected by Bonferroni.

To accommodate missing values in the effect analyses, the multiple imputation procedure was employed[28], with results based on 100 imputed datasets. This procedure saves cases for analysis and can be considered an intention-to-treat analysis. Analysis under multiple imputation is valid for randomly missed data[29]. All the analyses were conducted using STATA version 15.0.[30]. Differences were considered statistically significant if $P<0.05$.

Ethical approval and consent to participate

All participants provided written informed consent. The scientific and ethics committees of both the University Hospital of Canarias (ID: 2012_44) and the University Hospital Nuestra Señora de la Candelaria (ID: EPA-07/10) approved the study protocol. The study was performed in accordance with Good Clinical Practice standards, prevailing local regulatory requirements, and Declaration of Helsinki recommendations.

RESULTS

Study Participants

A total of 2334 patients and 211 healthcare professionals were included. Figure 1 shows the flowchart with cluster randomization of patients for each intervention, attendance at educational/training sessions of patients and professionals and the number of PROMs questionnaires received for each follow-up assessment. The patients´ baseline characteristic according to the intervention assignment can be seen in Ramallo-Fariña et al[9]. Mean age of the whole population was 55.7 ± 7.1 years, with 51.9% women. Mean baseline HbA1c was 7.3%/56 mmol/mol. From baseline, 49.4% of patients started with HbA1c levels within the accepted therapeutic goal (≤7%/53 mmol/mol). There were no statistically significant differences among groups in terms of their baseline characteristics.

Cognitive-attitudinal outcomes

Table 1 shows that the level of knowledge about diabetes is significantly higher for PTI (P=0.007) and CBI (P=0.008), compared with UC, at 12 months; and for PTI (P=0.005) at 24 months.

Patient empowerment was significantly higher for PFI and CBI groups, compared to UC at 12 months (P<0.001 for both comparisons). At 24 months, PTI and CBI also attained significantly higher scores than UC (P=0.002 and P=0.008, respectively); while differences with PFI are marginally significant.

Behavioral outcomes

Table 1 shows that the PTI group is significantly more adherent to the diet recommendations, compared to UC, after 12 months of follow-up. There is a difference of 0.87 (P<0.001) at 24 months. Adherence improves for CBI from 18 months, compared to UC, with differences of 0.7 (P=0.004) at 24 months. Adherence levels remain moderate for all patient groups throughout follow-up (see Table 2).

No differences were found in medication adherence, compared to UC (Table 1). However, average levels of medication adherence were significantly improved in all four groups, despite the high baseline levels (>3) (see Table 2).

Table 3 shows the reduction in the proportion of smokers who quit smoking during follow up in PTI (12 months), and CBI (18 months), compared to UC. The percentage of patients who quit smoking at 24 months was 41.2% for PTI (*P*=0.01) and 42.2% (*P*=0.01) for CBI, versus 21.4% for UC group. There were no statistically significant differences between groups in the baseline percentage of smokers (*P*=0.99).

Affective outcomes

Compared to UC, both PFI and CBI show statistically significant differences at 12 months for depression (*P*=0.003 and *P*=0.006, respectively), and anxiety (*P*=0.05 and *P*=0.003, respectively) (Table 1). These differences disappear at 24 months because all groups of patients improved (Table 2).

The diabetes distress score improved significantly compared to the UC group for CBI at 12 months (*P*=0.01) and for PTI and PFI at 24 months (*P*=0.01 and *P*=0.03, respectively). The score remained marginally significant for CBI (Table 1). At baseline, all patient groups showed moderate distress, which decreased to a low level from 12 months, except for the UC group, which did so at 24 months (Table 2).

Health-related quality of life and symptoms

HRQoL significantly improved for all intervention groups, at 12 months, compared to UC; a difference only maintained for PTI at 18 months (*P*=0.02) (Table 1).

Neuropathic symptom scores were significantly lower for the CBI group at 12 months (*P*=0.02) compared to the UC group. This difference disappeared at 24 months (Table 1). Mean baseline scores for all groups were under 4, considerably below the cut-off point of 7 for abnormal classification (Table 2).

Satisfaction

Table 4 shows the patients' satisfaction with the intervention received. While average scores were higher than 9/10, in all dimensions, for the group educational sessions, satisfaction with the web platform and SMS obtained scores above 8.

DISCUSSION

This article assesses the effect of interventions implemented by the INDICA study to improve T2DM outcomes on several health measures self-perceived by patients in the cognitive-attitudinal (knowledge, empowerment), behavioral (i.e., adherence to the dietary recommendations, medication and tobacco use), affective (anxiety, depression, distress) and health-related quality of life dimensions. The INDICA study is a pragmatic cluster-randomized study with two years follow up that assesses the effectiveness of multicomponent interventions for knowledge transfer and behavior modification of patients, families, and healthcare professionals (physicians and nurses) at the primary care level.

This study shows that one year after the start of follow-up, the CBI obtained significant improvements compared to UC in all variables except behavioral. The relative improvements observed ranged between 9.6% (knowledge) and 52.2% (HRQoL), with intermediate values for anxiety (26.1%) and depression (28.7%). The PTI and PFI also obtained significant improvements in HRQoL, although of less intensity (24.8% and 31.7%, respectively). There was divergence with the rest of the significant findings: the PTI group improved in knowledge, adherence to dietary recommendations and smoking cessation; while the PFI improved in depression and empowerment; but a significantly worse result than the UC group for diet adherence. After two years follow-up, there were no significant differences among groups in terms of HRQoL, anxiety or depression, mainly due to the improvement experienced by the UC group. The PTI group obtained the best global results, with significant improvements in terms of knowledge, distress, empowerment, adherence to diet and tobacco cessation. For these last three variables, the CBI was also significantly better than UC, while PFI exceeded the UC group only for distress measures. A significantly worse result in knowledge was obtained. There were no differences in medication adherence, although a ceiling effect could have occurred, since all groups showed high scores at baseline. Overall, the best results were observed in both groups including patients (PTI and CBI), similar to previous clinical outcomes. This is not surprising, given the straightforward and continuous application of these patient interventions, and the high reported satisfaction levels with all intervention components (educational sessions, web resources and SMS). Previous studies that combined education and training with support phone calls, assessing interventions aimed

at empowering diabetes patients to improve self-care and outcomes, showed inconsistent results between clinical variables and PROMS[31,32]. The use of one-way messages such as those used in INDICA, appears to improve HbA1c levels modestly but significantly and consistently[33]. In addition, continuous advances in smart mobile technology provide new possibilities for diabetes self-management, despite the fact that evidence on the effectiveness of these new functionalities remains scarce and uncertain[34,35].

Reduction in the number of smokers in interventions applied directly to patients (PTI and CBI) in regard to UC that remain significant at 24 months with percentages of approximately 42% which is 2.5 times the result obtained by the most extended pharmacologic intervention (replacement nicotine therapy). This is according to a meta-analysis published recently[36] which puts this reduction at 16.9% of the intervened group compared to 10.4% of the control group in studies with follow up varying from six to 24 months.

The intervention effect on professionals raises questions. At one year of follow-up, the PFI and CBI groups obtained improvements in psychological variables not affected by the intervention targeted exclusively at patients (PTI) (i.e., empowerment, anxiety, depression). These findings could be interpreted as the lasting result of better shared decision-making/patient-centered care by professionals trained in this care model. However, the PTI group was the only group to show significant improvements in behavioral variables (diet adherence and tobacco consumption); while PFI obtained significantly worse results for diet adherence from month six, and CBI did not show significant benefits, for these two outcomes, until 18 months. These negative findings from groups containing professionals are repeated after two years in the case of knowledge, a variable in which the CBI group did not obtain significant differences. This interpretation should be considered cautiously given the analysis limitations, since the differences between intervention groups have not been statistically contrasted. As a recent Cochrane review[37] reported, current evidence on the effect of interventions to promote shared decision making by healthcare professionals shows benefits when decision making is assessed by external observers but not by patient's assessment; furthermore, no significant effects were observed in most patient-reported outcomes[37]. Given the paucity and limited quality of available studies, more focused research is needed to draw solid conclusions about the effect of interventions aimed at professionals, and the

mechanisms by which these interventions translate into psychological, behavioral and health changes of patients.

The assessment of clinical outcome measures in the INDICA study [9] for the total sample recruited regardless of Hb1Ac levels (only 50.6% of all participants had baseline HbA1c concentrations >7%, with a mean of 7.3%), showed an early and significant but temporary reduction in HbA1c for the PTI group, compared to UC, from 3 to 6 months. Even so, more than 30% of the intervened patients (PTI and CBI) attained statistically and clinically relevant reductions in HbA1c (> 0.4%); significantly higher than UC at 12 and 18 months.

In the group of patients with baseline HbA1c greater than 7% (uncontrolled patients), the magnitude of the intervention effect on clinical outcomes was greater, especially in the PTI group compared to the UC group, with significant differences up to 18 months, and a significant area under the curve at 24 months for PTI compared to UC[9]. These results are supported by other studies that report greater intervention effects in patients with higher HbA1c levels[38,39]. Longer-term reductions in blood pressure were also found in the two groups in which professionals were intervened, with smaller effects in the remaining clinical measures (lipid profile, body mass index, serum creatinine and glomerular filtration rate). Some of these results are more related to changes in medication than lifestyles. From a cost-effectiveness perspective, small differences were observed between groups after two years follow up. The PTI was more effective and less costly than CBI and PFI, in patients with HbA1c>7%[10]. This prompted the conclusion that interventions focused on patients with the highest needs would limit the impact on the health care sector budget.

This study has several limitations. The high number of instruments and measurement times increase the risk of type 1 error, which explains the decision not to compare intervention groups with each other. Moreover, the use of PROMs makes it necessary to know the minimum clinically significant differences of every instrument used. This difference, however, has not been investigated for most of them, and there is currently no consensus on the appropriate method (distribution or anchor-based) and/or statistics (e.g., absolute versus relative reduction)[40]. Furthermore, the use of PROMs implies by definition an unblind assessment of results, which is added to the impossibility of blinding the participants regarding the intervention. Despite these limitations, the INDICA study presents some distinctive characteristics from other published studies that assess the impact of interventions promoting empowerment, self-management and behavior

modification to patients and professionals: 1) a robust design (pragmatic cluster-randomized controlled trial with a factorial design for intervention arms) with a long follow-up (two years); 2) incorporation of the different actors involved in disease management (patients and family caregivers and primary care professionals; 3) greater external validity by including patients regardless of their baseline HbA1c levels; 4) incorporation of ICT-based components to the intervention that favors applicability and access, in a cost-effective manner, to a growing number of patients; and 5) inclusion of a large sample size with 2334 patients and 211 healthcare professionals.

In conclusion, all the interventions assessed improved patients HRQoL at one year of follow-up, with differences according to the intervention in the remaining PROMs examined. The intervention targeted exclusively at patients (PTI) significantly improved knowledge, empowerment, distress, dietary recommendation adherence and tobacco cessation, up to two years of follow-up. Although the clinical relevance of these effects is uncertain, except in the case of smoking cessation, these results are promising since they reflect improvements in all personal domains assessed (cognitive, attitudinal, affective, behavioral), which highlight the importance of behavioral factors to attain good health outcomes. The intervention on professionals improved affective variables at one year of follow-up, but showed virtually no effects at two years together with a negative effect on diet adherence and no effect on tobacco consumption, which emphasizes the need for more focused evaluative research on this type of intervention. For both target groups (patients and professionals), the use of ICT can be a major help to improve care access and continuity; as well as effectiveness and cost-effectiveness in T2DM self-management.

STATEMENTS

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Conflicts of interest/Competing interests
The authors declare that they have no competing interest.

Competing interests
The authors declare that they have no competing interest.

Availability of data and material
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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YRF, LGP, LRR, AMW, MRR and PSA contributed to the study design. SKG, GM, CGM, CDA and MRR developed the contents and gave the educational sessions to patients. Also, SKG, GM, CGM, CDA and MRR recruited participants and collected data. YRF, MAGB and HGP contributed to the statistical analyses. YRF, ARS, LGP, AMW and PSA were part of the writing committee of the manuscript. All authors reviewed, commented on, and approved the final manuscript.

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Table 1. Adjusted difference in the mean of each group compared to the control group

	6 Months	p value	12 Months	p value	18 Months	p value	24 Months	p value
Cognitive- attitudinal outcomes								
Knowledge (DIATEK): F=47.3 p<0.001; ICC PHCP =0.06 ICC; subject|PHCP=0.35								
PTI	-	-	0.64 (0.17 to 1.11)	**0.007**	-	-	0.65 (0.2 to 1.11)	**0.005**
PFI	-	-	-0.38 (-0.85 to 0.09)	0.11	-	-	-0.6 (-1.06 to -0.14)	**0.01**
CBI	-	-	0.63 (0.16 to 1.11)	**0.008**	-	-	0.34 (-0.12 to 0.8)	0.15
Empowerment (DES-SF): F=17.3 p<0.001; ICC PHCP =0.08 ICC; subject|PHCP=0.08								
PTI	-	-	1.58 (-0.59 to 3.75)	0.15	-	-	3.04 (1.08 to 4.99)	**0.002**
PFI	-	-	3.95 (1.9 to 6)	**<0.001**	-	-	1.84 (-0.11 to 3.79)	0.07
CBI	-	-	3.97 (1.9 to 6.04)	**<0.001**	-	-	2.63 (0.68 to 4.58)	**0.008**
Behavioral outcomes								
Adherence dietary recommendations (MEDAS): F=25.0 p<0.001; ICC PHCP = 0.03; ICC subject|PHCP=0.20								
PTI	0.22 (-0.25 to 0.69)	0.36	0.71 (0.17 to 1.24)	**0.01**	0.93 (0.46 to 1.41)	**<0.001**	0.87 (0.4 to 1.35)	**<0.001**
PFI	-0.58 (-1.04 to -0.11)	**0.01**	-0.96 (-1.46 to -0.47)	**<0.001**	0.17 (-0.31 to 0.64)	0.49	0.03 (-0.44 to 0.5)	0.90
CBI	0.44 (-0.03 to 0.91)	0.06	0.06 (-0.47 to 0.58)	0.83	0.88 (0.4 to 1.35)	**<0.001**	0.7 (0.22 to 1.17)	**0.004**
Medication adherence (MGLS): F=14.4 p<0.001; ICC PHCP =0.04; ICC subject|PHCP=0.20								
PTI	0.09 (-0.11 to 0.3)	0.37	0.09 (-0.12 to 0.3)	0.39	0.13 (-0.09 to 0.34)	0.24	0.16 (-0.04 to 0.36)	0.12
PFI	0.01 (-0.2 to 0.22)	0.90	-0.13 (-0.34 to 0.08)	0.24	-0.06 (-0.26 to 0.15)	0.58	0.09 (-0.11 to 0.3)	0.39
CBI	0.03 (-0.18 to 0.24)	0.77	-0.19 (-0.41 to 0.03)	0.08	0 (-0.21 to 0.21)	0.98	-0.1 (-0.31 to 0.11)	0.36
Affective outcomes								
Depression (BDI-II): F=53.6 p<0.001; ICC PHCP = 0.05; ICC subject|PHCP=0.34								
PTI	-	-	-1.91 (-3.99 to 0.17)	0.07	-	-	-0.76 (-2.68 to 1.16)	0.44
PFI	-	-	-2.99 (-4.99 to -1)	**0.003**	-	-	0.37 (-1.56 to 2.3)	0.71
CBI	-	-	-3 (-5.13 to -0.87)	**0.006**	-	-	0.23 (-1.73 to 2.19)	0.82
Anxiety (STAI-S): F=36.0 p<0.001; ICC PHCP =0.07 ICC; subject|PHCP=0.32								
PTI	-	-	-2.25 (-5.75 to 1.25)	0.21	-	-	-2.18 (-5.54 to 1.18)	0.20
PFI	-	-	-3.47 (-6.95 to 0.02)	**0.05**	-	-	-0.39 (-3.78 to 2.99)	0.82
CBI	-	-	-5.4 (-8.99 to -1.81)	**0.003**	-	-	-0.50 (-3.9 to 2.9)	0.77
Distress (DDS2): F=14.9 p<0.001; ICC PHCP =.05 ICC; subject|PHCP=0.25								
PTI	-	-	-0.23 (-0.53 to 0.07)	0.13	-	-	-0.34 (-0.62 to -0.07)	**0.01**
PFI	-	-	-0.24 (-0.53 to 0.05)	0.10	-	-	-0.31 (-0.58 to -0.04)	**0.03**

CBI	-	-	-0.36 (-0.65 to -0.07)	**0.01**	-	-	-0.24 (-0.51 to 0.03)	0.08
Health- related quality of life and symptoms								
Health- related quality of life (ADDQoL-19): F=25.3 p<0.001; ICC PHCP = 0.04; ICC subject|PHCP=0.34								
PTI	0.09 (-0.24 to 0.42)	0.60	0.40 (0.04 to 0.76)	**0.03**	0.39 (0.05 to 0.72)	**0.02**	0.16 (-0.17 to 0.48)	0.34
PFI	-0.09 (-0.42 to 0.23)	0.56	0.51 (0.16 to 0.86)	**0.005**	-0.02 (-0.35 to 0.31)	0.89	-0.06 (-0.38 to 0.26)	0.71
CBI	0.03 (-0.3 to 0.35)	0.88	0.84 (0.49 to 1.18)	**<0.001**	0.21 (-0.13 to 0.54)	0.23	-0.05 (-0.38 to 0.28)	0.77
Neuropathic symptom (MNSI): F=59.8 p<0.001; ICC PHCP =0.02 ICC; subject|PHCP=0.32								
PTI	-	-	-0.35 (-0.8 to 0.09)	0.12	-	-	-0.08 (-0.49 to 0.33)	0.70
PFI	-	-	-0.42 (-0.87 to 0.03)	0.07	-	-	0.35 (-0.07 to 0.78)	0.11
CBI	-	-	-0.57 (-1.04 to -0.1)	**0.02**	-	-	0.31 (-0.12 to 0.74)	0.16

CBI Is a combined intervention for patients and professionals; ICC Intraclass correlation coefficient; PFI Intervention only for healthcare professionals at primary care; PTI Intervention only for patients and family members; PHCP Primary Care Health Practices

Table 2. Adjusted means for each group and intragroup differences compared with the baseline measurement

	Adjusted means in each group (95%CI)					Difference in intragroup of adjusted means compared to baseline (95%CI)					
	Baseline	6 Months	12 Months	18 Months	24 Months	B-6M	p value	B-12M	p value	B-18M	p value	B-24M	p value
Cognitive-attitudinal outcomes													
Knowledge (DIATEK)													
PTI	6.4 (6.3 to 6.5)	-	7.2 (6.9 to 7.5)	-	7.4 (7.1 to 7.7)	-	-	0.82 (0.48 to 1.2)	**<0.001**	-	-	1.03 (0.71 to 1.36)	**<0.001**
PFI	6.5 (6.3 to 6.7)	-	6.2 (5.8 to 6.5)	-	6.1 (5.8 to 6.5)	-	-	-0.31 (-0.63 to 0.02)	0.07	-	-	-0.32 (-0.64 to 0.01)	0.058
CBI	6.5 (6.4 to 6.6)	-	7.2 (6.8 to 7.5)	-	7.1 (6.8 to 7.4)	-	-	0.7 (0.36 to 1.03)	**<0.001**	-	-	0.6 (0.27 to 0.94)	**<0.001**
UC	6.2 (6.1 to 6.3)	-	6.5 (6.2 to 6.9)	-	6.7 (6.4 to 7.1)	-	-	0.3 (-0.04 to 0.63)	**0.08**	-	-	0.5 (0.18 to 0.82)	**0.002**
Empowerment (DES-SF)													
PTI	26.4 (25.8 to 27.0)	-	29.5 (27.9 to 31.0)	-	33.5 (32.1 to 34.9)	-	-	3.08 (1.6 to 4.6)	**<0.001**	-	-	7.1 (5.7 to 8.5)	**<0.001**
PFI	26.3 (25.2 to 27.4)	-	31.9 (30.5 to 33.2)	-	32.3 (30.9 to 33.7)	-	-	5.6 (4.2 to 6.9)	**<0.001**	-	-	6.02 (4.7 to 7.4)	**<0.001**
CBI	27.6 (27.0 to 28.3)	-	31.9 (30.4 to 33.3)	-	33.1 (31.7 to 34.5)	-	-	4.3 (2.8 to 5.7)	**<0.001**	-	-	5.7 (4.1 to 6.9)	**<0.001**
UC	26.1 (25.5 to 26.7)	-	27.9 (26.4 to 29.4)	-	30.5 (29.1 to 31.8)	-	-	1.8 (0.26 to 3.3)	**0.02**	-	-	4.3 (2.9 to 5.7)	**<0.001**
Behavioral outcomes													
Adherence dietary recommendations (MEDAS)													
PTI	8 (7.8 to 8.1)	7.6 (7.2 to 7.9)	9.1 (8.7 to 9.4)	8.3 (7.9 to 8.6)	8.7 (8.3 to 9)	-0.43 (-0.77 to -0.09)	**0.01**	1.1 (0.71 to 1.5)	**<0.001**	0.27 (-0.07 to 0.62)	0.12	0.68 (0.34 to 1.02)	**<0.001**
PFI	8.2 (7.9 to 8.5)	6.8 (6.4 to 7.1)	7.4 (7.1 to 7.7)	7.5 (7.1 to 7.8)	7.8 (7.5 to 8.2)	-1.5 (-1.8 to -1.1)	**<0.001**	-0.82 (-1.2 to -0.49)	**<0.001**	-0.82 (-1.2 to -0.49)	**<0.001**	-0.4 (-0.74 to -0.07)	**0.018**
CBI	8.3 (8.1 to 8.5)	7.8 (7.4 to 8.1)	8.4 (8.0 to 8.8)	8.2 (7.9 to 8.5)	8.5 (8.1 to 8.8)	-0.51 (-0.84 to -0.17)	**0.003**	0.13 (-0.24 to 0.51)	0.49	-0.08 (-0.43 to 0.26)	0.63	0.2 (-0.14 to 0.54)	0.26
UC	8.02 (7.9 to 8.2)	7.3 (7.0 to 7.7)	8.4 (8.0 to 8.7)	7.3 (7.0 to 7.7)	7.8 (7.5 to 8.1)	-0.69 (-1.0 to -0.36)	**<0.001**	0.34 (-0.02 to 0.7)	0.07	-0.7 (-1.0 to -0.37)	**<0.001**	-0.24 (-0.57 to 0.1)	0.16
Medication adherence (MGLS)													
PTI	3.1 (3.1 to 3.2)	3.5 (3.4 to 3.7)	3.6 (3.4 to 3.7)	3.6 (3.5 to 3.8)	3.6 (3.5 to 3.7)	0.41 (0.26 to 0.56)	**<0.001**	0.45 (0.29 to 0.6)	**<0.001**	0.5 (0.35 to 0.65)	**<0.001**	0.48 (0.33 to 0.62)	**<0.001**

PFI	3.3 (3.2 to 3.3)	3.5 (3.3 to 3.6)	3.3 (3.2 to 3.5)	3.4 (3.3 to 3.6)	3.5 (3.4 to 3.7)	0.18 (0.03 to 0.33)	**0.02**	0.08 (-0.07 to 0.22)	0.32	0.16 (0.02 to 0.31)	**0.026**	0.25 (0.11 to 0.4)	**0.001**
CBI	3.3 (3.3 to 3.3)	3.5 (3.3 to 3.6)	3.3 (3.1 to 3.4)	3.5 (3.3 to 3.6)	3.3 (3.2 to 3.5)	0.17 (0.02 to 0.32)	**0.02**	-0.01 (-0.18 to 0.15)	0.87	0.2 (0.05 to 0.35)	**0.01**	0.04 (-0.11 to 0.2)	0.60
UC	3.2 (3.1 to 3.3)	3.4 (3.3 to 3.6)	3.5 (3.3 to 3.6)	3.5 (3.3 to 3.6)	3.4 (3.3 to 3.6)	0.23 (0.08 to 0.38)	**0.002**	0.27 (0.12 to 0.42)	**<0.001**	0.29 (0.14 to 0.43)	**<0.001**	0.23 (0.08 to 0.37)	**0.002**
Affective outcomes													
Depression (BDI-II)													
PTI	10.9 (10.4 to 11.5)	-	8.5 (7.1 to 9.9)	-	6.1 (4.7 to 7.5)	-	-	-2.4 (-3.7 to -0.96)	**0.001**	-	-	-4.9 (-6.2 to -3.5)	**<0.001**
PFI	11.0 (9.9 to 12.1)	-	7.5 (6.1 to 8.8)	-	7.2 (5.8 to 8.6)	-	-	-3.6 (-4.9 to -2.2)	**<0.001**	-	-	-3.8 (-5.2 to -2.4)	**<0.001**
CBI	11.7 (10.9 to 12.4)	-	7.5 (5.9 to 8.9)	-	7.1 (5.7 to 8.5)	-	-	-4.2 (-5.7 to -2.7)	**<0.001**	-	-	-4.6 (-5.9 to -3.1)	**<0.001**
UC	11.4 (10.9 to 11.9)	-	10.5 (8.9 to 11.9)	-	6.7 (5.5 to 8.2)	-	-	-0.94 (-2.4 to 0.55)	0.22	-	-	-4.5 (-5.9 to -3.2)	**<0.001**
Anxiety (STAI-S)													
PTI	21.5 (20.7 to 22.2)	-	18.4 (15.9 to 20.9)	-	14.5 (12.0 to 16.9)	-	-	-3.0 (-5.5 to -0.55)	**0.017**	-	-	-7 (-9.4 to -4.6)	**<0.001**
PFI	20.6 (18.8 to 22.4)	-	17.2 (14.8 to 19.6)	-	16.2 (13.8 to 18.7)	-	-	-3.4 (-5.8 to -1)	**0.006**	-	-	-4.4 (-6.8 to -1.9)	**<0.001**
CBI	23.2 (22.0 to 24.3)	-	15.3 (12.8 to 17.8)	-	16.1 (13.7 to 18.6)	-	-	-7.9 (-10.4 to -5.4)	**<0.001**	-	-	-7.0 (-9.5 to -4.6)	**<0.001**
UC	21.9 (21.2 to 22.7)	-	20.7 (18.1 to 23.2)	-	16.6 (14.3 to 19.0)	-	-	-1.3 (-3.8 to 1.3)	0.32	-	-	-5.3 (-7.7 to -2.9)	**<0.001**
Distress (DDS2)													
PTI	2.8 (2.6 to 2.8)	-	1.9 (1.7 to 2.2)	-	1.6 (1.4 to 1.8)	-	-	-0.72 (-0.93 to -0.51)	**<0.001**	-	-	-1.1 (-1.2 to -0.86)	**<0.001**
PFI	2.5 (2.3 to 2.6)	-	1.9 (1.8 to 2.1)	-	1.7 (1.5 to 1.9)	-	-	-0.5 (-0.7 to -0.31)	**<0.001**	-	-	-0.79 (-0.98 to -0.6)	**<0.001**
CBI	2.7 (2.6 to 2.8)	-	1.8 (1.6 to 2.0)	-	1.7 (1.5 to 1.9)	-	-	-0.91 (-1.1 to -0.71)	**<0.001**	-	-	-1.01 (-1.2 to -0.82)	**<0.001**
UC	2.6 (2.5 to 2.6)	-	2.1 (1.9 to 2.4)	-	1.97 (1.8 to 2.2)	-	-	-0.36 (-0.58 to -0.15)	**0.001**	-	-	-0.58 (-0.77 to -0.39)	**<0.001**
Health- related quality of life and symptoms													
Health- related quality of life (ADDQoL-19)													
PTI	-1.7 (-1.8 to -1.6)	-1.0 (-1.3 to -0.8)	-1.2 (-1.5 to -0.97)	-0.85 (-1.1 to -0.61)	-0.76 (-0.99 to -0.53)	0.69 (0.46 to 0.93)	**<0.001**	0.52 (0.27 to 0.76)	**<0.001**	0.89 (0.65 to 1.1)	**<0.001**	0.97 (0.74 to 1.2)	**<0.001**
PFI	-1.7	-1.2	-1.1	-1.3	-0.98	0.43	**<0.001**	0.55	**<0.001**	0.4	**0.001**	0.68	**<0.001**

	(-1.8 to -1.5)	(-1.5 to -1)	(-1.3 to -0.88)	(-1.5 to -1.0)	(-1.2 to -0.75)	(0.21 to 0.66)		(0.32 to 0.78)		(0.17 to 0.63)		(0.45 to 0.9)	
CBI	-1.8 (-1.9 to -1.6)	-1.1 (-1.3 to -0.87)	-0.78 (-1.0 to -0.54)	-1.0 (-1.3 to -0.79)	-0.97 (-1.2 to -0.73)	0.65 (0.42 to 0.88)	**<0.001**	0.98 (0.74 to 1.2)	**<0.001**	0.73 (0.49 to 0.96)	**<0.001**	0.78 (0.54 to 1.0)	**<0.001**
UC	-2.1 (-2.2 to -1.9)	-1.1 (-1.4 to -0.9)	-1.6 (-1.9 to -1.4)	-1.2 (-1.5 to -1)	-0.92 (-1.2 to -0.69)	0.92 (0.7 to 1.2)	**<0.001**	0.44 (0.18 to 0.7)	**0.001**	0.82 (0.59 to 1.1)	**<0.001**	1.1 (0.9 to 1.4)	**<0.001**
Neuropathic symptom (MNSI)													
PTI	3.1 (3 to 3.2)	-	2.8 (2.5 to 3.1)	-	2.4 (2.1 to 2.7)	-	-	-0.29 (-0.61 to 0.02)	0.07	-	-	-0.69 (-0.99 to -0.4)	**<0.001**
PFI	3.3 (3.0 to 3.6)	-	2.8 (2.5 to 3.1)	-	2.9 (2.5 to 3.2)	-	-	-0.55 (-0.86 to -0.23)	**0.001**	-	-	-0.45 (-0.76 to -0.13)	**0.005**
CBI	3.3 (3.1 to 3.4)	-	2.6 (2.3 to 2.9)	-	2.8 (2.5 to 3.1)	-	-	-0.67 (-1.0 to -0.31)	**<0.001**	-	-	-0.46 (-0.78 to -0.13)	**0.006**
UC	3.3 (3.2 to 3.5)	-	3.1 (2.9 to 3.5)	-	2.5 (2.2 to 2.8)	-	-	-0.15 (-0.47 to 0.17)	0.36	-	-	-0.82 (-1.1 to -0.54)	**<0.001**

CBI Is a combined intervention for patients and professionals; M: month; PFI Intervention only for healthcare professionals at primary care; PTI Intervention only for patients and family members; UC usual care or control group.

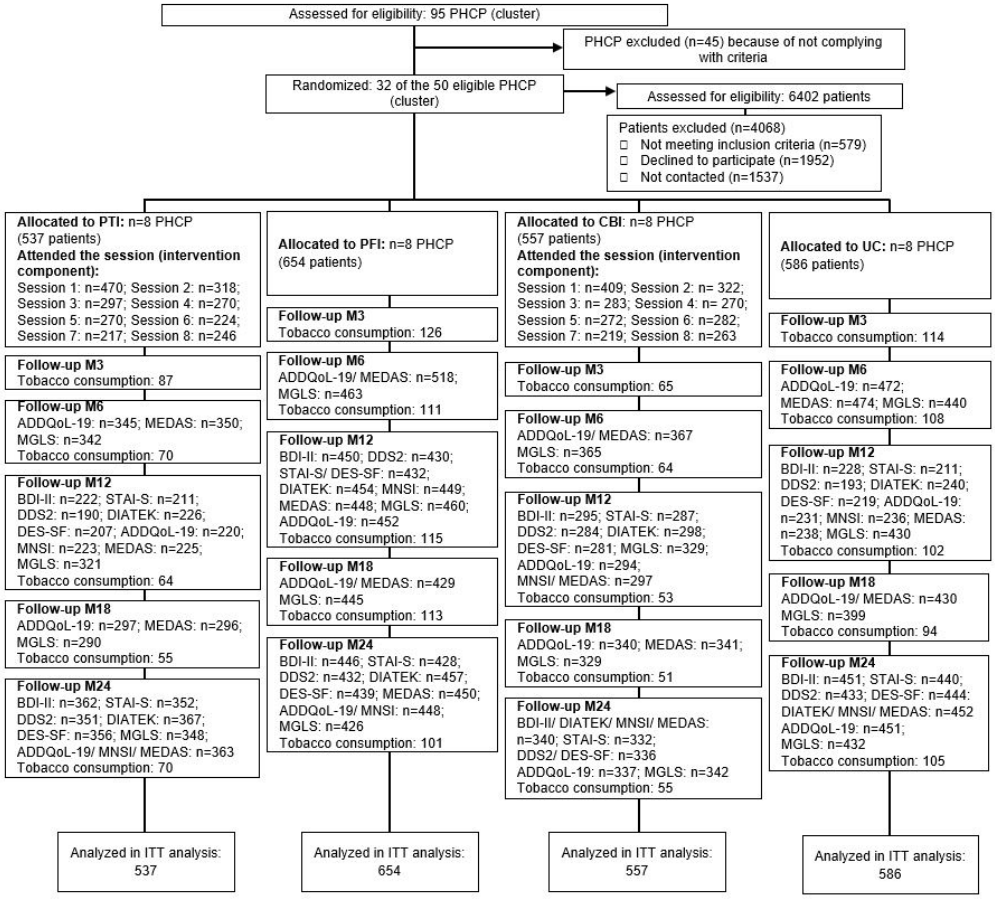
Table 3. Proportion of patients who stop smoking at each follow up compared to the control group

	PTI (n=114)	PFI (n=156)	CBI (n=109)	UC (n=145)	P value global	P value PTI vs UC	P value PFI vs UC	P value CBI vs UC
3 Months	15 (13.2)	14 (9)	17 (15.6)	15 (10.3)	0.54	0.99	0.99	0.99
6 Months	33 (28.9)	12 (7.7)	26 (23.9)	22 (15.2)	0.003	0.11	0.22	0.99
12 Months	38 (33.3)	27 (17.3)	31 (28.4)	21 (14.5)	0.014	0.018	0.99	0.11
18 Months	42 (36.8)	31 (19.9)	41 (37.6)	27 (18.6)	0.004	0.04	0.99	0.03
24 Months	47 (41.2)	37 (23.7)	46 (42.2)	31 (21.4)	0.002	0.012	0.99	0.012

CBI Is a 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 or control group.

Table 4. Patient satisfaction with the intervention received (only those who made use of each intervention component)

	n	mean (95%CI)
Conventional group educational program		
Usability		
Environment generated	592	9.53 (9.46 to 9.60)
Exchange of experiences with participants and educator	588	9.59 (9.53 to 9.66)
Educator's work	587	9.79 (9.74 to 9.83)
Quality of materials	587	9.56 (9.49 to 9.64)
Personal satisfaction		
The sessions helped me get to know my diabetes better	591	9.67 (9.61 to 9.73)
I found the sessions useful	593	9.60 (9.52 to 9.67)
The sessions motivated me to look after my health better	590	9.62 (9.55 to 9.69)
General		
General satisfaction	589	9.70 (9.65 to 9.76)
I would recommend the sessions	588	9.77 (9.72 to 9.82)
Website platform		
Usability		
Access to the content	253	8.30 (8.02 to 8.58)
Usability of the web	251	8.59 (8.33 to 8.85)
Patient outcomes follow up charts	215	8.37 (8.03 to 8.72)
Quality of materials	229	8.81 (8.53 to 9.08)
Access to videos of the sessions	216	8.76 (8.47 to 9.05)
General		
General satisfaction	237	8.56 (8.30 to 8.82)
I would recommend using the website	239	8.81 (8.56 to 9.05)
Semi-automated mobile phone messages		
Usability		
Reading SMS	585	9.51 (9.41 to 9.61)
Usefulness of reminders	576	9.33 (9.22 to 9.45)
Personal satisfaction		
They adapt to my needs	579	9.04 (8.90 to 9.18)
They motivate me to look after myself	576	9.15 (9.02 to 9.28)
I would like to continue receiving them	552	8.80 (8.59 to 9.00)
General		
General satisfaction	572	9.23 (9.09 to 9.37)



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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	See the published protocol
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	7

		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n.a.
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n.a.
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	See the clinical outcomes paper published
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	https://implem

			entationscience.biomedcentral.com/articles/10.1186/s13012-015-0233-1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Patient-reported outcome measures for knowledge transfer and behavior modification interventions in type 2 diabetes. The INDICA study: a multi-arm cluster randomized controlled trial

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TITLE PAGE

Patient-reported outcome measures for knowledge transfer and behavior modification interventions in type 2 diabetes. The INDICA study: a multi-arm cluster randomized controlled trial

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ABSTRACT

Objective

This study assesses the effectiveness of different interventions of knowledge transfer and behavior modification to improve type 2 diabetes mellitus (T2DM) patients' reported outcomes measures (PROMs) in the long-term.

Methods

The INDICA study is an open, community-based pragmatic, multicenter, controlled trial with random allocation by clusters to usual care (UC) or to one of the three interventions. The intervention for patients (PTI) included an educational group program, logs and a web-based platform for monitoring, and automated SMS. The intervention for professionals (PFI) included an educational program, a decision support tool embedded into the electronic clinical record, and periodic feedback about patients' results. A third group received both PTI and PFI (combined intervention, CBI). A total of 2,334 uncomplicated T2DM patients and 211 healthcare professionals were included of 32 Primary Care Centers in Canary Islands (Spain). The measurements included cognitive-attitudinal, behavioral, affective and health related quality of life (HQoL) variables. Mixed models were performed.

Results

Compared to UC at 24 months, the PTI group significantly improved knowledge (P=0.005), self-empowerment (P=0.002), adherence to dietary recommendations (P<0.001), and distress (P=0.01). The PFI group improved at 24 months in distress (P=0.03) and at 12 months there were improvements in depression (P=0.003), anxiety (P=0.05), HQoL (P=0.005), and self-empowerment (P<0.001). The CBI group improved at 24 months in self-empowerment (P=0.008) and adherence to dietary recommendations (P=0.004) and at 12 months in knowledge (P=0.008), depression (P=0.006), anxiety (P=0.003), distress (P=0.01), HQoL (P<0.001), and neuropathic symptoms (P=0.02). Statistically significant improvements were also observed at 24 months in the proportion of patients who quit smoking for PTI and CBI (41.5% in PTI and 42.3% in CBI vs. 21.2% in the UC group).

Conclusions

Assessed interventions to improve PROMs in T2DM attain effectiveness for knowledge, self-empowerment, distress, diet adherence, and tobacco cessation. PTI produced the most lasting benefits.

Trial Registration: ClinicalTrials.gov NCT01657227 (August 6, 2012) https://clinicaltrials.gov/ct2/show/NCT01657227

Keywords: Primary Care, Diabetes & Endocrinology, Quality in health Care, Health Informatics

Strengths and Limitation of this study

- The INDICA study provides randomized evidence on the effectiveness of complex interventions to improve outcomes in type 2 diabetes mellitus patients, with a longer follow up than previous studies.
- All relevant stakeholders in the community are involved in the INDICA study (patients and family caregivers and primary care professionals).
- The trial included a large sample of patients with type 2 diabetes regardless of their baseline HbA1c level, reinforcing the external validity of the results.
- The INDICA interventions with ICT-based components favor applicability and access, in a cost-effective manner, to a growing number of patients.
- A limitation in the use of PROMs is the absence of well-established empirically derived minimum clinically significant differences

INTRODUCTION

Many type 2 diabetes mellitus (T2DM) patients do not achieve the recommended treatment goals for glycemic control[1]. This might be due to inappropriate health care access and/or clinical management. Moreover, psychological and emotional aspects, such as knowledge of the disease or diabetes-related distress, are also important issues for an appropriate self-management and glycemic control[2, 3]. Previous research has shown the value of patient-reported outcome measure (PROMs) to monitor these variables in diabetes[4], which contribute to patient empowerment and patient-centered care[5]. PROMs are generally assessed with standardized, validated questionnaires aimed to measure patients' perception of their health status, perceived level of impairment, disability or health-related quality of life[6].

Interventions that aim to empower people with chronic illnesses and specifically diabetes have included distinct strategies such as educational programs, websites, support phone calls, text messages and other technological resources[4, 7-10], in order to improve patients' diabetes knowledge, self-management, psychological outcomes and health status. However, the results obtained have been mixed, with a considerable number of studies showing no effect of the interventions[8-11]. The INDICA study is a pragmatic, cluster-randomized controlled trial with two years follow-up that assesses the effectiveness and cost-effectiveness of multicomponent interventions for knowledge transfer and behavior modification of T2DM patients, their families, and healthcare professionals (physicians and nurses) in a large number of Primary Care Health Practices (PHCP). These interventions combine conventional group educational and training activities with different information and communication technology (ICT)-based interventions to guide the decisions of the main actors involved in the management of T2DM[12]. The intervention for patients (PTI) included an educational group program led by trained nurses, consisting of eight face-to-face sessions (one every three months over two years); continuous self-monitoring by means of logs and a web-based platform; and tailored automated SMS to provide continuous support to patients and to reinforce self-care and lifestyle changes. The intervention for professionals (PFI) included an educational program to update their diabetes knowledge, a decision support tool embedded into the electronic clinical record with recommendations based on best

available scientific knowledge, adapted to the specific needs of every patient, and periodic feedback about patients' results.

The results on the effectiveness of these interventions on clinical outcomes can be seen in Ramallo-Fariña et al.[13], and the cost-effectiveness evaluation can be reviewed in García-Pérez et al.[14]. The aim of this article is to report the effect of the INDICA interventions on a set of PROMs assessed in the trial: cognitive-attitudinal (knowledge, empowerment), behavioral (adherence to the dietary recommendation, medication and tobacco use), affective (anxiety, depression, distress) and health-related quality of life dimensions. These outcomes are commonly targeted for most diabetes interventions because of their association with critical, longer-term outcomes, such as functional capacity[15], complications[16-18], mortality[19], healthcare costs[20], and quality of life[21].

METHODS

Trial design

The INDICA study is an open, community-based pragmatic, multicenter, controlled trial with random allocation by clusters to usual care or one of three multicomponent interventions of knowledge transfer and behavior modification. One intervention was aimed at patient and family members (PTI); another intervention was aimed at primary care healthcare professionals (physicians and nurses) (PFI) and the third intervention combined the other two (CBI). In the control group, both patients/families and physicians/nurses received the usual activities provided by the PHCP. The full study protocol has been published before[12].

Study Participants

The INDICA study included adults aged 18 to 65 years who had been diagnosed with T2DM at least one year before, did not have any diabetes-related complications, and used a mobile phone regularly[12]. Family Care Units (FCU) in each PCHP, comprised of a family physician and a nurse, were the recruitment unit. All PHCPs included had to have at least eight FCUs and the availability of appropriate facilities to provide educational group sessions. FCUs planning or awaiting placement changes among PHCP in the first six months after the project began were excluded.

Setting and recruitment

PHCPs were randomly selected in the islands of Tenerife, Gran Canaria, Lanzarote, and La Palma (Canary Islands, Spain). Moreover, FCUs were randomly selected from all consenting FCUs at each PHCP. The electronic clinical records (ECR) of all potentially eligible patients in selected FCUs were screened to verify inclusion and exclusion criteria.

Patient and public involvement

Patients were actively involved in the design of the trial. Two associations of patients with T2DM in the Canary Island 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 the elaboration 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 objective of another publication. Finally, we established a commitment with patients and healthcare professionals to share the results with them in an easy-to-understand way.

Random assignment

Randomization was applied at different levels. First, three different strata were created according to the geographic areas in the more populated islands (Tenerife and Gran Canaria). Second, four PHCP (clusters) were randomly allocated to every geographic stratum and block permutation was used to assign PHCPs to the study arms; the PHCP being the sampling unit. La Palma and Lanzarote (less populated islands) were geographically divided into four zones with only one eligible PHCP available in each zone randomly assigned to one of the study arms. In every island, all arms were equally distributed. Six FCUs were randomly selected, from all those consenting to participate in each PHCP. From all patients fulfilling inclusion criteria and consenting to participate in each PHCP, 15 were randomly selected per FCU. Exceptionally, more than six FCUs or more than 15 patients per FCU were selected, to try to recruit 90 patients in every PHCP. However, it was not posible to attain this objective of 90 patients in all PHCP as there were insufficient patients in all FCU selected that complied with the inclusion and exclusion criteria.

FCU and patient randomization were performed by simple generation from a list of random numbers.

Interventions

Patient interventions

Patients recruited to the PTI and CBI groups received a complex intervention of knowledge transfer and behavior modification, informed by conceptual frameworks of behavioral change[16]. The intervention combined: A) an eight-session, conventional, group educational program given by a nurse specialized in diabetes; B) monitoring of physical activity, diet, drug adherence, mood, blood pressure, and blood glucose readings by daily use of paper workbooks, complemented by weekly access to a website platform

to upload paper workbook data; and C) continuous, personalized feedback by semi-automated mobile phone messages (SMS), modified according to the website information.

Interventions for primary care professionals

Primary care professionals recruited to the PFI and CBI groups received a complex intervention of knowledge transfer and decision support, informed by the determinants of behavior change suggested by Michie et al.[22] for its design and implementation. The intervention included: A) an educational and interactive group program of two sessions to update clinical management information and promote patient-centered care; B) an automated decision aid tool, based on a CPG for T2DM embedded into the electronic clinical record; and C) monthly computerized graphic feedback, which displayed a set of processes and outcome indicators for all T2DM patients of the corresponding FCU compared to other FCU in their setting and the FCU with the best results. Both interventions were applied during the two years follow-up.

Duration of fieldwork

Fieldwork took place between February 2013 and October 2016. The first year and the following two years were devoted to recruitment of patients and healthcare providers, and intervention and follow-up, respectively. As interventions were maintained over time, intervention and follow-up periods overlapped.

Outcomes

Cognitive-attitudinal outcomes

To assess potential changes in patient knowledge about T2DM and its self-management, we developed a specific instrument created in the context of this project, named DIATEK, which consisted of 30 questions. Each item has four response options and only one correct answer. Items examined risk factors for disease development and deterioration, objective values for biochemical parameters; recommendations on nutrition, physical activity, drug use and self-management. The total score, obtained by adding all correct responses, and ranging from 0 to 30, was later rescaled from 0 to 10.

The Diabetes Empowerment Scale-Short Form (DES-SF)[23] is a validated questionnaire designed to evaluate psychosocial self-efficacy in diabetes. DES-SF is the short form of the original DES, which includes eight items (need for change, developing a plan, overcoming barriers, asking for support, supporting oneself, coping with emotion, motivating oneself, and making diabetes care choices appropriate for one's priorities and circumstances) with responses on a five-point Likert scale and an overall range from eight to 40, according to increasing patient empowerment.

Behavioral outcomes

The Mediterranean Diet Adherence Screener (MEDAS)[24] is a validated questionnaire to assess dietary recommendation adherence, which consists of 14 targets for food consumption, rated with one point for each target attained. According to the final score, patients are classified as having low (0-6 points), moderate (7-10) or high adherence (11-14 points) to the Mediterranean diet.

The Morisky Medication Adherence Scale (MGLS)[25] assesses drug-treatment adherence, by means of a validated four-item self-report instrument and a final score ranging from 0 to 4. Patients are considered adherent, only if they obtain four points.

Smoking status was monitored from baseline and during follow-up, to check for potential cessation throughout the study.

Affective outcomes

The State Trait Anxiety Inventory (STAI-S)[26] is a validated patient-reporting questionnaire that includes two non-dependent scales; the applied state-anxiety scale (STAI State) and the trait-anxiety scale (STAI Trait). It assesses transient emotional state or condition as characterized by subjective feelings of tension and apprehension that can fluctuate in time and intensity. The STAI-S includes 20 items, with each item scored on a four-point Likert scale. Anxiety is defined by a cut-off point ≥ 30.

The Beck Depression Inventory II (BDI-II)[27] consists of 21 items scored on a four-point scale from 0 ("not at all") to 3 ("most of the time"). The items assess depression symptoms in the last two weeks. All item scores are added to a maximum score of 63. A BDI-II score of ≥ 14 indicates mild depressive symptoms.

The Diabetes Distress Scale (DDS2)[28] is a validated two-item diabetes distress-screening instrument that asks respondents to rate, on a six-point scale, the degree of distress caused by the two following items: (1) feeling overwhelmed by the demands of living with diabetes and (2) feeling that I am often failing with my diabetes regimen. High Diabetes distress can be identified by an average score ≥ 3 or more, low distress by scores under two, and moderate distress by the scores in between.

Health- related quality of life and symptoms

The Audit of Diabetes-Dependent Quality of life (ADDQoL-19)[29] is a specific HRQoL questionnaire for diabetes. It assesses 19 domains, each with its impact and importance index to provide an integrated score for each domain. The sum of the score in each domain forms the global score (range: -9 to 3). The lower the score, the worse the quality of life.

The Michigan Neuropathy Screening Instrument (MNSI)[30] is an instrument that measures the incidence of distal diabetic peripheral polyneuropathy. It is composed of 15 self-administered items, in which the abnormal responses are added. A score of seven or more is considered abnormal.

Satisfaction

An ad-hoc self-completed questionnaire (INDICA-SATP) was developed to measure satisfaction with each component of the interventions in PTI and CBI groups. It was measured in the 24-month follow-up in patients who, having attended the group educational program, also used the web platform or received the semi-automated mobile phone messages. Satisfaction with each component was valued from 0 to 10 points, with 10 reflecting maximum satisfaction.

All information, including demographic data, overall and personal health history, diabetes health status, current medications, smoking status, and risk factors for complications, was obtained in a face to face interview at baseline and at 3, 6, 12, 18 and 24 months of follow-up. Similarly, all self-administered questionnaires (ADDQoL-19, BDI-II, DES-SF, DDS2, DIATEK, MEDAS, STAI-S, MGLS and MNSI), were distributed and collected at baseline, and at 12 and 24 months follow-up. ADDQol-19, MEDAS and MGLS were also applied at 6 and 18 months.

Two other questionnaires were included in the trial registry and the published protocol[12], the *International Physical Activity Questionnaire* (IPAQ) and a scale

developed for this project to assess patients' attitudinal changes regarding lifestyles (INDICA-LSQ). However, the data quality checking identified many inconsistent or meaningless responses to these questionnaires, which indicates that patients did not correctly understand the instructions. Therefore, we decided to exclude them from the analyses.

Statistical Analysis

Multilevel mixed models including the baseline value of dependent variables and time elapsed since diagnosis (in years) as covariates were implemented for all PROMs. First level variables are those corresponding to each measurement along follow-up (repeated time measurements). The second level includes patient variables (the baseline value of dependent variables and time elapsed since diagnosis) and third level variables correspond to PHCP in which patients are grouped (the variable arm to which PHCP was assigned is included in this level). The effect that identifies the intervention arm has been considered fixed for the different PHCP, whilst the intercept has been considered random. The model also included an interaction term between arm and month, which allows for differences in the intervention effect between follow-up assessments[31]. The intraclass correlation coefficient (ICC) was obtained for each model for the PHCP and by patient according to their PHCP. The adjusted estimated mean was calculated for each follow up moment compared to baseline; and its statistical significance was calculated by means of the model already set out. The relative improvement for each follow-up was obtained as the ratio between the adjusted difference in mean between the intervention and control group and the mean of the control group.

A logistic regression model was implemented to compare the proportion of patients who quit smoking at each follow-up, by intervention arm. Only basal smokers were included in the analysis.

Analysis was performed on an intention-to-treat basis, that is, participants were analyzed in the group to which they were randomized. Missed values were treated by means of multiple imputation procedures[32], with results based on 100 imputed datasets (missed values from all follow up visits were imputed). Analysis under multiple imputation is valid for randomly missed data[33]. We compared the results of imputed and non-imputed data. All the analyses were conducted using STATA version 15.0[34]. Differences were considered statistically significant if $P<0.05$.

Ethical approval and consent to participate

All participants provided written informed consent. The scientific and ethics committees of both the University Hospital of Canarias (ID: 2012_44) and the University Hospital Nuestra Señora de la Candelaria (ID: EPA-07/10) approved the study protocol. The study was performed in accordance with Good Clinical Practice standards, prevailing local regulatory requirements, and Declaration of Helsinki recommendations.

RESULTS

Study Participants

A total of 2334 patients and 211 healthcare professionals were included. Figure 1 shows the flowchart with cluster randomization of patients for each intervention, attendance at educational/training sessions of patients and professionals and the number of PROMs questionnaires received for each follow-up assessment. The patients´ baseline characteristic according to the intervention assignment can be seen in Ramallo-Fariña et al.[13]. Mean age of the whole population was 55.7 ± 7.1 years, with 51.9% women. Mean baseline HbA1c was 7.3%/56 mmol/mol. From baseline, 49.4% of patients started with HbA1c levels within the accepted therapeutic goal (≤7%/53 mmol/mol). There were no statistically significant differences among groups in terms of their baseline characteristics.

Intention-to-treat results, reported below, were very similar to those obtained with non-imputed data. Only three discrepancies were observed that will be discussed in the corresponding outcome section. Results at all time points are shown in Tables 1 (inter-group differences), 2 and 3 (intra-group changes).

Cognitive-attitudinal outcomes

Table 1 shows that the level of knowledge about diabetes is significantly higher for PTI (P=0.007) and CBI (P=0.008), compared with UC, at 12 months; and for PTI (P=0.005) at 24 months.

Patient empowerment was significantly higher for PFI and CBI groups, compared to UC at 12 months (P<0.001 for both comparisons). Analysis of non-imputed data led to a P-value of 0.05 for the difference between PTI and UC, favoring the former, at this time point. At 24 months, PTI and CBI also attained significantly higher scores than UC (P=0.002 and P=0.008, respectively); while differences with PFI are marginally significant.

Behavioral outcomes

Table 1 shows that the PTI group is significantly more adherent to the diet recommendations, compared to UC, after 12 months of follow-up. There is a difference of 0.87 (P<0.001) at 24 months. Adherence improves for CBI from 18 months, compared

to UC, with differences of 0.7 (P=0.004) at 24 months. Adherence levels remain moderate for all patient groups throughout follow-up (see Table 2).

No differences were found in medication adherence, compared to UC (Table 1). However, average levels of medication adherence were significantly improved in all four groups, despite the high baseline levels (>3) (see Table 2).

Table 4 shows the reduction in the proportion of smokers who quit smoking during follow up in PTI (12 months), and CBI (18 months), compared to UC. With non-imputed data the reduction was statistically significant from month 6 for PTI (P=0.023) and month 12 for CBI (P=0.025). The percentage of patients who quit smoking at 24 months was 41.5% for PTI (P=0.012) and 42.3% (P=0.012) for CBI, versus 21.2% for UC group. There were no statistically significant differences between groups in the baseline percentage of smokers (P=0.99).

Affective outcomes

Compared to UC, both PFI and CBI show statistically significant differences at 12 months for depression (P=0.003 and P=0.006, respectively), and anxiety (P=0.05 and P=0.003, respectively) (Table 1). These differences disappear at 24 months because all groups of patients improved (Table 2).

The diabetes distress score improved significantly compared to the UC group for CBI at 12 months (P=0.01) and for PTI and PFI at 24 months (P=0.01 and P=0.03, respectively). The score remained marginally significant for CBI (Table 1). At baseline, all patient groups showed moderate distress, which decreased to a low level from 12 months, except for the UC group, which did so at 24 months (Table 2).

Health-related quality of life and symptoms

HRQoL significantly improved for all intervention groups, at 12 months, compared to UC; a difference only maintained for PTI at 18 months (P=0.02) (Table 1).

Neuropathic symptom scores were significantly lower for the CBI group at 12 months (P=0.02) compared to the UC group (the analysis of non-imputed data led to a non-significant result, P=0.12). This difference disappeared at 24 months (Table 1). Mean baseline scores for all groups were under 4, considerably below the cut-off point of 7 for abnormal classification (Table 3).

Satisfaction

Table 5 shows the patients' satisfaction with the intervention received. While average scores were higher than 9/10, in all dimensions, for the group educational sessions, satisfaction with the web platform and SMS obtained scores above 8.

Table 6 shows a summary of the results at 12 and 24 months.

For all PROMs, ICC values were low in every PHCP. Variance homogeneity was verified and thus reflected a very small effect associated with PHCP for interventions and control groups (similar results among PHCP in every arm). The ICC at the patient level was broad, accounting for considerable variations among individuals.

DISCUSSION

This article assesses the effect of interventions implemented by the INDICA study to improve T2DM outcomes on several health measures self-perceived by patients in the cognitive-attitudinal (knowledge, empowerment), behavioral (i.e., adherence to the dietary recommendations, medication and tobacco use), affective (anxiety, depression, distress) and health-related quality of life dimensions. The INDICA study is a pragmatic cluster-randomized study with two years follow up that assesses the effectiveness of multicomponent interventions for knowledge transfer and behavior modification of patients, families, and healthcare professionals (physicians and nurses) at the primary care level.

At one-year follow-up, the combined intervention lead to obtaining significant results in all outcomes except diet and medication adherence. Relative improvements compared to usual care ranged between 9.6% (knowledge) and 52.2% (HRQoL), with intermediate values for anxiety (26.1%) and depression (28.7%). Significant improvements in HRQoL were also obtained for the PTI and PFI groups, although of less intensity (24.8% and 31.7%, respectively). However, they showed different results in the remaining variables: the PTI group improved in terms of knowledge and behavioral outcomes (i.e., diet and smoking), while the PFI improved in regard to empowerment and depression, but obtained a significantly worse result than the UC group for diet adherence.

After two years of follow-up, there were no significant differences in HRQoL, anxiety or depression, mainly due to the improvement experienced by the UC group in these variables. The PTI group obtained the best overall results, with significant improvements in the cognitive (i.e., knowledge, empowerment), affective (i.e., diabetes distress) and behavioral (i.e., diet and tobacco) variables. The same significant results were obtained for the combined intervention, except for knowledge and distress. Finally, the PFI group outperformed usual care only for distress, and showed a significantly worse result in regard to knowledge. There were no statistically significant differences in medication adherence during all the follow-up, although a ceiling effect could have occurred, since all groups showed high scores at baseline.

Therefore, the best results were observed in both groups including patients (PTI and CBI), similar to the findings observed on clinical outcomes[13]. This is not

surprising, given the straightforward and continuous application of these patient interventions, and the high reported satisfaction levels with all the intervention components (educational sessions, web resources and SMS). Previous studies that combined education and training with support phone calls, assessing interventions aimed at empowering diabetes patients to improve self-care and outcomes, showed inconsistent results between clinical variables and PROMS[8, 9]. The use of one-way messages such as those used in INDICA, appears to significantly and consistently improve HbA1c levels, although with a small-to-moderate effect-size (-0.38%, 95%CI: -0.53; -0.23)[10]. In addition, continuous advances in smart mobile technology provide new possibilities for diabetes self-management, despite the fact that evidence on the effectiveness of these new functionalities remains scarce and uncertain[11, 35].

Reduction in the number of smokers in interventions applied directly to patients (PTI and CBI) in regard to UC that remain significant at 24 months with percentages of approximately 42% which is 2.5 times the result obtained by the most extended pharmacologic intervention (replacement nicotine therapy). This is according to a meta-analysis published recently[36] which puts this reduction at 16.9% of the intervened group compared to 10.4% of the control group in studies with follow up varying from six to 24 months.

The intervention effect on professionals raises questions. At one year of follow-up, the PFI and CBI groups obtained improvements in psychological variables not affected by the intervention targeted exclusively at patients (PTI) (i.e., empowerment, anxiety, depression). These findings could be interpreted as the lasting result of better shared decision-making/patient-centered care by professionals trained in this care model. However, the PTI group was the only group to show significant improvements in behavioral variables (diet adherence and tobacco consumption); while PFI obtained significantly worse results for diet adherence from the sixth month, and CBI did not show significant benefits for these two outcomes until 18 months. These negative findings from groups containing professionals are repeated after two years in the case of knowledge, a variable in which the CBI group did not obtain significant differences. This interpretation should be considered cautiously given the analysis limitations, since the differences between intervention groups have not been statistically contrasted. As a recent Cochrane review[37] reported, current evidence on the effect of interventions to promote shared decision making by healthcare professionals shows benefits when decision making is

assessed by external observers but not by patient's assessment; furthermore, no significant effects were observed in most patient-reported outcomes[37]. Given the paucity and limited quality of available studies, more focused research is needed to draw solid conclusions about the effect of interventions aimed at professionals, and the mechanisms by which these interventions translate into psychological, behavioral and health changes of patients.

The assessment of clinical outcome measures in the INDICA study[13] for the total sample recruited regardless of Hb1Ac levels (only 50.6% of all participants had baseline HbA1c concentrations >7%, with a mean of 7.3%), showed an early and significant but temporary reduction in HbA1c for the PTI group, compared to UC, from 3 to 6 months. Even so, more than 30% of the intervened patients (PTI and CBI) attained statistically and clinically relevant reductions in HbA1c (>0.4%); significantly higher than UC at 12 and 18 months.

In the group of patients with baseline HbA1c greater than 7% (uncontrolled patients), the magnitude of the intervention effect on clinical outcomes was greater, especially in the PTI group compared to the UC group, with significant differences up to 18 months, and a significant area under the curve at 24 months for PTI compared to UC[13]. These results are supported by other studies that report greater intervention effects in patients with higher HbA1c levels[38, 39]. Longer-term reductions in blood pressure were also found in the two groups in which professionals were intervened, with smaller effects in the remaining clinical measures (lipid profile, body mass index, serum creatinine and glomerular filtration rate). Some of these results are more related to changes in medication than lifestyles. From a cost-effectiveness perspective, small differences were observed between groups after two years follow up. The PTI was more effective and less costly than CBI and PFI, in patients with HbA1c>7%[14]. This prompted the conclusion that interventions focused on patients with the highest needs would limit the impact on the health care sector budget.

This study has several limitations. The high number of instruments and measurement times increase the risk of type 1 error, which explains the decision not to compare intervention groups with each other. Moreover, the use of PROMs makes it necessary to know the minimum clinically significant differences of every instrument used. This difference, however, has not been investigated for most of them, and there is currently no consensus on the appropriate method (distribution or anchor-based) and/or statistics (e.g., absolute versus relative reduction)[40]. Furthermore, the use of PROMs implies by

definition an unblind assessment of results, which is added to the impossibility of blinding the participants regarding the intervention. Finally, the INDICA study was not designed to test the efficacy of every single component of the interventions assessed (e.g., text messages vs. patient education vs web content). Despite these limitations, the INDICA study presents some distinctive characteristics from other published studies that assess the impact of interventions promoting empowerment, self-management and behavior modification to patients and professionals: 1) a robust design (pragmatic cluster-randomized controlled trial with a factorial design for intervention arms) with a long follow-up (two years); 2) incorporation of the different actors involved in disease management (patients and family caregivers and primary care professionals; 3) greater external validity by including patients regardless of their baseline HbA1c levels; 4) incorporation of ICT-based components to the intervention that favors applicability and access, in a cost-effective manner, to a growing number of patients; and 5) inclusion of a large sample size with 2334 patients and 211 healthcare professionals.

In conclusion, all the interventions assessed improved patients HRQoL at one year of follow-up, with differences according to the intervention in the remaining PROMs examined. The intervention targeted exclusively at patients (PTI) significantly improved knowledge, empowerment, distress, dietary recommendation adherence and tobacco cessation, up to two years of follow-up. Although the clinical relevance of these effects is uncertain, except in the case of smoking cessation, these results are promising since they reflect improvements in all personal domains assessed (cognitive, attitudinal, affective, behavioral), which highlight the importance of behavioral factors to attain good health outcomes. The intervention on professionals improved affective variables at one year of follow-up, but showed virtually no effects at two years together with a negative effect on diet adherence and no effect on tobacco consumption, which emphasizes the need for more focused evaluative research on this type of intervention. For both target groups (patients and professionals), the use of ICT can be a major help to improve care access and continuity; as well as effectiveness and cost-effectiveness in T2DM self-management.

STATEMENTS

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Conflicts of interest/Competing interests

The authors declare that they have no competing interest.

Competing interests

The authors declare that they have no competing interest.

Availability of data and material

The datasets generated and/or analyzed 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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Author Contributions

YRF, LGP, LRR, AMW, MRR and PSA contributed to the study design. SKG, GM, CGM, CDA and MRR developed the contents and gave the educational sessions to patients. Also, SKG, GM, CGM, CDA and MRR recruited participants and collected data. YRF, MAGB and HGP contributed to the statistical analyses. YRF, ARS, LGP, AMW and PSA were part of the writing committee of the manuscript. All authors reviewed, commented on, and approved the final manuscript.

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Table 1. Adjusted difference in the mean of each group compared to the control group

	6 Months	*P* value	12 Months	*P* value	18 Months	*P* value	24 Months	*P* value
Cognitive-attitudinal outcomes								
Knowledge (DIATEK): F=47.3 *P*<0.001; ICC PHCP =0.06; ICC subject|PHCP=0.35								
PTI	-	-	0.64 (0.17 to 1.11)	**0.007**	-	-	0.65 (0.2 to 1.11)	**0.005**
PFI	-	-	-0.38 (-0.85 to 0.09)	0.11	-	-	-0.6 (-1.06 to -0.14)	**0.01**
CBI	-	-	0.63 (0.16 to 1.11)	**0.008**	-	-	0.34 (-0.12 to 0.8)	0.15
Empowerment (DES-SF): F=17.3 *P*<0.001; ICC PHCP =0.08; ICC; subject|PHCP=0.08								
PTI	-	-	1.58 (-0.59 to 3.75)	0.15	-	-	3.04 (1.08 to 4.99)	**0.002**
PFI	-	-	3.95 (1.9 to 6)	**<0.001**	-	-	1.84 (-0.11 to 3.79)	0.07
CBI	-	-	3.97 (1.9 to 6.04)	**<0.001**	-	-	2.63 (0.68 to 4.58)	**0.008**
Behavioral outcomes								
Adherence dietary recommendations (MEDAS): F=25.0 *P*<0.001; ICC PHCP = 0.03; ICC subject|PHCP=0.20								
PTI	0.22 (-0.25 to 0.69)	0.36	0.71 (0.17 to 1.24)	**0.01**	0.93 (0.46 to 1.41)	**<0.001**	0.87 (0.4 to 1.35)	**<0.001**
PFI	-0.58 (-1.04 to -0.11)	**0.01**	-0.96 (-1.46 to -0.47)	**<0.001**	0.17 (-0.31 to 0.64)	0.49	0.03 (-0.44 to 0.5)	0.90
CBI	0.44 (-0.03 to 0.91)	0.06	0.06 (-0.47 to 0.58)	0.83	0.88 (0.4 to 1.35)	**<0.001**	0.7 (0.22 to 1.17)	**0.004**
Medication adherence (MGLS): F=14.4 *P*<0.001; ICC PHCP =0.04; ICC subject|PHCP=0.20								
PTI	0.09 (-0.11 to 0.3)	0.37	0.09 (-0.12 to 0.3)	0.39	0.13 (-0.09 to 0.34)	0.24	0.16 (-0.04 to 0.36)	0.12
PFI	0.01 (-0.2 to 0.22)	0.90	-0.13 (-0.34 to 0.08)	0.24	-0.06 (-0.26 to 0.15)	0.58	0.09 (-0.11 to 0.3)	0.39
CBI	0.03 (-0.18 to 0.24)	0.77	-0.19 (-0.41 to 0.03)	0.08	0 (-0.21 to 0.21)	0.98	-0.1 (-0.31 to 0.11)	0.36
Affective outcomes								
Depression (BDI-II): F=53.6 *P*<0.001; ICC PHCP = 0.05; ICC subject|PHCP=0.34								
PTI	-	-	-1.91 (-3.99 to 0.17)	0.07	-	-	-0.76 (-2.68 to 1.16)	0.44
PFI	-	-	-2.99 (-4.99 to -1)	**0.003**	-	-	0.37 (-1.56 to 2.3)	0.71
CBI	-	-	-3 (-5.13 to -0.87)	**0.006**	-	-	0.23 (-1.73 to 2.19)	0.82
Anxiety (STAI-S): F=36.0 *P*<0.001; ICC PHCP =0.07 ICC; subject|PHCP=0.32								
PTI	-	-	-2.25 (-5.75 to 1.25)	0.21	-	-	-2.18 (-5.54 to 1.18)	0.20
PFI	-	-	-3.47 (-6.95 to 0.02)	**0.05**	-	-	-0.39 (-3.78 to 2.99)	0.82
CBI	-	-	-5.4 (-8.99 to -1.81)	**0.003**	-	-	-0.50 (-3.9 to 2.9)	0.77
Distress (DDS2): F=14.9 *P*<0.001; ICC PHCP =.05 ICC; subject|PHCP=0.25								
PTI	-	-	-0.23 (-0.53 to 0.07)	0.13	-	-	-0.34 (-0.62 to -0.07)	**0.01**
PFI	-	-	-0.24 (-0.53 to 0.05)	0.10	-	-	-0.31 (-0.58 to -0.04)	**0.03**

CBI	-	-	-0.36 (-0.65 to -0.07)	**0.01**	-	-	-0.24 (-0.51 to 0.03)	0.08
Health-related quality of life and symptoms								
Health-related quality of life (ADDQoL-19): F=25.3 *P*<0.001; ICC PHCP = 0.04; ICC subject|PHCP=0.34								
PTI	0.09 (-0.24 to 0.42)	0.60	0.40 (0.04 to 0.76)	**0.03**	0.39 (0.05 to 0.72)	**0.02**	0.16 (-0.17 to 0.48)	0.34
PFI	-0.09 (-0.42 to 0.23)	0.56	0.51 (0.16 to 0.86)	**0.005**	-0.02 (-0.35 to 0.31)	0.89	-0.06 (-0.38 to 0.26)	0.71
CBI	0.03 (-0.3 to 0.35)	0.88	0.84 (0.49 to 1.18)	**<0.001**	0.21 (-0.13 to 0.54)	0.23	-0.05 (-0.38 to 0.28)	0.77
Neuropathic symptom (MNSI): F=59.8 *P*<0.001; ICC PHCP =0.02 ICC; subject|PHCP=0.32								
PTI	-	-	-0.35 (-0.8 to 0.09)	0.12	-	-	-0.08 (-0.49 to 0.33)	0.70
PFI	-	-	-0.42 (-0.87 to 0.03)	0.07	-	-	0.35 (-0.07 to 0.78)	0.11
CBI	-	-	-0.57 (-1.04 to -0.1)	**0.02**	-	-	0.31 (-0.12 to 0.74)	0.16

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.

CBI, is a combined intervention for patients and professionals; ICC, Intraclass correlation coefficient; PFI, Intervention only for healthcare professionals at primary care; PTI, Intervention only for patients and family members; PHCP, Primary Care Health Practices.

Table 2. Adjusted means for each group and intragroup differences compared with the baseline measurement (cognitive-attitudinal, behavioral and affective outcomes)

	Adjusted means in each group (95%CI)					Difference in intragroup of adjusted means compared to baseline (95%CI)					
	Baseline	6 Months	12 Months	18 Months	24 Months	B-6M	*P* value	B-12M	*P* value	B-18M	*P* value	B-24M	*P* value
Cognitive-attitudinal outcomes													
Knowledge (DIATEK)													
PTI	6.4 (6.3 to 6.5)	-	7.2 (6.9 to 7.5)	-	7.4 (7.1 to 7.7)	-	-	0.82 (0.48 to 1.2)	**<0.001**	-	-	1.03 (0.71 to 1.36)	**<0.001**
PFI	6.5 (6.3 to 6.7)	-	6.2 (5.8 to 6.5)	-	6.1 (5.8 to 6.5)	-	-	-0.31 (-0.63 to 0.02)	0.07	-	-	-0.32 (-0.64 to 0.01)	0.058
CBI	6.5 (6.4 to 6.6)	-	7.2 (6.8 to 7.5)	-	7.1 (6.8 to 7.4)	-	-	0.7 (0.36 to 1.03)	**<0.001**	-	-	0.6 (0.27 to 0.94)	**<0.001**
UC	6.2 (6.1 to 6.3)	-	6.5 (6.2 to 6.9)	-	6.7 (6.4 to 7.1)	-	-	0.3 (-0.04 to 0.63)	**0.08**	-	-	0.5 (0.18 to 0.82)	**0.002**
Empowerment (DES-SF)													
PTI	26.4 (25.8 to 27.0)	-	29.5 (27.9 to 31.0)	-	33.5 (32.1 to 34.9)	-	-	3.08 (1.6 to 4.6)	**<0.001**	-	-	7.1 (5.7 to 8.5)	**<0.001**
PFI	26.3 (25.2 to 27.4)	-	31.9 (30.5 to 33.2)	-	32.3 (30.9 to 33.7)	-	-	5.6 (4.2 to 6.9)	**<0.001**	-	-	6.02 (4.7 to 7.4)	**<0.001**
CBI	27.6 (27.0 to 28.3)	-	31.9 (30.4 to 33.3)	-	33.1 (31.7 to 34.5)	-	-	4.3 (2.8 to 5.7)	**<0.001**	-	-	5.7 (4.1 to 6.9)	**<0.001**
UC	26.1 (25.5 to 26.7)	-	27.9 (26.4 to 29.4)	-	30.5 (29.1 to 31.8)	-	-	1.8 (0.26 to 3.3)	**0.02**	-	-	4.3 (2.9 to 5.7)	**<0.001**
Behavioral outcomes													
Adherence dietary recommendations (MEDAS)													
PTI	8 (7.8 to 8.1)	7.6 (7.2 to 7.9)	9.1 (8.7 to 9.4)	8.3 (7.9 to 8.6)	8.7 (8.3 to 9)	-0.43 (-0.77 to -0.09)	**0.01**	1.1 (0.71 to 1.5)	**<0.001**	0.27 (-0.07 to 0.62)	0.12	0.68 (0.34 to 1.02)	**<0.001**
PFI	8.2 (7.9 to 8.5)	6.8 (6.4 to 7.1)	7.4 (7.1 to 7.7)	7.5 (7.1 to 7.8)	7.8 (7.5 to 8.2)	-1.5 (-1.8 to -1.1)	**<0.001**	-0.82 (-1.2 to -0.49)	**<0.001**	-0.82 (-1.2 to -0.49)	**<0.001**	-0.4 (-0.74 to -0.07)	**0.018**
CBI	8.3 (8.1 to 8.5)	7.8 (7.4 to 8.1)	8.4 (8.0 to 8.8)	8.2 (7.9 to 8.5)	8.5 (8.1 to 8.8)	-0.51 (-0.84 to -0.17)	**0.003**	0.13 (-0.24 to 0.51)	0.49	-0.08 (-0.43 to 0.26)	0.63	0.2 (-0.14 to 0.54)	0.26
UC	8.02 (7.9 to 8.2)	7.3 (7.0 to 7.7)	8.4 (8.0 to 8.7)	7.3 (7.0 to 7.7)	7.8 (7.5 to 8.1)	-0.69 (-1.0 to -0.36)	**<0.001**	0.34 (-0.02 to 0.7)	0.07	-0.7 (-1.0 to -0.37)	**<0.001**	-0.24 (-0.57 to 0.1)	0.16
Medication adherence (MGLS)													
PTI	3.1	3.5	3.6	3.6	3.6	0.41	**<0.001**	0.45	**<0.001**	0.5	**<0.001**	0.48	**<0.001**

	(3.1 to 3.2)	(3.4 to 3.7)	(3.4 to 3.7)	(3.5 to 3.8)	(3.5 to 3.7)	(0.26 to 0.56)		(0.29 to 0.6)		(0.35 to 0.65)		(0.33 to 0.62)	
PFI	3.3 (3.2 to 3.3)	3.5 (3.3 to 3.6)	3.3 (3.2 to 3.5)	3.4 (3.3 to 3.6)	3.5 (3.4 to 3.7)	0.18 (0.03 to 0.33)	**0.02**	0.08 (-0.07 to 0.22)	0.32	0.16 (0.02 to 0.31)	**0.026**	0.25 (0.11 to 0.4)	**0.001**
CBI	3.3 (3.3 to 3.3)	3.5 (3.3 to 3.6)	3.3 (3.1 to 3.4)	3.5 (3.3 to 3.6)	3.3 (3.2 to 3.5)	0.17 (0.02 to 0.32)	**0.02**	-0.01 (-0.18 to 0.15)	0.87	0.2 (0.05 to 0.35)	**0.01**	0.04 (-0.11 to 0.2)	0.60
UC	3.2 (3.1 to 3.3)	3.4 (3.3 to 3.6)	3.5 (3.3 to 3.6)	3.5 (3.3 to 3.6)	3.4 (3.3 to 3.6)	0.23 (0.08 to 0.38)	**0.002**	0.27 (0.12 to 0.42)	**<0.001**	0.29 (0.14 to 0.43)	**<0.001**	0.23 (0.08 to 0.37)	**0.002**
Affective outcomes													
Depression (BDI-II)													
PTI	10.9 (10.4 to 11.5)	-	8.5 (7.1 to 9.9)	-	6.1 (4.7 to 7.5)	-	-	-2.4 (-3.7 to -0.96)	**0.001**	-	-	-4.9 (-6.2 to -3.5)	**<0.001**
PFI	11.0 (9.9 to 12.1)	-	7.5 (6.1 to 8.8)	-	7.2 (5.8 to 8.6)	-	-	-3.6 (-4.9 to -2.2)	**<0.001**	-	-	-3.8 (-5.2 to -2.4)	**<0.001**
CBI	11.7 (10.9 to 12.4)	-	7.5 (5.9 to 8.9)	-	7.1 (5.7 to 8.5)	-	-	-4.2 (-5.7 to -2.7)	**<0.001**	-	-	-4.6 (-5.9 to -3.1)	**<0.001**
UC	11.4 (10.9 to 11.9)	-	10.5 (8.9 to 11.9)	-	6.7 (5.5 to 8.2)	-	-	-0.94 (-2.4 to 0.55)	0.22	-	-	-4.5 (-5.9 to -3.2)	**<0.001**
Anxiety (STAI-S)													
PTI	21.5 (20.7 to 22.2)	-	18.4 (15.9 to 20.9)	-	14.5 (12.0 to 16.9)	-	-	-3.0 (-5.5 to -0.55)	**0.017**	-	-	-7 (-9.4 to -4.6)	**<0.001**
PFI	20.6 (18.8 to 22.4)	-	17.2 (14.8 to 19.6)	-	16.2 (13.8 to 18.7)	-	-	-3.4 (-5.8 to -1)	**0.006**	-	-	-4.4 (-6.8 to -1.9)	**<0.001**
CBI	23.2 (22.0 to 24.3)	-	15.3 (12.8 to 17.8)	-	16.1 (13.7 to 18.6)	-	-	-7.9 (-10.4 to -5.4)	**<0.001**	-	-	-7.0 (-9.5 to -4.6)	**<0.001**
UC	21.9 (21.2 to 22.7)	-	20.7 (18.1 to 23.2)	-	16.6 (14.3 to 19.0)	-	-	-1.3 (-3.8 to 1.3)	0.32	-	-	-5.3 (-7.7 to -2.9)	**<0.001**
Distress (DDS2)													
PTI	2.8 (2.6 to 2.8)	-	1.9 (1.7 to 2.2)	-	1.6 (1.4 to 1.8)	-	-	-0.72 (-0.93 to -0.51)	**<0.001**	-	-	-1.1 (-1.2 to -0.86)	**<0.001**
PFI	2.5 (2.3 to 2.6)	-	1.9 (1.8 to 2.1)	-	1.7 (1.5 to 1.9)	-	-	-0.5 (-0.7 to -0.31)	**<0.001**	-	-	-0.79 (-0.98 to -0.6)	**<0.001**
CBI	2.7 (2.6 to 2.8)	-	1.8 (1.6 to 2.0)	-	1.7 (1.5 to 1.9)	-	-	-0.91 (-1.1 to -0.71)	**<0.001**	-	-	-1.01 (-1.2 to -0.82)	**<0.001**
UC	2.6 (2.5 to 2.6)	-	2.1 (1.9 to 2.4)	-	1.97 (1.8 to 2.2)	-	-	-0.36 (-0.58 to -0.15)	**0.001**	-	-	-0.58 (-0.77 to -0.39)	**<0.001**

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.

B, baseline; CBI, is a combined intervention for patients and professionals; M, month; PFI, Intervention only for healthcare professionals at primary care; PTI, Intervention only for patients and family members; UC, usual care or control group.

Table 3. Adjusted means for each group and intragroup differences compared with the baseline measurement (health-related quality of life and symptoms)

	Adjusted means in each group (95%CI)					Difference in intragroup of adjusted means compared to baseline (95%CI)					
	Baseline	**6 Months**	**12 Months**	**18 Months**	**24 Months**	**B-6M**	***P* value**	**B-12M**	***P* value**	**B-18M**	***P* value**	**B-24M**	***P* value**
Health-related quality of life and symptoms													
Health-related quality of life (ADDQoL-19)													
PTI	-1.7 (-1.8 to -1.6)	-1.0 (-1.3 to -0.8)	-1.2 (-1.5 to -0.97)	-0.85 (-1.1 to -0.61)	-0.76 (-0.99 to -0.53)	0.69 (0.46 to 0.93)	**<0.001**	0.52 (0.27 to 0.76)	**<0.001**	0.89 (0.65 to 1.1)	**<0.001**	0.97 (0.74 to 1.2)	**<0.001**
PFI	-1.7 (-1.8 to -1.5)	-1.2 (-1.5 to -1)	-1.1 (-1.3 to -0.88)	-1.3 (-1.5 to -1.0)	-0.98 (-1.2 to -0.75)	0.43 (0.21 to 0.66)	**<0.001**	0.55 (0.32 to 0.78)	**<0.001**	0.4 (0.17 to 0.63)	**0.001**	0.68 (0.45 to 0.9)	**<0.001**
CBI	-1.8 (-1.9 to -1.6)	-1.1 (-1.3 to -0.87)	-0.78 (-1.0 to -0.54)	-1.0 (-1.3 to -0.79)	-0.97 (-1.2 to -0.73)	0.65 (0.42 to 0.88)	**<0.001**	0.98 (0.74 to 1.2)	**<0.001**	0.73 (0.49 to 0.96)	**<0.001**	0.78 (0.54 to 1.0)	**<0.001**
UC	-2.1 (-2.2 to -1.9)	-1.1 (-1.4 to -0.9)	-1.6 (-1.9 to -1.4)	-1.2 (-1.5 to -1)	-0.92 (-1.2 to -0.69)	0.92 (0.7 to 1.2)	**<0.001**	0.44 (0.18 to 0.7)	**0.001**	0.82 (0.59 to 1.1)	**<0.001**	1.1 (0.9 to 1.4)	**<0.001**
Neuropathic symptom (MNSI)													
PTI	3.1 (3 to 3.2)	-	2.8 (2.5 to 3.1)	-	2.4 (2.1 to 2.7)	-	-	-0.29 (-0.61 to 0.02)	0.07	-	-	-0.69 (-0.99 to -0.4)	**<0.001**
PFI	3.3 (3.0 to 3.6)	-	2.8 (2.5 to 3.1)	-	2.9 (2.5 to 3.2)	-	-	-0.55 (-0.86 to -0.23)	**0.001**	-	-	-0.45 (-0.76 to -0.13)	**0.005**
CBI	3.3 (3.1 to 3.4)	-	2.6 (2.3 to 2.9)	-	2.8 (2.5 to 3.1)	-	-	-0.67 (-1.0 to -0.31)	**<0.001**	-	-	-0.46 (-0.78 to -0.13)	**0.006**
UC	3.3 (3.2 to 3.5)	-	3.1 (2.9 to 3.5)	-	2.5 (2.2 to 2.8)	-	-	-0.15 (-0.47 to 0.17)	0.36	-	-	-0.82 (-1.1 to -0.54)	**<0.001**

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.

B, baseline; CBI, is a combined intervention for patients and professionals; M, month; PFI, Intervention only for healthcare professionals at primary care; PTI, Intervention only for patients and family members; UC, usual care or control group

Table 4. Proportion of patients who stop smoking at each follow up compared to the control group

	PTI (n=114)	PFI (n=156)	CBI (n=109)	UC (n=145)	*P* value global	*P* value PTI vs UC	*P* value PFI vs UC	P value CBI vs UC
3 Months	12.8	8.7	15.4	10.4	0.54	0.99	0.99	0.99
6 Months	28.5	7.5	24.2	15.4	0.003	0.11	0.22	0.99
12 Months	33.1	17.4	28.4	14.3	0.014	0.018	0.99	0.11
18 Months	36.7	19.6	37.6	18.8	0.004	0.04	0.99	0.03
24 Months	41.5	23.4	42.3	21.2	0.002	0.012	0.99	0.012

Only basal smokers are included in the analysis.

CBI, is a 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 or control group.

Table 5. Patient satisfaction with the intervention received (only those who made use of each intervention component)

	n	mean (95%CI)
Conventional group educational program		
Usability		
Environment generated	592	9.53 (9.46 to 9.60)
Exchange of experiences with participants and educator	588	9.59 (9.53 to 9.66)
Educator's work	587	9.79 (9.74 to 9.83)
Quality of materials	587	9.56 (9.49 to 9.64)
Personal satisfaction		
The sessions helped me get to know my diabetes better	591	9.67 (9.61 to 9.73)
I found the sessions useful	593	9.60 (9.52 to 9.67)
The sessions motivated me to look after my health better	590	9.62 (9.55 to 9.69)
General		
General satisfaction	589	9.70 (9.65 to 9.76)
I would recommend the sessions	588	9.77 (9.72 to 9.82)
Website platform		
Usability		
Access to the content	253	8.30 (8.02 to 8.58)
Usability of the web	251	8.59 (8.33 to 8.85)
Patient outcomes follow up charts	215	8.37 (8.03 to 8.72)
Quality of materials	229	8.81 (8.53 to 9.08)
Access to videos of the sessions	216	8.76 (8.47 to 9.05)
General		
General satisfaction	237	8.56 (8.30 to 8.82)
I would recommend using the website	239	8.81 (8.56 to 9.05)
Semi-automated mobile phone messages		
Usability		
Reading SMS	585	9.51 (9.41 to 9.61)
Usefulness of reminders	576	9.33 (9.22 to 9.45)
Personal satisfaction		
They adapt to my needs	579	9.04 (8.90 to 9.18)
They motivate me to look after myself	576	9.15 (9.02 to 9.28)
I would like to continue receiving them	552	8.80 (8.59 to 9.00)
General		
General satisfaction	572	9.23 (9.09 to 9.37)

Table 6. Significant differences compared to usual care for the three intervention groups.

	PTI		PFI		CBI	
	12 months	24 months	12 months	24 months	12 months	24 months
Cognitive/attitudinal						
Knowledge (DIATEK)	**	**		↓**	**	
Empowerment (DES)		**	***		***	**
Behavioural						
Diet (MEDAS)	**	***	↓***			**
Adherence (MGLS)						
Smoking	*	*			*	*
Affective						
Depression (BDI-II)			**		**	
Anxiety (STAI-S)			*		**	
Diabetes Distress (DDS2)		**		*	**	
HRQOL						
HRQoL (ADDQoL-19)	*		**		***	
Neuropathy (MNSI)					*	

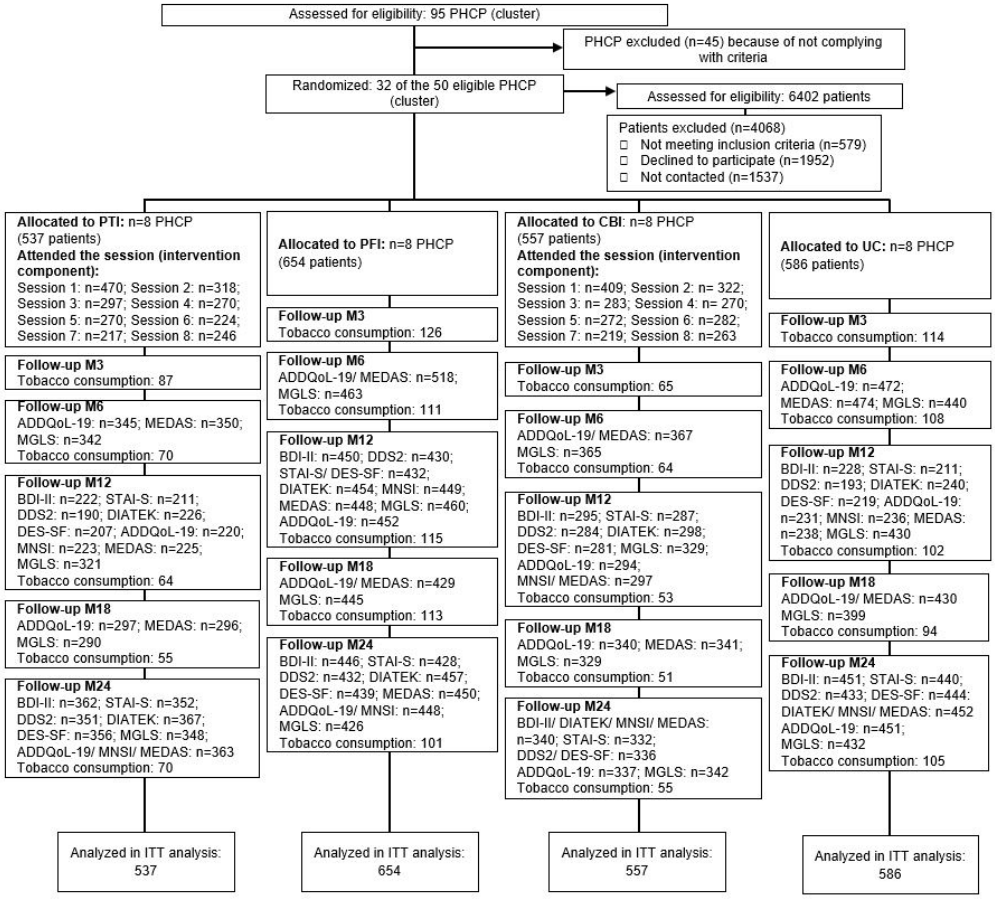
↓ represent worsening compare to usual care.

*$P \leq 0.05$.

**$P \leq 0.01$.

***$P \leq 0.001$.

CBI, is a 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 or control group.



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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	See the published protocol
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	7

		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n.a.
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n.a.
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	See the clinical outcomes paper published
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	https://implem

			entationscience.biomedcentral.com/articles/10.1186/s13012-015-0233-1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Patient-reported outcome measures for knowledge transfer and behavior modification interventions in type 2 diabetes. The INDICA study: a multi-arm cluster randomized controlled trial

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TITLE PAGE

Patient-reported outcome measures for knowledge transfer and behavior modification interventions in type 2 diabetes. The INDICA study: a multi-arm cluster randomized controlled trial

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ABSTRACT

Objective: This study assesses the effectiveness of different interventions of knowledge transfer and behavior modification to improve type 2 diabetes mellitus (T2DM) patients' reported outcomes measures (PROMs) in the long-term. **Design:** Open, community-based pragmatic, multicenter, controlled trial with random allocation by clusters to usual care (UC) or to one of the three interventions.

Participants: A total of 2,334 uncomplicated T2DM patients and 211 healthcare professionals were included of 32 Primary Care Centers.

Setting: Primary Care Centers in Canary Islands (Spain).

Intervention: The intervention for patients (PTI) included an educational group program, logs and a web-based platform for monitoring, and automated SMS. The intervention for professionals (PFI) included an educational program, a decision support tool embedded into the electronic clinical record, and periodic feedback about patients' results. A third group received both PTI and PFI (combined intervention, CBI).

Outcome measure: Cognitive-attitudinal, behavioral, affective and health related quality of life (HQoL) variables..

Results: Compared to UC at 24 months, the PTI group significantly improved knowledge (P=0.005), self-empowerment (P=0.002), adherence to dietary recommendations (P<0.001), and distress (P=0.01). The PFI group improved at 24 months in distress (P=0.03) and at 12 months there were improvements in depression (P=0.003), anxiety (P=0.05), HQoL (P=0.005), and self-empowerment (P<0.001). The CBI group improved at 24 months in self-empowerment (P=0.008) and adherence to dietary recommendations (P=0.004) and at 12 months in knowledge (P=0.008), depression (P=0.006), anxiety (P=0.003), distress (P=0.01), HQoL (P<0.001), and neuropathic symptoms (P=0.02). Statistically significant improvements were also observed at 24 months in the proportion of patients who quit smoking for PTI and CBI (41.5% in PTI and 42.3% in CBI vs. 21.2% in the UC group).

Conclusions: Assessed interventions to improve PROMs in T2DM attain effectiveness for knowledge, self-empowerment, distress, diet adherence, and tobacco cessation. PTI produced the most lasting benefits.

Trial Registration: ClinicalTrials.gov NCT01657227 (August 6, 2012) https://clinicaltrials.gov/ct2/show/NCT01657227

Keywords: Primary Care, Diabetes & Endocrinology, Quality in health Care, Health Informatics

Strengths and Limitation of this study

- The INDICA study provides randomized evidence on the effectiveness of complex interventions to improve outcomes in type 2 diabetes mellitus patients, with a longer follow up than previous studies.
- All relevant stakeholders in the community are involved in the INDICA study (patients and family caregivers and primary care professionals).
- The trial included a large sample of patients with type 2 diabetes regardless of their baseline HbA1c level, reinforcing the external validity of the results.
- The INDICA interventions with ICT-based components favor applicability and access, in a cost-effective manner, to a growing number of patients.
- A limitation in the use of PROMs is the absence of well-established empirically derived minimum clinically significant differences

INTRODUCTION

Many type 2 diabetes mellitus (T2DM) patients do not achieve the recommended treatment goals for glycemic control[1]. This might be due to inappropriate health care access and/or clinical management. Moreover, psychological and emotional aspects, such as knowledge of the disease or diabetes-related distress, are also important issues for an appropriate self-management and glycemic control[2, 3]. Previous research has shown the value of patient-reported outcome measure (PROMs) to monitor these variables in diabetes[4], which contribute to patient empowerment and patient-centered care[5]. PROMs are generally assessed with standardized, validated questionnaires aimed to measure patients' perception of their health status, perceived level of impairment, disability or health-related quality of life[6].

Interventions that aim to empower people with chronic illnesses and specifically diabetes have included distinct strategies such as educational programs, websites, support phone calls, text messages and other technological resources[4, 7-10], in order to improve patients' diabetes knowledge, self-management, psychological outcomes and health status. However, the results obtained have been mixed, with a considerable number of studies showing no effect of the interventions[8-11]. The INDICA study is a pragmatic, cluster-randomized controlled trial with two years follow-up that assesses the effectiveness and cost-effectiveness of multicomponent interventions for knowledge transfer and behavior modification of T2DM patients, their families, and healthcare professionals (physicians and nurses) in a large number of Primary Care Health Practices (PHCP). These interventions combine conventional group educational and training activities with different information and communication technology (ICT)-based interventions to guide the decisions of the main actors involved in the management of T2DM[12]. The intervention for patients (PTI) included an educational group program led by trained nurses, consisting of eight face-to-face sessions (one every three months over two years); continuous self-monitoring by means of logs and a web-based platform; and tailored automated SMS to provide continuous support to patients and to reinforce self-care and lifestyle changes. The intervention for professionals (PFI) included an educational program to update their diabetes knowledge, a decision support tool embedded into the electronic clinical record with recommendations based on best

available scientific knowledge, adapted to the specific needs of every patient, and periodic feedback about patients' results.

The results on the effectiveness of these interventions on clinical outcomes can be seen in Ramallo-Fariña et al.[13], and the cost-effectiveness evaluation can be reviewed in García-Pérez et al.[14]. The aim of this article is to report the effect of the INDICA interventions on a set of PROMs assessed in the trial: cognitive-attitudinal (knowledge, empowerment), behavioral (adherence to the dietary recommendation, medication and tobacco use), affective (anxiety, depression, distress) and health-related quality of life dimensions. These outcomes are commonly targeted for most diabetes interventions because of their association with critical, longer-term outcomes, such as functional capacity[15], complications[16-18], mortality[19], healthcare costs[20], and quality of life[21].

METHODS

Trial design

The INDICA study is an open, community-based pragmatic, multicenter, controlled trial with random allocation by clusters to usual care or one of three multicomponent interventions of knowledge transfer and behavior modification. One intervention was aimed at patient and family members (PTI); another intervention was aimed at primary care healthcare professionals (physicians and nurses) (PFI) and the third intervention combined the other two (CBI). In the control group, both patients/families and physicians/nurses received the usual activities provided by the PHCP. The full study protocol has been published before[12].

Study Participants

The INDICA study included adults aged 18 to 65 years who had been diagnosed with T2DM at least one year before, did not have any diabetes-related complications, and used a mobile phone regularly[12]. Family Care Units (FCU) in each PHCP, comprised of a family physician and a nurse, were the recruitment unit. All PHCPs included had to have at least eight FCUs and the availability of appropriate facilities to provide educational group sessions. FCUs planning or awaiting placement changes among PHCP in the first six months after the project began were excluded.

Setting and recruitment

PHCPs were randomly selected in the islands of Tenerife, Gran Canaria, Lanzarote, and La Palma (Canary Islands, Spain). Moreover, FCUs were randomly selected from all consenting FCUs at each PHCP. The electronic clinical records (ECR) of all potentially eligible patients in selected FCUs were screened to verify inclusion and exclusion criteria.

Patient and public involvement

Patients were actively involved in the design of the trial. Two associations of patients with T2DM in the Canary Island 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 the elaboration 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 objective of another publication. Finally, we established a commitment with patients and healthcare professionals to share the results with them in an easy-to-understand way.

Random assignment

Randomization was applied at different levels. First, three different strata were created according to the geographic areas in the more populated islands (Tenerife and Gran Canaria). Second, four PHCP (clusters) were randomly allocated to every geographic stratum and block permutation was used to assign PHCPs to the study arms; the PHCP being the sampling unit. La Palma and Lanzarote (less populated islands) were geographically divided into four zones with only one eligible PHCP available in each zone randomly assigned to one of the study arms. In every island, all arms were equally distributed. Six FCUs were randomly selected, from all those consenting to participate in each PHCP. From all patients fulfilling inclusion criteria and consenting to participate in each PHCP, 15 were randomly selected per FCU. Exceptionally, more than six FCUs or more than 15 patients per FCU were selected, to try to recruit 90 patients in every PHCP. However, it was not possible to attain this objective of 90 patients in all PHCP as there were insufficient patients in all FCU selected that complied with the inclusion and exclusion criteria.

FCU and patient randomization were performed by simple generation from a list of random numbers.

Interventions

Patient interventions

Patients recruited to the PTI and CBI groups received a complex intervention of knowledge transfer and behavior modification, informed by conceptual frameworks of behavioral change[16]. The intervention combined: A) an eight-session, conventional, group educational program given by a nurse specialized in diabetes; B) monitoring of physical activity, diet, drug adherence, mood, blood pressure, and blood glucose readings by daily use of paper workbooks, complemented by weekly access to a website platform

to upload paper workbook data; and C) continuous, personalized feedback by semi-automated mobile phone messages (SMS), modified according to the website information.

Interventions for primary care professionals

Primary care professionals recruited to the PFI and CBI groups received a complex intervention of knowledge transfer and decision support, informed by the determinants of behavior change suggested by Michie et al.[22] for its design and implementation. The intervention included: A) an educational and interactive group program of two sessions to update clinical management information and promote patient-centered care; B) an automated decision aid tool, based on a CPG for T2DM embedded into the electronic clinical record; and C) monthly computerized graphic feedback, which displayed a set of processes and outcome indicators for all T2DM patients of the corresponding FCU compared to other FCU in their setting and the FCU with the best results. Both interventions were applied during the two years follow-up.

Duration of fieldwork

Fieldwork took place between February 2013 and October 2016. The first year and the following two years were devoted to recruitment of patients and healthcare providers, and intervention and follow-up, respectively. As interventions were maintained over time, intervention and follow-up periods overlapped.

Outcomes

Cognitive-attitudinal outcomes

To assess potential changes in patient knowledge about T2DM and its self-management, we developed a specific instrument created in the context of this project, named DIATEK, which consisted of 30 questions. Each item has four response options and only one correct answer. Items examined risk factors for disease development and deterioration, objective values for biochemical parameters; recommendations on nutrition, physical activity, drug use and self-management. The total score, obtained by adding all correct responses, and ranging from 0 to 30, was later rescaled from 0 to 10.

The Diabetes Empowerment Scale-Short Form (DES-SF)[23] is a validated questionnaire designed to evaluate psychosocial self-efficacy in diabetes. DES-SF is the short form of the original DES, which includes eight items (need for change, developing a plan, overcoming barriers, asking for support, supporting oneself, coping with emotion, motivating oneself, and making diabetes care choices appropriate for one's priorities and circumstances) with responses on a five-point Likert scale and an overall range from eight to 40, according to increasing patient empowerment.

Behavioral outcomes

The Mediterranean Diet Adherence Screener (MEDAS)[24] is a validated questionnaire to assess dietary recommendation adherence, which consists of 14 targets for food consumption, rated with one point for each target attained. According to the final score, patients are classified as having low (0-6 points), moderate (7-10) or high adherence (11-14 points) to the Mediterranean diet.

The Morisky Medication Adherence Scale (MGLS)[25] assesses drug-treatment adherence, by means of a validated four-item self-report instrument and a final score ranging from 0 to 4. Patients are considered adherent, only if they obtain four points.

Smoking status was monitored from baseline and during follow-up, to check for potential cessation throughout the study.

Affective outcomes

The State Trait Anxiety Inventory (STAI-S)[26] is a validated patient-reporting questionnaire that includes two non-dependent scales; the applied state-anxiety scale (STAI State) and the trait-anxiety scale (STAI Trait). It assesses transient emotional state or condition as characterized by subjective feelings of tension and apprehension that can fluctuate in time and intensity. The STAI-S includes 20 items, with each item scored on a four-point Likert scale. Anxiety is defined by a cut-off point ≥ 30.

The Beck Depression Inventory II (BDI-II)[27] consists of 21 items scored on a four-point scale from 0 ("not at all") to 3 ("most of the time"). The items assess depression symptoms in the last two weeks. All item scores are added to a maximum score of 63. A BDI-II score of ≥ 14 indicates mild depressive symptoms.

The Diabetes Distress Scale (DDS2)[28] is a validated two-item diabetes distress-screening instrument that asks respondents to rate, on a six-point scale, the degree of distress caused by the two following items: (1) feeling overwhelmed by the demands of living with diabetes and (2) feeling that I am often failing with my diabetes regimen. High Diabetes distress can be identified by an average score ≥ 3 or more, low distress by scores under two, and moderate distress by the scores in between.

Health- related quality of life and symptoms

The Audit of Diabetes-Dependent Quality of life (ADDQoL-19)[29] is a specific HRQoL questionnaire for diabetes. It assesses 19 domains, each with its impact and importance index to provide an integrated score for each domain. The sum of the score in each domain forms the global score (range: -9 to 3). The lower the score, the worse the quality of life.

The Michigan Neuropathy Screening Instrument (MNSI)[30] is an instrument that measures the incidence of distal diabetic peripheral polyneuropathy. It is composed of 15 self-administered items, in which the abnormal responses are added. A score of seven or more is considered abnormal.

Satisfaction

An ad-hoc self-completed questionnaire (INDICA-SATP) was developed to measure satisfaction with each component of the interventions in PTI and CBI groups. It was measured in the 24-month follow-up in patients who, having attended the group educational program, also used the web platform or received the semi-automated mobile phone messages. Satisfaction with each component was valued from 0 to 10 points, with 10 reflecting maximum satisfaction.

All information, including demographic data, overall and personal health history, diabetes health status, current medications, smoking status, and risk factors for complications, was obtained in a face to face interview at baseline and at 3, 6, 12, 18 and 24 months of follow-up. Similarly, all self-administered questionnaires (ADDQoL-19, BDI-II, DES-SF, DDS2, DIATEK, MEDAS, STAI-S, MGLS and MNSI), were distributed and collected at baseline, and at 12 and 24 months follow-up. ADDQol-19, MEDAS and MGLS were also applied at 6 and 18 months.

Two other questionnaires were included in the trial registry and the published protocol[12], the *International Physical Activity Questionnaire* (IPAQ) and a scale

developed for this project to assess patients' attitudinal changes regarding lifestyles (INDICA-LSQ). However, the data quality checking identified many inconsistent or meaningless responses to these questionnaires, which indicates that patients did not correctly understand the instructions. Therefore, we decided to exclude them from the analyses.

Statistical Analysis

Multilevel mixed models including the baseline value of dependent variables and time elapsed since diagnosis (in years) as covariates were implemented for all PROMs. First level variables are those corresponding to each measurement along follow-up (repeated time measurements). The second level includes patient variables (the baseline value of dependent variables and time elapsed since diagnosis) and third level variables correspond to PHCP in which patients are grouped (the variable arm to which PHCP was assigned is included in this level). The effect that identifies the intervention arm has been considered fixed for the different PHCP, whilst the intercept has been considered random. The model also included an interaction term between arm and month, which allows for differences in the intervention effect between follow-up assessments[31]. The intraclass correlation coefficient (ICC) was obtained for each model for the PHCP and by patient according to their PHCP. The adjusted estimated mean was calculated for each follow up moment compared to baseline; and its statistical significance was calculated by means of the model already set out. The relative improvement for each follow-up was obtained as the ratio between the adjusted difference in mean between the intervention and control group and the mean of the control group.

A logistic regression model was implemented to compare the proportion of patients who quit smoking at each follow-up, by intervention arm. Only basal smokers were included in the analysis.

Analysis was performed on an intention-to-treat basis, that is, participants were analyzed in the group to which they were randomized. Missing values were treated by means of multiple imputation procedures[32], with results based on 100 imputed datasets (missing values from all follow up visits were imputed). Analysis under multiple imputation is valid for randomly missing data[33]. We compared the results of imputed and non-imputed data. All the analyses were conducted using STATA version 15.0[34]. Differences were considered statistically significant if $P<0.05$.

Ethical approval and consent to participate

All participants provided written informed consent. The scientific and ethics committees of both the University Hospital of Canarias (ID: 2012_44) and the University Hospital Nuestra Señora de la Candelaria (ID: EPA-07/10) approved the study protocol. The study was performed in accordance with Good Clinical Practice standards, prevailing local regulatory requirements, and Declaration of Helsinki recommendations.

RESULTS

Study Participants

A total of 2334 patients and 211 healthcare professionals were included. Figure 1 shows the flowchart with cluster randomization of patients for each intervention, attendance at educational/training sessions of patients and professionals and the number of PROMs questionnaires received for each follow-up assessment. The patients´ baseline characteristic according to the intervention assignment can be seen in Ramallo-Fariña et al.[13]. Mean age of the whole population was 55.7 ± 7.1 years, with 51.9% women. Mean baseline HbA1c was 7.3%/56 mmol/mol. From baseline, 49.4% of patients started with HbA1c levels within the accepted therapeutic goal (≤7%/53 mmol/mol). There were no statistically significant differences among groups in terms of their baseline characteristics.

Intention-to-treat results, reported below, were very similar to those obtained with non-imputed data. Only three discrepancies were observed that will be discussed in the corresponding outcome section. Results at all time points are shown in Tables 1 (inter-group differences), 2 and 3 (intra-group changes).

Cognitive-attitudinal outcomes

Table 1 shows that the level of knowledge about diabetes is significantly higher for PTI (P=0.007) and CBI (P=0.008), compared with UC, at 12 months; and for PTI (P=0.005) at 24 months.

Patient empowerment was significantly higher for PFI and CBI groups, compared to UC at 12 months (P<0.001 for both comparisons). Analysis of non-imputed data led to a P-value of 0.05 for the difference between PTI and UC, favoring the former, at this time point. At 24 months, PTI and CBI also attained significantly higher scores than UC (P=0.002 and P=0.008, respectively); while differences with PFI are marginally significant.

Behavioral outcomes

Table 1 shows that the PTI group is significantly more adherent to the diet recommendations, compared to UC, after 12 months of follow-up. There is a difference of 0.87 (P<0.001) at 24 months. Adherence improves for CBI from 18 months, compared

to UC, with differences of 0.7 (*P*=0.004) at 24 months. Adherence levels remain moderate for all patient groups throughout follow-up (see Table 2).

No differences were found in medication adherence, compared to UC (Table 1). However, average levels of medication adherence were significantly improved in all four groups, despite the high baseline levels (>3) (see Table 2).

Table 3 shows the reduction in the proportion of smokers who quit smoking during follow up in PTI (12 months), and CBI (18 months), compared to UC. With non-imputed data the reduction was statistically significant from month 6 for PTI (*P*=0.023) and month 12 for CBI (*P*=0.025). The percentage of patients who quit smoking at 24 months was 41.5% for PTI (*P*=0.012) and 42.3% (*P*=0.012) for CBI, versus 21.2% for UC group. There were no statistically significant differences between groups in the baseline percentage of smokers (*P*=0.99).

Affective outcomes

Compared to UC, both PFI and CBI show statistically significant differences at 12 months for depression (*P*=0.003 and *P*=0.006, respectively), and anxiety (*P*=0.05 and *P*=0.003, respectively) (Table 1). These differences disappear at 24 months because all groups of patients improved (Table 2).

The diabetes distress score improved significantly compared to the UC group for CBI at 12 months (*P*=0.01) and for PTI and PFI at 24 months (*P*=0.01 and *P*=0.03, respectively). The score remained marginally significant for CBI (Table 1). At baseline, all patient groups showed moderate distress, which decreased to a low level from 12 months, except for the UC group, which did so at 24 months (Table 2).

Health-related quality of life and symptoms

HRQoL significantly improved for all intervention groups, at 12 months, compared to UC; a difference only maintained for PTI at 18 months (*P*=0.02) (Table 1).

Neuropathic symptom scores were significantly lower for the CBI group at 12 months (*P*=0.02) compared to the UC group (the analysis of non-imputed data led to a non-significant result, *P*=0.12). This difference disappeared at 24 months (Table 1). Mean baseline scores for all groups were under 4, considerably below the cut-off point of 7 for abnormal classification (Table 4).

Satisfaction

Table 5 shows the patients' satisfaction with the intervention received. While average scores were higher than 9/10, in all dimensions, for the group educational sessions, satisfaction with the web platform and SMS obtained scores above 8.

Table 6 shows a summary of the results at 12 and 24 months.

For all PROMs, ICC values were close to zero at the PHCP levelthus reflected a very small effect associated with PHCP for interventions and control groups (similar results among PHCP in every arm). The ICC at the patient level was broad, accounting for considerable variations among individuals.

DISCUSSION

This article assesses the effect of interventions implemented by the INDICA study to improve T2DM outcomes on several health measures self-perceived by patients in the cognitive-attitudinal (knowledge, empowerment), behavioral (i.e., adherence to the dietary recommendations, medication and tobacco use), affective (anxiety, depression, distress) and health-related quality of life dimensions. The INDICA study is a pragmatic cluster-randomized study with two years follow up that assesses the effectiveness of multicomponent interventions for knowledge transfer and behavior modification of patients, families, and healthcare professionals (physicians and nurses) at the primary care level.

At one-year follow-up, the combined intervention lead to obtaining significant results in all outcomes except diet and medication adherence. Relative improvements compared to usual care ranged between 9.6% (knowledge) and 52.2% (HRQoL), with intermediate values for anxiety (26.1%) and depression (28.7%). Significant improvements in HRQoL were also obtained for the PTI and PFI groups, although of less intensity (24.8% and 31.7%, respectively). However, they showed different results in the remaining variables: the PTI group improved in terms of knowledge and behavioral outcomes (i.e., diet and smoking), while the PFI improved in regard to empowerment and depression, but obtained a significantly worse result than the UC group for diet adherence.

After two years of follow-up, there were no significant differences in HRQoL, anxiety or depression, mainly due to the improvement experienced by the UC group in these variables. The PTI group obtained the best overall results, with significant improvements in the cognitive (i.e., knowledge, empowerment), affective (i.e., diabetes distress) and behavioral (i.e., diet and tobacco) variables. The same significant results were obtained for the combined intervention, except for knowledge and distress. Finally, the PFI group outperformed usual care only for distress, and showed a significantly worse result in regard to knowledge. There were no statistically significant differences in medication adherence during all the follow-up, although a ceiling effect could have occurred, since all groups showed high scores at baseline.

Therefore, the best results were observed in both groups including patients (PTI and CBI), similar to the findings observed on clinical outcomes[13]. This is not

surprising, given the straightforward and continuous application of these patient interventions, and the high reported satisfaction levels with all the intervention components (educational sessions, web resources and SMS). Previous studies that combined education and training with support phone calls, assessing interventions aimed at empowering diabetes patients to improve self-care and outcomes, showed inconsistent results between clinical variables and PROMS[8, 9]. The use of one-way messages such as those used in INDICA, appears to significantly and consistently improve HbA1c levels, although with a small-to-moderate effect-size (-0.38%, 95%CI: -0.53; -0.23)[10]. In addition, continuous advances in smart mobile technology provide new possibilities for diabetes self-management, despite the fact that evidence on the effectiveness of these new functionalities remains scarce and uncertain[11, 35].

Reduction in the number of smokers in interventions applied directly to patients (PTI and CBI) in regard to UC that remain significant at 24 months with percentages of approximately 42% which is 2.5 times the result obtained by the most extended pharmacologic intervention (replacement nicotine therapy). This is according to a meta-analysis published recently[36] which puts this reduction at 16.9% of the intervened group compared to 10.4% of the control group in studies with follow up varying from six to 24 months.

The intervention effect on professionals raises questions. At one year of follow-up, the PFI and CBI groups obtained improvements in psychological variables not affected by the intervention targeted exclusively at patients (PTI) (i.e., empowerment, anxiety, depression). These findings could be interpreted as the lasting result of better shared decision-making/patient-centered care by professionals trained in this care model. However, the PTI group was the only group to show significant improvements in behavioral variables (diet adherence and tobacco consumption); while PFI obtained significantly worse results for diet adherence from the sixth month, and CBI did not show significant benefits for these two outcomes until 18 months. These negative findings from groups containing professionals are repeated after two years in the case of knowledge, a variable in which the CBI group did not obtain significant differences. This interpretation should be considered cautiously given the analysis limitations, since the differences between intervention groups have not been statistically contrasted. As a recent Cochrane review[37] reported, current evidence on the effect of interventions to promote shared decision making by healthcare professionals shows benefits when decision making is

assessed by external observers but not by patient's assessment; furthermore, no significant effects were observed in most patient-reported outcomes[37]. Given the paucity and limited quality of available studies, more focused research is needed to draw solid conclusions about the effect of interventions aimed at professionals, and the mechanisms by which these interventions translate into psychological, behavioral and health changes of patients.

The assessment of clinical outcome measures in the INDICA study[13] for the total sample recruited regardless of Hb1Ac levels (only 50.6% of all participants had baseline HbA1c concentrations >7%, with a mean of 7.3%), showed an early and significant but temporary reduction in HbA1c for the PTI group, compared to UC, from 3 to 6 months. Even so, more than 30% of the intervened patients (PTI and CBI) attained statistically and clinically relevant reductions in HbA1c (>0.4%); significantly higher than UC at 12 and 18 months.

In the group of patients with baseline HbA1c greater than 7% (uncontrolled patients), the magnitude of the intervention effect on clinical outcomes was greater, especially in the PTI group compared to the UC group, with significant differences up to 18 months, and a significant area under the curve at 24 months for PTI compared to UC[13]. These results are supported by other studies that report greater intervention effects in patients with higher HbA1c levels[38, 39]. Longer-term reductions in blood pressure were also found in the two groups in which professionals were intervened, with smaller effects in the remaining clinical measures (lipid profile, body mass index, serum creatinine and glomerular filtration rate). Some of these results are more related to changes in medication than lifestyles. From a cost-effectiveness perspective, small differences were observed between groups after two years follow up. The PTI was more effective and less costly than CBI and PFI, in patients with HbA1c>7%[14]. This prompted the conclusion that interventions focused on patients with the highest needs would limit the impact on the health care sector budget.

This study has several limitations. The high number of instruments and measurement times increase the risk of type 1 error, which explains the decision not to compare intervention groups with each other. Moreover, the use of PROMs makes it necessary to know the minimum clinically significant differences of every instrument used. This difference, however, has not been investigated for most of them, and there is currently no consensus on the appropriate method (distribution or anchor-based) and/or statistics (e.g., absolute versus relative reduction)[40]. Furthermore, the use of PROMs implies by

definition an unblind assessment of results, which is added to the impossibility of blinding the participants regarding the intervention. Finally, the INDICA study was not designed to test the efficacy of every single component of the interventions assessed (e.g., text messages vs. patient education vs web content). Despite these limitations, the INDICA study presents some distinctive characteristics from other published studies that assess the impact of interventions promoting empowerment, self-management and behavior modification to patients and professionals: 1) a robust design (pragmatic cluster-randomized controlled trial with a factorial design for intervention arms) with a long follow-up (two years); 2) incorporation of the different actors involved in disease management (patients and family caregivers and primary care professionals; 3) greater external validity by including patients regardless of their baseline HbA1c levels; 4) incorporation of ICT-based components to the intervention that favors applicability and access, in a cost-effective manner, to a growing number of patients; and 5) inclusion of a large sample size with 2334 patients and 211 healthcare professionals.

In conclusion, all the interventions assessed improved patients HRQoL at one year of follow-up, with differences according to the intervention in the remaining PROMs examined. The intervention targeted exclusively at patients (PTI) significantly improved knowledge, empowerment, distress, dietary recommendation adherence and tobacco cessation, up to two years of follow-up. Although the clinical relevance of these effects is uncertain, except in the case of smoking cessation, these results are promising since they reflect improvements in all personal domains assessed (cognitive, attitudinal, affective, behavioral), which highlight the importance of behavioral factors to attain good health outcomes. The intervention on professionals improved affective variables at one year of follow-up, but showed virtually no effects at two years together with a negative effect on diet adherence and no effect on tobacco consumption, which emphasizes the need for more focused evaluative research on this type of intervention. For both target groups (patients and professionals), the use of ICT can be a major help to improve care access and continuity; as well as effectiveness and cost-effectiveness in T2DM self-management.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

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Conflicts of interest/Competing interests

The authors declare that they have no competing interest.

Competing interests

The authors declare that they have no competing interest.

Availability of data and material

The datasets generated and/or analyzed 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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Author Contributions

YRF, LGP, LRR, AMW, MRR and PSA contributed to the study design. SKG, GM, CGM, CDA and MRR developed the contents and gave the educational sessions to patients. Also, SKG, GM, CGM, CDA and MRR recruited participants and collected data. YRF, MAGB and HGP contributed to the statistical analyses. YRF, ARS, LGP, AMW and PSA were part of the writing committee of the manuscript. All authors reviewed, commented on, and approved the final manuscript.

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Table 1. Adjusted difference in the mean of each group compared to the control group

	6 Months	*P* value	12 Months	*P* value	18 Months	*P* value	24 Months	*P* value
Cognitive-attitudinal outcomes								
Knowledge (DIATEK): F=47.3 *P*<0.001; ICC PHCP =0.06; ICC subject|PHCP=0.35								
PTI	-	-	0.64 (0.17 to 1.11)	**0.007**	-	-	0.65 (0.2 to 1.11)	**0.005**
PFI	-	-	-0.38 (-0.85 to 0.09)	0.11	-	-	-0.6 (-1.06 to -0.14)	**0.01**
CBI	-	-	0.63 (0.16 to 1.11)	**0.008**	-	-	0.34 (-0.12 to 0.8)	0.15
Empowerment (DES-SF): F=17.3 *P*<0.001; ICC PHCP =0.08; ICC; subject|PHCP=0.08								
PTI	-	-	1.58 (-0.59 to 3.75)	0.15	-	-	3.04 (1.08 to 4.99)	**0.002**
PFI	-	-	3.95 (1.9 to 6)	**<0.001**	-	-	1.84 (-0.11 to 3.79)	0.07
CBI	-	-	3.97 (1.9 to 6.04)	**<0.001**	-	-	2.63 (0.68 to 4.58)	**0.008**
Behavioral outcomes								
Adherence dietary recommendations (MEDAS): F=25.0 *P*<0.001; ICC PHCP = 0.03; ICC subject|PHCP=0.20								
PTI	0.22 (-0.25 to 0.69)	0.36	0.71 (0.17 to 1.24)	**0.01**	0.93 (0.46 to 1.41)	**<0.001**	0.87 (0.4 to 1.35)	**<0.001**
PFI	-0.58 (-1.04 to -0.11)	**0.01**	-0.96 (-1.46 to -0.47)	**<0.001**	0.17 (-0.31 to 0.64)	0.49	0.03 (-0.44 to 0.5)	0.90
CBI	0.44 (-0.03 to 0.91)	0.06	0.06 (-0.47 to 0.58)	0.83	0.88 (0.4 to 1.35)	**<0.001**	0.7 (0.22 to 1.17)	**0.004**
Medication adherence (MGLS): F=14.4 *P*<0.001; ICC PHCP =0.04; ICC subject|PHCP=0.20								
PTI	0.09 (-0.11 to 0.3)	0.37	0.09 (-0.12 to 0.3)	0.39	0.13 (-0.09 to 0.34)	0.24	0.16 (-0.04 to 0.36)	0.12
PFI	0.01 (-0.2 to 0.22)	0.90	-0.13 (-0.34 to 0.08)	0.24	-0.06 (-0.26 to 0.15)	0.58	0.09 (-0.11 to 0.3)	0.39
CBI	0.03 (-0.18 to 0.24)	0.77	-0.19 (-0.41 to 0.03)	0.08	0 (-0.21 to 0.21)	0.98	-0.1 (-0.31 to 0.11)	0.36
Affective outcomes								
Depression (BDI-II): F=53.6 *P*<0.001; ICC PHCP = 0.05; ICC subject|PHCP=0.34								
PTI	-	-	-1.91 (-3.99 to 0.17)	0.07	-	-	-0.76 (-2.68 to 1.16)	0.44
PFI	-	-	-2.99 (-4.99 to -1)	**0.003**	-	-	0.37 (-1.56 to 2.3)	0.71
CBI	-	-	-3 (-5.13 to -0.87)	**0.006**	-	-	0.23 (-1.73 to 2.19)	0.82
Anxiety (STAI-S): F=36.0 *P*<0.001; ICC PHCP =0.07 ICC; subject|PHCP=0.32								
PTI	-	-	-2.25 (-5.75 to 1.25)	0.21	-	-	-2.18 (-5.54 to 1.18)	0.20
PFI	-	-	-3.47 (-6.95 to 0.02)	**0.05**	-	-	-0.39 (-3.78 to 2.99)	0.82
CBI	-	-	-5.4 (-8.99 to -1.81)	**0.003**	-	-	-0.50 (-3.9 to 2.9)	0.77
Distress (DDS2): F=14.9 *P*<0.001; ICC PHCP =.05 ICC; subject|PHCP=0.25								
PTI	-	-	-0.23 (-0.53 to 0.07)	0.13	-	-	-0.34 (-0.62 to -0.07)	**0.01**
PFI	-	-	-0.24 (-0.53 to 0.05)	0.10	-	-	-0.31 (-0.58 to -0.04)	**0.03**

CBI	-	-	-0.36 (-0.65 to -0.07)	**0.01**	-	-	-0.24 (-0.51 to 0.03)	0.08
Health-related quality of life and symptoms								
Health-related quality of life (ADDQoL-19): F=25.3 *P*<0.001; ICC PHCP = 0.04; ICC subject|PHCP=0.34								
PTI	0.09 (-0.24 to 0.42)	0.60	0.40 (0.04 to 0.76)	**0.03**	0.39 (0.05 to 0.72)	**0.02**	0.16 (-0.17 to 0.48)	0.34
PFI	-0.09 (-0.42 to 0.23)	0.56	0.51 (0.16 to 0.86)	**0.005**	-0.02 (-0.35 to 0.31)	0.89	-0.06 (-0.38 to 0.26)	0.71
CBI	0.03 (-0.3 to 0.35)	0.88	0.84 (0.49 to 1.18)	**<0.001**	0.21 (-0.13 to 0.54)	0.23	-0.05 (-0.38 to 0.28)	0.77
Neuropathic symptom (MNSI): F=59.8 *P*<0.001; ICC PHCP =0.02 ICC; subject|PHCP=0.32								
PTI	-	-	-0.35 (-0.8 to 0.09)	0.12	-	-	-0.08 (-0.49 to 0.33)	0.70
PFI	-	-	-0.42 (-0.87 to 0.03)	0.07	-	-	0.35 (-0.07 to 0.78)	0.11
CBI	-	-	-0.57 (-1.04 to -0.1)	**0.02**	-	-	0.31 (-0.12 to 0.74)	0.16

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.

CBI, is a combined intervention for patients and professionals; ICC, Intraclass correlation coefficient; PFI, Intervention only for healthcare professionals at primary care; PTI, Intervention only for patients and family members; PHCP, Primary Care Health Practices.

Table 2. Adjusted means for each group and intragroup differences compared with the baseline measurement (cognitive-attitudinal, behavioral and affective outcomes)

	Adjusted means in each group (95%CI)					Difference in intragroup of adjusted means compared to baseline (95%CI)					
	Baseline	6 Months	12 Months	18 Months	24 Months	B-6M	*P* value	B-12M	*P* value	B-18M	*P* value	B-24M	*P* value
Cognitive-attitudinal outcomes													
Knowledge (DIATEK)													
PTI	6.4 (6.3 to 6.5)	-	7.2 (6.9 to 7.5)	-	7.4 (7.1 to 7.7)	-	-	0.82 (0.48 to 1.2)	**<0.001**	-	-	1.03 (0.71 to 1.36)	**<0.001**
PFI	6.5 (6.3 to 6.7)	-	6.2 (5.8 to 6.5)	-	6.1 (5.8 to 6.5)	-	-	-0.31 (-0.63 to 0.02)	0.07	-	-	-0.32 (-0.64 to 0.01)	0.058
CBI	6.5 (6.4 to 6.6)	-	7.2 (6.8 to 7.5)	-	7.1 (6.8 to 7.4)	-	-	0.7 (0.36 to 1.03)	**<0.001**	-	-	0.6 (0.27 to 0.94)	**<0.001**
UC	6.2 (6.1 to 6.3)	-	6.5 (6.2 to 6.9)	-	6.7 (6.4 to 7.1)	-	-	0.3 (-0.04 to 0.63)	**0.08**	-	-	0.5 (0.18 to 0.82)	**0.002**
Empowerment (DES-SF)													
PTI	26.4 (25.8 to 27.0)	-	29.5 (27.9 to 31.0)	-	33.5 (32.1 to 34.9)	-	-	3.08 (1.6 to 4.6)	**<0.001**	-	-	7.1 (5.7 to 8.5)	**<0.001**
PFI	26.3 (25.2 to 27.4)	-	31.9 (30.5 to 33.2)	-	32.3 (30.9 to 33.7)	-	-	5.6 (4.2 to 6.9)	**<0.001**	-	-	6.02 (4.7 to 7.4)	**<0.001**
CBI	27.6 (27.0 to 28.3)	-	31.9 (30.4 to 33.3)	-	33.1 (31.7 to 34.5)	-	-	4.3 (2.8 to 5.7)	**<0.001**	-	-	5.7 (4.1 to 6.9)	**<0.001**
UC	26.1 (25.5 to 26.7)	-	27.9 (26.4 to 29.4)	-	30.5 (29.1 to 31.8)	-	-	1.8 (0.26 to 3.3)	**0.02**	-	-	4.3 (2.9 to 5.7)	**<0.001**
Behavioral outcomes													
Adherence dietary recommendations (MEDAS)													
PTI	8 (7.8 to 8.1)	7.6 (7.2 to 7.9)	9.1 (8.7 to 9.4)	8.3 (7.9 to 8.6)	8.7 (8.3 to 9)	-0.43 (-0.77 to -0.09)	**0.01**	1.1 (0.71 to 1.5)	**<0.001**	0.27 (-0.07 to 0.62)	0.12	0.68 (0.34 to 1.02)	**<0.001**
PFI	8.2 (7.9 to 8.5)	6.8 (6.4 to 7.1)	7.4 (7.1 to 7.7)	7.5 (7.1 to 7.8)	7.8 (7.5 to 8.2)	-1.5 (-1.8 to -1.1)	**<0.001**	-0.82 (-1.2 to -0.49)	**<0.001**	-0.82 (-1.2 to -0.49)	**<0.001**	-0.4 (-0.74 to -0.07)	**0.018**
CBI	8.3 (8.1 to 8.5)	7.8 (7.4 to 8.1)	8.4 (8.0 to 8.8)	8.2 (7.9 to 8.5)	8.5 (8.1 to 8.8)	-0.51 (-0.84 to -0.17)	**0.003**	0.13 (-0.24 to 0.51)	0.49	-0.08 (-0.43 to 0.26)	0.63	0.2 (-0.14 to 0.54)	0.26
UC	8.02 (7.9 to 8.2)	7.3 (7.0 to 7.7)	8.4 (8.0 to 8.7)	7.3 (7.0 to 7.7)	7.8 (7.5 to 8.1)	-0.69 (-1.0 to -0.36)	**<0.001**	0.34 (-0.02 to 0.7)	0.07	-0.7 (-1.0 to -0.37)	**<0.001**	-0.24 (-0.57 to 0.1)	0.16
Medication adherence (MGLS)													
PTI	3.1	3.5	3.6	3.6	3.6	0.41	**<0.001**	0.45	**<0.001**	0.5	**<0.001**	0.48	**<0.001**

	(3.1 to 3.2)	(3.4 to 3.7)	(3.4 to 3.7)	(3.5 to 3.8)	(3.5 to 3.7)	(0.26 to 0.56)		(0.29 to 0.6)		(0.35 to 0.65)		(0.33 to 0.62)	
PFI	3.3 (3.2 to 3.3)	3.5 (3.3 to 3.6)	3.3 (3.2 to 3.5)	3.4 (3.3 to 3.6)	3.5 (3.4 to 3.7)	0.18 (0.03 to 0.33)	**0.02**	0.08 (-0.07 to 0.22)	0.32	0.16 (0.02 to 0.31)	**0.026**	0.25 (0.11 to 0.4)	**0.001**
CBI	3.3 (3.3 to 3.3)	3.5 (3.3 to 3.6)	3.3 (3.1 to 3.4)	3.5 (3.3 to 3.6)	3.3 (3.2 to 3.5)	0.17 (0.02 to 0.32)	**0.02**	-0.01 (-0.18 to 0.15)	0.87	0.2 (0.05 to 0.35)	**0.01**	0.04 (-0.11 to 0.2)	0.60
UC	3.2 (3.1 to 3.3)	3.4 (3.3 to 3.6)	3.5 (3.3 to 3.6)	3.5 (3.3 to 3.6)	3.4 (3.3 to 3.6)	0.23 (0.08 to 0.38)	**0.002**	0.27 (0.12 to 0.42)	**<0.001**	0.29 (0.14 to 0.43)	**<0.001**	0.23 (0.08 to 0.37)	**0.002**
Affective outcomes													
Depression (BDI-II)													
PTI	10.9 (10.4 to 11.5)	-	8.5 (7.1 to 9.9)	-	6.1 (4.7 to 7.5)	-	-	-2.4 (-3.7 to -0.96)	**0.001**	-	-	-4.9 (-6.2 to -3.5)	**<0.001**
PFI	11.0 (9.9 to 12.1)	-	7.5 (6.1 to 8.8)	-	7.2 (5.8 to 8.6)	-	-	-3.6 (-4.9 to -2.2)	**<0.001**	-	-	-3.8 (-5.2 to -2.4)	**<0.001**
CBI	11.7 (10.9 to 12.4)	-	7.5 (5.9 to 8.9)	-	7.1 (5.7 to 8.5)	-	-	-4.2 (-5.7 to -2.7)	**<0.001**	-	-	-4.6 (-5.9 to -3.1)	**<0.001**
UC	11.4 (10.9 to 11.9)	-	10.5 (8.9 to 11.9)	-	6.7 (5.5 to 8.2)	-	-	-0.94 (-2.4 to 0.55)	0.22	-	-	-4.5 (-5.9 to -3.2)	**<0.001**
Anxiety (STAI-S)													
PTI	21.5 (20.7 to 22.2)	-	18.4 (15.9 to 20.9)	-	14.5 (12.0 to 16.9)	-	-	-3.0 (-5.5 to -0.55)	**0.017**	-	-	-7 (-9.4 to -4.6)	**<0.001**
PFI	20.6 (18.8 to 22.4)	-	17.2 (14.8 to 19.6)	-	16.2 (13.8 to 18.7)	-	-	-3.4 (-5.8 to -1)	**0.006**	-	-	-4.4 (-6.8 to -1.9)	**<0.001**
CBI	23.2 (22.0 to 24.3)	-	15.3 (12.8 to 17.8)	-	16.1 (13.7 to 18.6)	-	-	-7.9 (-10.4 to -5.4)	**<0.001**	-	-	-7.0 (-9.5 to -4.6)	**<0.001**
UC	21.9 (21.2 to 22.7)	-	20.7 (18.1 to 23.2)	-	16.6 (14.3 to 19.0)	-	-	-1.3 (-3.8 to 1.3)	0.32	-	-	-5.3 (-7.7 to -2.9)	**<0.001**
Distress (DDS2)													
PTI	2.8 (2.6 to 2.8)	-	1.9 (1.7 to 2.2)	-	1.6 (1.4 to 1.8)	-	-	-0.72 (-0.93 to -0.51)	**<0.001**	-	-	-1.1 (-1.2 to -0.86)	**<0.001**
PFI	2.5 (2.3 to 2.6)	-	1.9 (1.8 to 2.1)	-	1.7 (1.5 to 1.9)	-	-	-0.5 (-0.7 to -0.31)	**<0.001**	-	-	-0.79 (-0.98 to -0.6)	**<0.001**
CBI	2.7 (2.6 to 2.8)	-	1.8 (1.6 to 2.0)	-	1.7 (1.5 to 1.9)	-	-	-0.91 (-1.1 to -0.71)	**<0.001**	-	-	-1.01 (-1.2 to -0.82)	**<0.001**
UC	2.6 (2.5 to 2.6)	-	2.1 (1.9 to 2.4)	-	1.97 (1.8 to 2.2)	-	-	-0.36 (-0.58 to -0.15)	**0.001**	-	-	-0.58 (-0.77 to -0.39)	**<0.001**

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.

B, baseline; CBI, is a combined intervention for patients and professionals; M, month; PFI, Intervention only for healthcare professionals at primary care; PTI, Intervention only for patients and family members; UC, usual care or control group.

Table 3. Proportion of patients who stop smoking at each follow up compared to the control group

	PTI (n=114)	PFI (n=156)	CBI (n=109)	UC (n=145)	*P* value global	*P* value PTI vs UC	*P* value PFI vs UC	P value CBI vs UC
3 Months	12.8	8.7	15.4	10.4	0.54	0.99	0.99	0.99
6 Months	28.5	7.5	24.2	15.4	0.003	0.11	0.22	0.99
12 Months	33.1	17.4	28.4	14.3	0.014	0.018	0.99	0.11
18 Months	36.7	19.6	37.6	18.8	0.004	0.04	0.99	0.03
24 Months	41.5	23.4	42.3	21.2	0.002	0.012	0.99	0.012

Only basal smokers are included in the analysis.

CBI, is a 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 or control group.

Table 4. Adjusted means for each group and intragroup differences compared with the baseline measurement (health-related quality of life and symptoms)

	Adjusted means in each group (95%CI)					Difference in intragroup of adjusted means compared to baseline (95%CI)					
	Baseline	**6 Months**	**12 Months**	**18 Months**	**24 Months**	**B-6M**	***P* value**	**B-12M**	***P* value**	**B-18M**	***P* value**	**B-24M**	***P* value**
Health-related quality of life and symptoms													
Health-related quality of life (ADDQoL-19)													
PTI	-1.7 (-1.8 to -1.6)	-1.0 (-1.3 to -0.8)	-1.2 (-1.5 to -0.97)	-0.85 (-1.1 to -0.61)	-0.76 (-0.99 to -0.53)	0.69 (0.46 to 0.93)	**<0.001**	0.52 (0.27 to 0.76)	**<0.001**	0.89 (0.65 to 1.1)	**<0.001**	0.97 (0.74 to 1.2)	**<0.001**
PFI	-1.7 (-1.8 to -1.5)	-1.2 (-1.5 to -1)	-1.1 (-1.3 to -0.88)	-1.3 (-1.5 to -1.0)	-0.98 (-1.2 to -0.75)	0.43 (0.21 to 0.66)	**<0.001**	0.55 (0.32 to 0.78)	**<0.001**	0.4 (0.17 to 0.63)	**0.001**	0.68 (0.45 to 0.9)	**<0.001**
CBI	-1.8 (-1.9 to -1.6)	-1.1 (-1.3 to -0.87)	-0.78 (-1.0 to -0.54)	-1.0 (-1.3 to -0.79)	-0.97 (-1.2 to -0.73)	0.65 (0.42 to 0.88)	**<0.001**	0.98 (0.74 to 1.2)	**<0.001**	0.73 (0.49 to 0.96)	**<0.001**	0.78 (0.54 to 1.0)	**<0.001**
UC	-2.1 (-2.2 to -1.9)	-1.1 (-1.4 to -0.9)	-1.6 (-1.9 to -1.4)	-1.2 (-1.5 to -1)	-0.92 (-1.2 to -0.69)	0.92 (0.7 to 1.2)	**<0.001**	0.44 (0.18 to 0.7)	**0.001**	0.82 (0.59 to 1.1)	**<0.001**	1.1 (0.9 to 1.4)	**<0.001**
Neuropathic symptom (MNSI)													
PTI	3.1 (3 to 3.2)	-	2.8 (2.5 to 3.1)	-	2.4 (2.1 to 2.7)	-	-	-0.29 (-0.61 to 0.02)	0.07	-	-	-0.69 (-0.99 to -0.4)	**<0.001**
PFI	3.3 (3.0 to 3.6)	-	2.8 (2.5 to 3.1)	-	2.9 (2.5 to 3.2)	-	-	-0.55 (-0.86 to -0.23)	**0.001**	-	-	-0.45 (-0.76 to -0.13)	**0.005**
CBI	3.3 (3.1 to 3.4)	-	2.6 (2.3 to 2.9)	-	2.8 (2.5 to 3.1)	-	-	-0.67 (-1.0 to -0.31)	**<0.001**	-	-	-0.46 (-0.78 to -0.13)	**0.006**
UC	3.3 (3.2 to 3.5)	-	3.1 (2.9 to 3.5)	-	2.5 (2.2 to 2.8)	-	-	-0.15 (-0.47 to 0.17)	0.36	-	-	-0.82 (-1.1 to -0.54)	**<0.001**

The models were adjusted by the baseline value of dependent variables and time elapsed since diagnosis.

B, baseline; CBI, is a combined intervention for patients and professionals; M, month; PFI, Intervention only for healthcare professionals at primary care; PTI, Intervention only for patients and family members; UC, usual care or control group

Table 5. Patient satisfaction with the intervention received (only those who made use of each intervention component)

	n	mean (95%CI)
Conventional group educational program		
Usability		
Environment generated	592	9.53 (9.46 to 9.60)
Exchange of experiences with participants and educator	588	9.59 (9.53 to 9.66)
Educator's work	587	9.79 (9.74 to 9.83)
Quality of materials	587	9.56 (9.49 to 9.64)
Personal satisfaction		
The sessions helped me get to know my diabetes better	591	9.67 (9.61 to 9.73)
I found the sessions useful	593	9.60 (9.52 to 9.67)
The sessions motivated me to look after my health better	590	9.62 (9.55 to 9.69)
General		
General satisfaction	589	9.70 (9.65 to 9.76)
I would recommend the sessions	588	9.77 (9.72 to 9.82)
Website platform		
Usability		
Access to the content	253	8.30 (8.02 to 8.58)
Usability of the web	251	8.59 (8.33 to 8.85)
Patient outcomes follow up charts	215	8.37 (8.03 to 8.72)
Quality of materials	229	8.81 (8.53 to 9.08)
Access to videos of the sessions	216	8.76 (8.47 to 9.05)
General		
General satisfaction	237	8.56 (8.30 to 8.82)
I would recommend using the website	239	8.81 (8.56 to 9.05)
Semi-automated mobile phone messages		
Usability		
Reading SMS	585	9.51 (9.41 to 9.61)
Usefulness of reminders	576	9.33 (9.22 to 9.45)
Personal satisfaction		
They adapt to my needs	579	9.04 (8.90 to 9.18)
They motivate me to look after myself	576	9.15 (9.02 to 9.28)
I would like to continue receiving them	552	8.80 (8.59 to 9.00)
General		
General satisfaction	572	9.23 (9.09 to 9.37)

Table 6. Significant differences compared to usual care for the three intervention groups.

	PTI		PFI		CBI	
	12 months	24 months	12 months	24 months	12 months	24 months
Cognitive/attitudinal						
Knowledge (DIATEK)	**	**		↓**	**	
Empowerment (DES)		**	***		***	**
Behavioural						
Diet (MEDAS)	**	***	↓***			**
Adherence (MGLS)						
Smoking	*	*			*	*
Affective						
Depression (BDI-II)			**		**	
Anxiety (STAI-S)			*		**	
Diabetes Distress (DDS2)		**		*	**	
HRQOL						
HRQoL (ADDQoL-19)	*		**		***	
Neuropathy (MNSI)					*	

↓ represent worsening compare to usual care.

*$P \leq 0.05$.

**$P \leq 0.01$.

***$P \leq 0.001$.

CBI, is a 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 or control group.

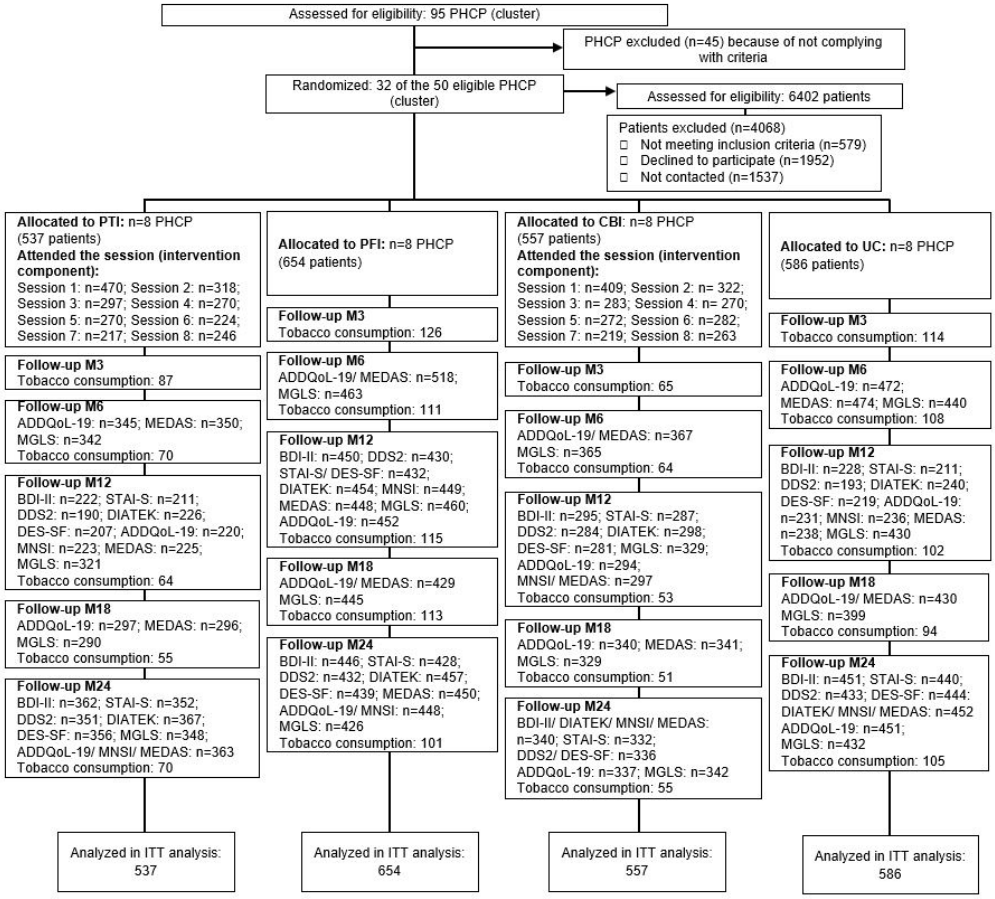

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

236x214mm (96 x 96 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8-9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	See the published protocol
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	7

		interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n.a.
	11b	If relevant, description of the similarity of interventions	n.a.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n.a.
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	n.a.
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	See the clinical outcomes paper published
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	16-17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	17
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	https://implem

			entationscience.biomedcentral.com/articles/10.1186/s13012-015-0233-1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.