"Diabetes Interactive Diary" (DID): a new telemedicine system enabling flexible diet and insulin therapy while improving the quality of life: an open label, international, multicentre, randomized study

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Short running title: Telemedicine system in type 1 diabetes

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Objective: A widespread use of carbohydrate (CHO) counting is limited by its complex education. This study compares a Diabetes Interactive Diary (DID) with standard CHO counting in terms of metabolic and weight control, time required for education, quality of life, and treatment satisfaction.

Research design and methods: Adults with T1DM were randomized to DID (Group A, N=67) or standard education (Group B, N=63), and followed-up for 6 months. A subgroup also completed SF-36 and WHO-DTSQ questionnaires at each visit.

Results: Of 130 patients (age 35.7±9.4 years; diabetes duration 16.5±10.5 years), 11 dropped out. Time for education was of 6 hours (range 2-15) in group A and 12 hours (2.5-25) in group B (p=0.07). HbA1c reduction was similar in both groups (Group A: from 8.2±0.8 to 7.8±0.8; Group B: from 8.4±0.7 to 7.9±1.1; p=0.68). Non-significant differences in favor of Group A were documented for FBG and body weight. No severe hypoglycemic episode occurred.

WHO-DTSQ scores increased significantly more in group A (from 26.7±4.4 to 30.3±4.5) than in group B (from 27.5±4.8 to 28.6±5.1) (p=0.04). Role physical, general health, vitality, and role emotional SF-36 scores improved significantly more in group A than in group B.

Conclusions: DID is at least as effective as traditional CHO counting education, allowing dietary freedom to a larger proportion of T1DM patients. DID is safe, requires less time for education, and is associated with lower weight gain. DID significantly improved treatment satisfaction and several quality of life dimensions.

There is universal consensus about the link between tight glycemic control and prevention of diabetes complications. According to American Diabetes Association recommendations (1), good metabolic control can be achieved not only by regular self-monitoring blood glucose and HbA1c measurements, but also through a system by which nutritional care and the specific lifestyle recommendations are provided, involving patients in the decision-making process (medical nutrition therapy). Aims of medical nutrition therapy are to provide sufficient and appropriate energy intake, to encourage healthy lifelong eating habits, to achieve and maintain the best possible glycemic control and ideal body weight (2). Several studies documented that medical nutrition therapy and specific diet-related behaviors result in a decrease of 0.25–1.0% in HbA1c in patients with diabetes (3-5).

In this context, the carbohydrate (CHO) counting education represents a key-point (6). CHO counting consists of estimating the grams of carbohydrate in foods being eaten, and relating that to the insulin bolus dose. The method does not designate a specific percent of energy as CHO, but CHO intake is based on individual preferences, diabetes medication, and maintenance of energy balance. The only caveat is to not exceed energy requirements to avoid undesired weight gain (6-8).

A flexible CHO intake is immediately translated into a flexible insulin therapy (7), in which bolus insulin is adjusted to match the dietary carbohydrate at each meal, identifying the most appropriate dose needed by the patient. Previous studies documented that carbohydrate counting and insulin dose adjustment at each meal promote dietary freedom, quality of life, and glycemic control, without worsening severe hypoglycemia or cardiovascular risk (9).

However, it is clear that flexible diet and insulin therapy require complex training for patients, who need to be educated in the type and amount of CHO found in foods, portion estimation, glycemic index (GI), relationships among blood glucose levels and food/ diabetes medication/ physical activity, carbohydrate/ insulin ratio, and specific algorithms to adjust insulin doses (6,7). The complexity of this educational approach limits a widespread use of CHO counting as an effective strategy to promote dietary freedom, quality of life, and glycemic control.

New advanced technologies can represent a possible solution to overcome the complex educational requirement. Data so far available show that telemedicine solutions for diabetes care are feasible and acceptable, but their effectiveness in improving HbA1c, reducing costs while maintaining HbA1c levels, or improving other aspects of diabetes management is not fully clarified, due to methodological flaws in study design (10,11).

Among the new devices, the “Diabetes Interactive Diary” (DID) represents an automatic carbohydrate/insulin bolus calculator to be installed in the mobile phone of the patient; it also works as a telemedicine system based on the communication patient-physician via short text messages. Feasibility, acceptability, and safety of the DID have been already documented in a phase 1 study (12). We designed a randomized trial aiming to evaluate whether DID could be effective in improving metabolic control in type 1 diabetes, while avoiding weight gain and reducing time devoted to education. In

addition, the study investigated whether and to what extent DID could impact on quality of life.

RESEARCH DESIGN AND METHODS

DID system. The "Diabetes Interactive Diary (DID)" is a new tool incorporating different functions; it is a CHO/insulin bolus calculator, an information technology, and a telemedicine system based on the communication between health care professional (physician or dietician) and patient via text messages. It allows patients to manage a flexible diet and to calculate the matching insulin bolus at each meal. In addition, it includes an algorithm for the calculation of basal insulin dose, based on the values of fasting blood glucose and the presence of hypoglycemic episodes.

DID consists of software to be installed in the patient's mobile telephone and enables the phone to be used as a small computer to record the blood glucose values and dose of insulin injections real-time; the system is also able to suggest the daily CHO intake, summing the amount of CHO consumed progressively (figure 1). Every patient can decide what to eat during the meal choosing between all the foods listed in the software; the quantification of the total calories and CHO consumed is facilitated by a list of pictures showing the specific food and the amount ingested.

The CHO/Insulin ratio and the Glycemic Correction factor, identified and prescribed by the health care professional, together with other information already filled out in the DID (e.g. physical activity, glycemic target, insulin dose, specific events), allows it to automatically calculate and suggest the most appropriate insulin dose to be injected.

Besides the collection of data on blood glucose measurements, CHO intake and insulin doses, the use of DID is associated with a regular feedback for the patient. In fact, data stored in the mobile phone are periodically sent as short text messages and reviewed on the personal computer of the physician. Then, any new therapeutic and behavioral prescription can be sent from the computer to the mobile phone, improving the communication between patients and physician.

Study design and outcomes. The DID study was an open label, international, multicentre, randomized (1:1), parallel-group study, having the primary aim of evaluating whether the use of DID could improve glycemic control (HbA1c) in a shorter time and more easily than the CHO counting standard educational approach. Secondary end-points were changes in fasting blood glucose (FBG) levels, body weight, lipid profile (serum total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides), and blood pressure; furthermore, safety-related problems (frequency of hypoglycemic episodes and hospitalizations) and differences in time dedicated to educational activities were taken into consideration. Finally, quality of life and patient treatment satisfaction were investigated in the subgroup of Italian patients. Data were collected at baseline, and after 3 and 6 months after the randomization.

The study involved seven Diabetes Outpatient Clinics: three in Italy, two in England, and two in Spain. All the centers habitually adopted CHO counting education and used electronic databases.

Participants. Every centre was asked to enroll 20 patients satisfying all the following inclusion criteria: diagnosis of type 1 diabetes, age ≥18 years, patients

not previously educated to CHO counting, and treated with multiple daily injections of short-acting and long-acting insulin analogues, or with continuous subcutaneous insulin infusion (CSII); patients practiced self-monitoring of blood glucose at least 3 times a day. Other important requirements in the selection of patients were an adequate familiarity in the use of mobile phones, according to the physician judgment, and the possession of a personal mobile phone card. All the patients were requested to give written informed consent to gain entrance to the study.

Patients were excluded in case of treatment with NPH insulin or soluble regular insulin, eating disorders, pregnancy, inability to send or receive short text messages, inability or unwillingness to give the informed consent, or any other disease or condition may interfere with the compliance with the protocol or the study completion.

Randomization. Eligible patients were randomized to start the standard CHO counting educational program or the DID approach. Randomization was performed through a telephone call to the coordinating centre. Random lists were stratified by centre. To ensure equal allocation rates within centers, permuted block randomization has been used.

Interventions*.* Patients randomized to the experimental group attended a course on the use of DID lasting up to 2 weeks. The course was provided as an outpatient program of 3 encounters with the physician and/or dietician.

Patients randomized to the control group received the standard educational approach usually utilized in the center, and lasting up to 3 months. Prior to the start of the study, an investigators' meeting was organized to establish some fundamental rules in the educational training and in the prescription of CHO/Insulin ratio and the Correction Factor.

Data collection*:* At study entry (visit 0), at 3 months (visit 1) and at 6 months (visit 2), clinical information was collected on case report forms. Baseline information included socio-demographic (age, gender, highest level of school education reached) and clinical characteristics (diabetes duration, insulin therapy, presence and severity of diabetes complications, co-morbidities, concomitant treatments). Blood pressure, body weight, FBG, HbA1c and lipid profile were measured at each visit. Each of the local laboratories used standard methods to measure these parameters.

Additional information was collected at the end of the study, including the number of contacts between the patient and the diabetes specialist (both short text messages and office visits), and any serious hypoglycemic episode requiring medical intervention.

Changes in health-related quality of life sub-study: Changes in the health-related quality of life (HRQOL) were evaluated in the subgroup of Italian patients, using generic (SF-36 Health Survey) and diabetes-specific (WHO-Diabetes Treatment Satisfaction Questionnaire) measures:

- *T*he SF-36 Health Survey (SF-36) is one of the most widely used measures of HRQOL and consists of 36 items covering eight dimensions: physical functioning, role limitations caused by physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations caused by emotional health problems and mental health (13). These eight domains may be further aggregated into two summary measures: the

physical component summary (PCS) measure and the mental component summary (MCS) measure (13). These aggregated scores are transformed to norm-based scores (mean, 50; SD, 10), with higher scores indicating more favorable physical functioning/ psychological well-being. The SF-36 has been used in large-population studies and in many different clinical conditions, showing excellent psychometric properties (14). It has been translated and validated in several languages, including Italian (15).

- *T*he WHO-Diabetes Treatment Satisfaction Questionnaire (DTSQ) has been specifically designed to measure satisfaction with diabetes treatment regimens and is appropriate for patients with Type 1 and Type 2 diabetes (16). The instrument was originally developed to detect changes in satisfaction related to changes in treatment modalities but it is also appropriate for comparing levels of satisfaction in subjects using different treatment regimens. It is composed of 8 items, 6 of which are summed in a single score ranging from 0 (very dissatisfied) to 36 (very satisfied). The remaining 2 items are treated individually and explore the perceived frequency of hyperglycemic and hypoglycemic episodes. The WHO-DTSQ has been validated in the Italian language among type 1 and type 2 diabetic patients, showing adequate psychometric properties (17).

Statistical analysis. Sample size was estimated by assuming a between groups mean difference of 0.5% in HbA1c levels after 3 months, assuming a HbA1c standard deviation of 1.0 (as derived from the DID pilot study). Given these assumptions, 63 patients per group were needed to ensure a statistical power of 80% (α=0.05). Taking into account a drop-out rate of about 10%, 70 patients per group had to be enrolled. Analysis was based on all the patients randomized, according to the intention-to-treat principle. For patients lost to follow-up the last information available has been used, using the last observation carried forward approach. Comparison of HbA1c and other secondary end-points between groups was performed after 3 and 6 months from randomization based on the Mann-Whitney test. Within-group differences achieved after 3 and 6 months from randomization were evaluated using the Wilcoxon signed rank test. Since it was hypothesized that the telemedicine approach could help in achieving the desired goals in a shorter period of time, between groups mean differences at 3 and 6 months were compared separately, instead of using repeated measures analysis of variance.

RESULTS

Overall, 130 individuals were recruited (figure 1). Less patients than those scheduled (130 vs. 140) were involved, due to organizational problems in two centers. However, since results show a standard deviation of HbA1c of 0.76% and the drop-out rate was of 8.5%, the a posteriori study power to detect a difference between groups of 0.5% in HbA1c levels was of 95%. The study also had a statistical power of 80% to detect a between-group difference in HbA1c levels of 0.38%.

Patients' characteristics according to the randomization arm are shown in table 1. The two groups did not differ for any socio-demographic and clinical characteristic, with the exception of

slightly higher levels of triglycerides in the DID group. Patients in the DID arm also had a higher prevalence of retinopathy and symptomatic neuropathy, although statistical significance was not reached.

Overall, 11 patients dropped-out during the study, 2 in the standard group and 9 in the DID group (figure 1). In the control group, both patients were lost to follow-up. In the DID group, two patients found it difficult to use the DID system, four had difficulties in sending text messages due to poor mobile network coverage in their area, two were not compliant with visit scheduling, and one moved in another area.

Between- and within-group changes after three and six months are shown in table 2.

A significant reduction in HbA1c levels of about 0.5% was documented in both groups after three months and maintained till the end of study. This improvement in metabolic control was obtained by devoting to CHO counting education a median (range) of 6 (2-15) hours in the DID group and 12 (2.5-25) hours in the standard group (p=0.07). Furthermore, after six months there was a non-significant decrease in FBG in the DID group (from 182.8±85.6 to 162.9±67.0 mg/dl), and a non-significant increase in the standard group (from 176.9±68.4 to 186.3±79.1 mg/dl) (between-group p=0.13). Increase in body weight was lower in the DID group (+0.7±3.6 Kg) than in the standard group (+1.5±2.3 kg), but the difference was not statistically significant (p=0.22). Furthermore, while we found no differences in mean daily doses of short-acting insulin between the two groups (DID group: 20.6±8.2 UI/die; standard group: 20.1±7.8 UI/die; p=0.92), mean daily doses of long-acting insulin were lower in the DID group than in the standard group, although statistical significance was not reached (DID group: 17.4±7.4 UI/die; standard group: 21.4±10.0 UI/die; p=0.12).

The DID group showed a significant decrease in triglycerides levels in comparison with the standard group; no other between-group changes were documented.

Within-group changes were also considered. The DID group generally showed a tendency toward a small, not significant improvement in all the measures considered, while in the standard group all parameters, except diastolic blood pressure and HDL cholesterol, tended to slightly increase at the end of the study.

No patients in either group were admitted to hospital during the study, and none reported any severe hypoglycemic episode requiring assistance. In each group, two patients reported episodes of mild hypoglycemia (p=0.93).

The median (range) number of text messages sent by each patient during the study was 52 (6-75), while the number of text messages sent by the physician was 39 (22-70). In other words, patients sent about two text messages/week to their physician, and the physician regularly replied to confirm the therapeutic scheme or to modify the parameters set in the DID (CHO/Insulin ratio, insulin sensitivity factor, and/or blood glucose target). In terms of costs for the patient, assuming a cost of 10-15 Euro cents per message, and considering that on average each patient sent 52 SMSs, the overall cost sustained did not exceed 8 Euros.

Results of quality of life evaluation performed on the sub-sample of 60 patients enrolled in the Italian centers are shown in table 2. Clinical and socio-demographic characteristics at baseline did not differ between the two groups. A statistically significant difference in favor

of the DID group was documented for treatment satisfaction, as expressed by the WHO-DTSQ score. Similarly, the score testing the perceived frequency of hyperglycemic episodes significantly decreased after three months in the DID group but not in the control group. Several SF-36 subscales (role physical, general health, vitality, and role emotional) also showed significantly higher improvements in the DID group than in standard group.

In addition, pre-post within-group comparisons underline the beneficial effects of DID in the experimental group in terms of WHO-DSTQ-score, perceived frequency of hyperglycemic episodes, general health perception, and vitality; on the other hand, all scores within standard group tended to worsen at three months, **though statistical significance was not reached**.

CONCLUSIONS

The complexity of the educational approach needed to teach CHO counting and consequent insulin adjustment can represent an obstacle for many patients, thus limiting the possibility of its widespread use as an effective self-management tool. The CHO/insulin bolus calculator is coupled with a telemedicine system based on the short text messages. At the present time, the most common way of data communication between patient and diabetologist is represented by the paper diary, that is often perceived as a boring document not adequately filled in; furthermore, even if sufficiently complete, it cannot induce a day-by-day adjustment of the insulin dose and lifestyle (18). In contrast, DID is installed on the mobile phone, that is a familiar technology already used in the daily life by the vast majority of individuals. DID facilitates not only the automatic storage of blood glucose measurements, CHO intake, and insulin doses, but also the exchange of information between patient and care provider via text messages. To this respect, while previous, small studies have evaluated the efficacy of telemedicine systems mainly based on the transmission of self-monitoring of blood glucose values and feedback from the health care provider (10), this is to our knowledge the first study investigating a multi-purpose instrument, replacing the classical approach to insulin dose modification.

Our data show that DID can represent a useful device, incorporating several features helping patients promote dietary freedom and flexible insulin bolus. The first pilot study previously showed that the system is safe, easy to use, and well accepted by the vast majority of the patients. What these new results add is that the use of DID is at least as effective as the traditional educational approach to CHO counting in reducing HbA1c levels, while producing different concomitant benefits. Firstly, it allows to avoid the complexities of CHO counting and insulin dose adjustment with a halving in the time dedicated to education, and thus potentially increasing the proportion of individuals with T1DM adopting this method. Of note, despite the higher rate of dropouts in the DID group, only two patients interrupted the study due to difficulties in using the telecare system, thus confirming that the device can be easily used by the vast majority of patients.

In addition, the use of DID was associated with lower weight gain, probably due to the requirement of lower doses of long-acting insulin. It is worth mentioning that, despite the use of a lower doses of long-acting insulin,

patients assigned to the DID group showed a reduction in fasting plasma glucose levels during the study, while levels slightly increased in the control group. This finding is important in light of the need to adopt therapeutic strategies that achieve good metabolic control while minimizing insulin dosage.

The use of DID was also associated with a significant improvement in several mental and physical components of the SF-36 Health Survey, as compared to the standard group. This also translated into a marked improvement in treatment satisfaction, thus suggesting that the use of telemedicine can increase the level of acceptance of insulin treatment and help coping with the disease.

Some limitations of this study need to be discussed. Firstly, we were not able to measure the effect of DID in reducing glucose variability. In fact, by allowing a greater flexibility, one can speculate a positive effect of telemedicine also on post-prandial blood glucose excursions. Secondly, even if specific guidelines were established in the pre-study investigators' meeting, the DID educational intervention was influenced by the individual practice of the different international participating centers, thus varying in duration. Nevertheless, the randomization was stratified by center, making the comparison between telemedicine and usual care unbiased.

In conclusion, DID was at least as effective as traditional CHO counting education, allowing dietary freedom to a larger proportion of T1DM patients. DID required less time for education and did not increase the risk of hypoglycemic episodes. DID also significantly improved treatment satisfaction and several quality of life dimensions. Larger studies are needed to reach more solid conclusions regarding the effects of DID on FBG, body weight, and insulin dosage.

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Table 1: Patients' characteristics according to the randomization arm.

	DID (N=67)	**Standard (N=63)**	**p***
Males	44.8%	41.0%	0.67
Age	35.4±9.5	36.1±9.4	0.63
Highest level of school education completed:			0.23
Low level (less than college degree)	18.8%	17.7%	
Intermediate level (less than university degree)	68.7%	58.1%	
High level (university degree)	12.5%	24.2%	
Duration	17.1±10.3	15.8±10.7	0.37
Short-acting and/or Long-acting analogues	80.6%	80.9%	0.96
CSII	19.4%	19.1%	0.96
Self-monitoring (years)	14.7±7.3	13.2±8.4	0.10
N° of daily blood glucose tests	2.3±1.1	2.4±1.1	0.77
HbA1c (%)	8.2±0.8	8.4±0.7	0.19
Fasting glucose (mg(dl)	183±86	177±68	0.62
Systolic blood pressure (mmHg)	122±17	120±11	0.50
Diastolic blood pressure (mmHg)	74±7	74±8	0.72
Weight (Kg)	69.9±12	69.4±11.9	0.98
Total cholesterol (mg/dl)	180±30	184±34	0.40
Triglycerides (mg/dl)	95±55	80±54	0.03
HDL – cholesterol (mg/dl)	58±15	61±16	0.15
LDL – cholesterol (mg/dl)	102±28	106±27	0.37
Retinopathy	28.8%	20.6%	0.28
Lower limb complications	0%	1.6%	0.34
Nephropathy	4.6%	3.2%	0.67
Symptomatic Neuropathy	9.1%	3.2%	0.17

Data are mean±standard deviation or frequency
**p values refer to χ^2 for categorical variables and to Mann-Whitney test for continuous ones*

Table 2: Between - and within group differences in clinical parameters and quality of life scores at visit 2 and visit 3 with respect to baseline values.

	DID group (N=67)			**Standard group (N=63)**			**Between group***		**Within DID****		**Within Standard****	
	BASELINE	*3 MONTHS*	*6 MONTHS*	*BASELINE*	*3 MONTHS*	*6 MONTHS*	*p** (3 vs. 0)	*p** (6 vs. 0)	*p*** (3 vs. 0)	*p*** (6 vs. 0)	*p*** (3 vs. 0)	*p*** (6 vs 0)
HbA1c (%)	8.2±0.8	-0.5±0.8	-0.4±0.9	8.4±0.7	-0.4±0.6	-0.5±1	0.95	0.68	**<0.0001**	**<0.0001**	**<0.0001**	**0.0002**
FBG (mg/dl)	182.8±85.6	-1.7±105	-22±99.8	176.9±68.4	3.8±94.7	15.5±90.8	0.83	0.13	0.92	0.13	0.81	0.39
SBP (mmHg)	121.5±12.8	-1.8±13.7	-0.8±8.6	119.2±11.5	0.4±11	0.7±11.5	0.19	0.71	0.63	0.60	0.70	0.51
DBP (mmHg)	74.4±7.5	-2.4±7.9	-1.3±6.5	74.1±7.6	-2.3±6.8	-1.1±7.6	0.83	0.89	**0.0004**	0.16	**0.01**	0.27
Total chol. (mg/dl)	179.5±29.9	-3.8±29.1	-3.6±32.3	184.3±34	3.1±26.6	2.7±28.9	0.15	0.33	0.96	0.47	0.31	0.42
HDL-chol. (mg/dl)	57.6±15.3	0.9±9.4	1.6±8.5	61.1±16.4	-1.7±9.8	4.8±10.3	0.49	0.14	0.57	0.11	0.15	**0.0005**
LDL-chol. (mg/dl)	101.9±28	-0.8±26.4	-3.4±29.1	105.8±27.4	5.7±23.3	0.3±27.6	0.26	0.79	0.18	1.0	**0.05**	**0.05**
Triglycerides (mg/dl)	94.5±54.9	-10.7±48.8	-10.7±56.1	79.9±54	1.9±43.7	8.2±43.4	0.06	**0.04**	0.30	0.17	0.69	0.15
Weight (Kg)	69.9±11.8	-0.1±3.8	0.7±3.6	69.4±11.9	0.7±1.9	1.5±2.3	0.15	0.22	0.30	0.16	**0.006**	**<0.0001**
DTSQ* **												
Score	26.7±4.4	1.8±3.63	3.39±4.21	27.5±4.8	0.64±3.85	1.03±4	0.2	**0.04**	**0.009**	**0.0002**	0.43	0.17
Hyperglycemia	3.6±1.6	-1±1.36	-0.42±1.7	3.1±1.3	-0.32±1.65	0.2±1.8	**0.05**	0.19	**0.0006**	0.21	0.23	0.50
Hypoglycemia	2.3±1.1	0.37±1.34	0.53±1.66	2.5±1.5	-0.2±1.58	-0.1±1.74	0.08	0.16	0.19	0.12	0.51	0.76
SF-36* **												
Physical functioning	90±13.3	-3.27±16.75	4.28±12.3	94.1±8.3	-0.67±11.78	0.19±7.25	0.95	0.22	0.28	0.10	0.76	0.89
Role Physical	72.5±36.2	8.62±37.95	7.14±42.95	85.8±27.6	-12.06±38.16	0±28.34	**0.05**	0.27	0.26	0.49	0.09	0.96
Bodily Pain	78.4±21.5	3.93±18.32	-2.17±23.87	71.2±19.2	-2.51±21.43	10±25.47	0.35	0.09	0.29	0.51	0.67	**0.04**
General Health	56±23.3	4.75±8.91	6.47±16.82	61.4±16.4	-2.77±13.1	-4.61±14.69	**0.02**	**0.02**	**0.009**	0.06	0.30	0.08
Vitality	57.8±15.8	4.31±10.49	8.21±17.9	66.7±15.7	-5.05±13.88	0.27±14.09	**0.02**	0.1	**0.04**	**0.04**	0.07	0.91
Social Functioning	73.3±17.3	0.86±15.99	4.46±23.12	76.3±20.3	4.31±19.84	3.33±22.24	0.53	0.8	0.82	0.35	0.22	0.42
Role Emotional	60±36.5	14.94±40.42	17.85±52.49	83.9±27.8	-4.02±22.56	-4.02±35.53	**0.02**	**0.05**	0.07	0.14	0.33	0.51
Mental Health	68.7±16.3	-0.34±10.92	4±19.22	70.8±14.9	-1.37±12.1	-0.8±12.79	0.67	0.23	0.82	0.33	0.59	0.73
Physical Component Score	50.3±8.9	1.32±6.57	0.61±7.33	50.6±4.9	-1.7±7.03	1.03±4.86	0.09	0.77	0.39	0.72	0.27	0.27
Mental Component Score	43.5±10.63	2.23±8.08	4.23±12.48	48.1±8.1	-0.29±6.77	-0.76±10.18	0.18	0.14	0.16	0.11	0.84	0.70

*3 and 6 months columns show the mean variation at visit 2 and visit 3 with respect to baseline values; *p values refer to Mann-Whitney test;
** *p values refer to Wilcoxon signed rank test; ***Questionnaires administered to a subgroup of 60 patients (30 in DID group and 30 in standard group).*

Figure 1: Study flow-chart