THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Bergenstal RM, Johnson M, Passi R, et al. Automated insulin dosing guidance to optimise insulin management in patients with type 2 diabetes: a multicentre, randomised controlled trial. *Lancet* 2019; published online Feb 23. http://dx.doi.org/10.1016/S0140-6736(19)30368-X.

Supplementary material

About d-Nav®

d-Nav is designed to allow patients to enhance their insulin regimen. It does so by providing patients with dose-by-dose guidance, while preforming titration in the background. Rather than having the health care professional (HCP) "in the loop," i.e. titrating the insulin dosage, it keeps the physician "on the loop," allowing the health care provider to decide if the patient is using an appropriate insulin regimen knowing that d-Nav will titrate each dose.

From a patient perspective, d-Nav is primarily a dose calculator. It tells the patient how many units of insulin to inject. Dose guidance is based on a built-in insulin dosage function, similar to what a patient would be prescribed on a piece of paper. Before every scheduled injection, the patient would insert a test strip and apply blood to measure their glucose. d-Nav shows the glucose reading for a few seconds and then replaces the glucose value with an "event" screen, e.g. Breakfast. Based on the selected event and the stored dosage function d-Nav recommends a dose of insulin.

Under the hood, d-Nav continuously assesses the glucose readings and search for glucose patterns. These are used to automatically titrate the stored dosage function without HCP intervention. Different doses are adjusted independently from each other. For example, in a basal-bolus regimen: patterns in breakfast glucose are used to adjust the basal dose, patterns in lunch readings are used to adjust the breakfast dose, patterns in dinner readings are used to adjust lunch doses, and patterns in bedtime readings are used to adjust dinner doses. In a biphasic insulin regimen, patterns in breakfast glucose are used to adjust the dinner dose, patterns in dinner readings are used to adjust the breakfast dose.

It takes a full week before d-Nav is allowed to increase any doses, but doses can decrease as often as a "low glucose pattern" is detected. For example, two blood glucose readings below 65 mg/dl at lunch would immediately cause a reduction in breakfast dose. To increase a dose, four or more elevated glucose readings, for a single event such as "Breakfast," within the last week are required. Dose adjustments are proportional to the distance between the average glucose and the target range, i.e. if the average glucose is 250 mg/dl d-Nav would increase a dose by ~20%, while if the average glucose is 150mg/dl it will increase a dose by ~10%.

We have reported elsewhere results regarding patients' satisfaction and long-term outcomes with d-Nav (1-6). It was shown that on average d-Nav titrates the patient's dosage function every 6.4 days. Most patients respond very favorably to the simplicity of d-Nav, and often comment about the fact that it takes the guess-work out of insulin injections. It was further shown that patients were able to maintain A1c at goal for more than three years of continual use of d-Nav.

d-Nav is not designed to replace the treating physician but rather to support physicians' ability to treat patients using desired insulin regimens without increasing the workload. For example, if a patient is prescribed with once a day basal insulin alone and they come to the clinic 6 months later with an elevated A1c it is hard to know if it's the "wrong dose" or the "wrong regimen." With d-Nav it becomes clear that it is not a dose question since doses are constantly optimized by the device. Yet, if the physician sees a patient has a stable dose of long-acting insulin only regimen, a close to normal fasting glucose, and an elevated A1c, they can quickly realize that it's time to intensify the insulin therapy. The solution has been in use in the United Kingdom since 2012, supporting patient's insulin therapy for over 6 years(7).

References

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6. Rosenthal ES, Bashan E, Herman WH, Hodish I. The effort required to achieve and maintain optimal glycemic control. J Diabetes Complications. 2011;25(5):283-8.

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Legends of Supplementary figures

Supplementary figure 1: Distribution of HbA1c during the study. The dot plot depicts the distribution of HbA1c during the beginning of the study and at study end in both groups. Averages are labeled as black bars.

Supplementary Figure 2: Distribution of HbA1c changes during the study. The line plot depicts HbA1c changes independently in each participant.

Supplementary Figure 3: Mean glucose changes during the study. Results are Mean ± SEM.

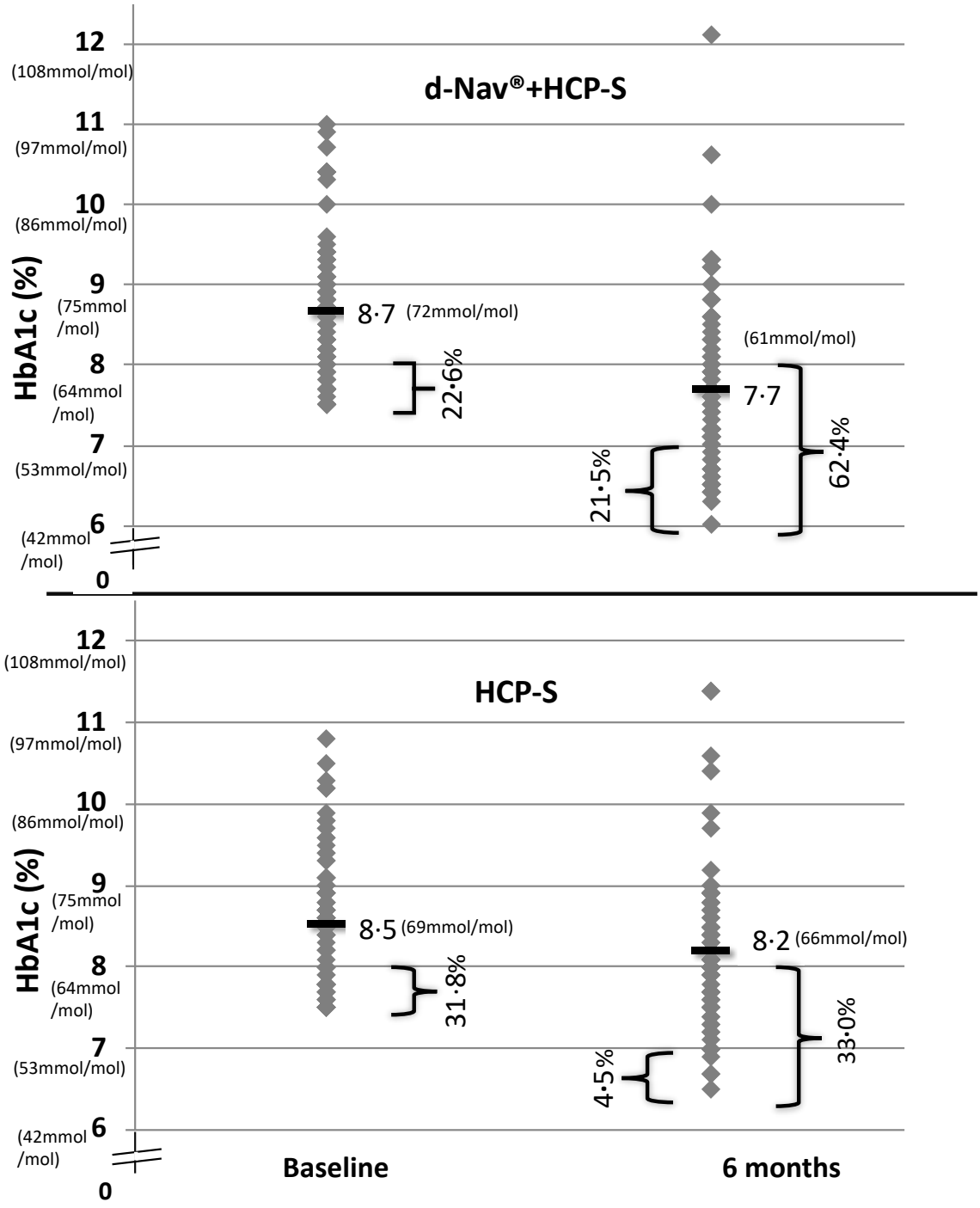
Supplementary Figure 4: Mean fasting glucose changes during the study. Results are Mean ± SEM.

Supplementary Figure 5: Average number of glucose measurements per week. Pre-enrolment information was obtained from screening questionnaires. When the reported frequency of glucose measurements exceeded 28 per week, the frequency was expressed as 35 per week. The frequency of glucose readings at 3 and 6 months, were calculated based on the last week before the visit. Solid line represents the mean expected 100% of the measurements per week and scattered line represent 80% of the expected (i.e., for long-acting insulin regimen the expected weekly measurement was 7 per week; for biphasic or pre-mixed regimen 14; for basal-bolus regimen with or without carbohydrate counting 28). For the d-Nav + HCP-S group 100% of the expected glucose measurements per week was 11.0 (80% was 8.8 per week) and for the HCP-S 10.4 (80% was 8.3 per week). Results are Mean ± SEM.

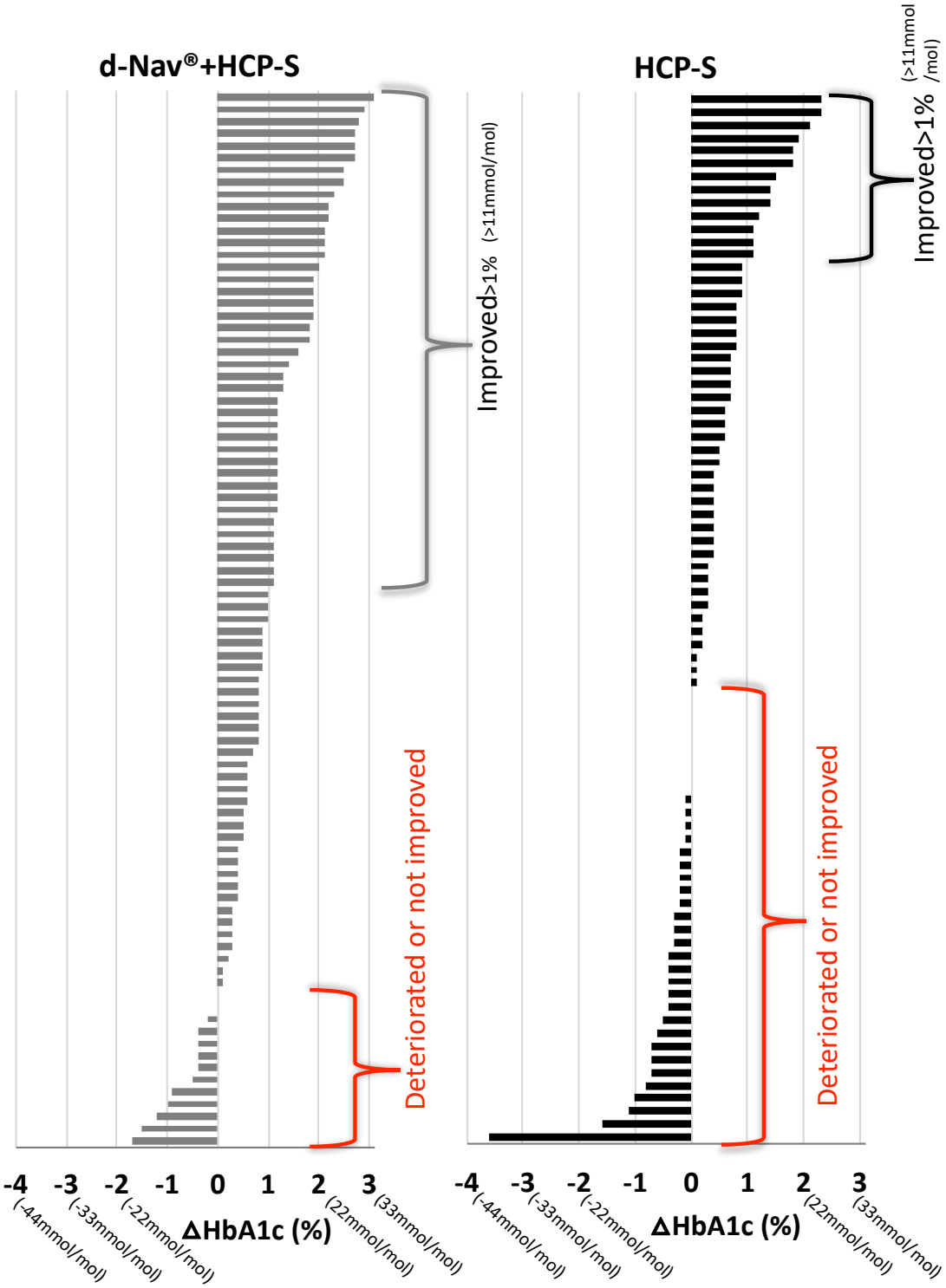
For all figures, d-Nav + HCP-S denotes d-Nav + healthcare professional support and HCP-S denotes health care professional support alone.

Supplementary figures

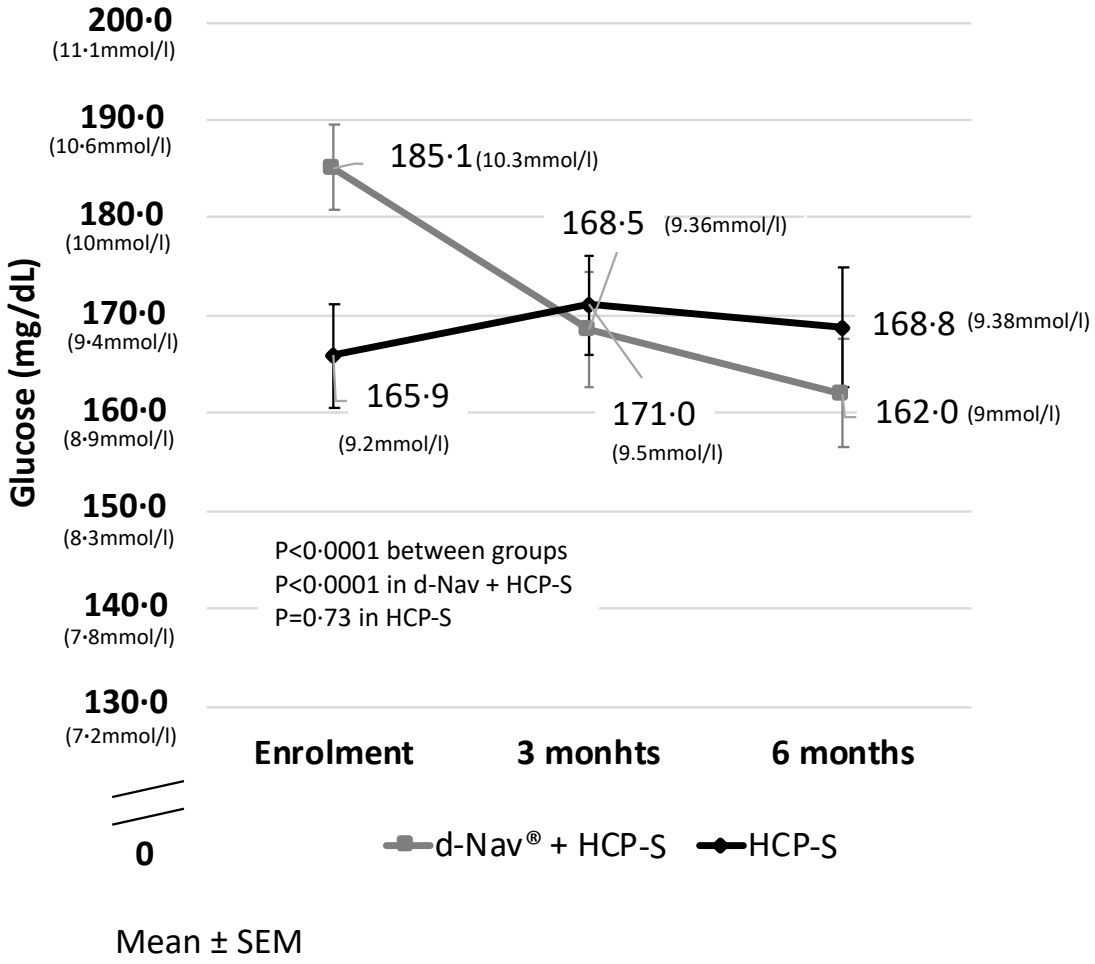
<u>Supplementary Figure 1:</u> Distribution of HbA1c during the study.



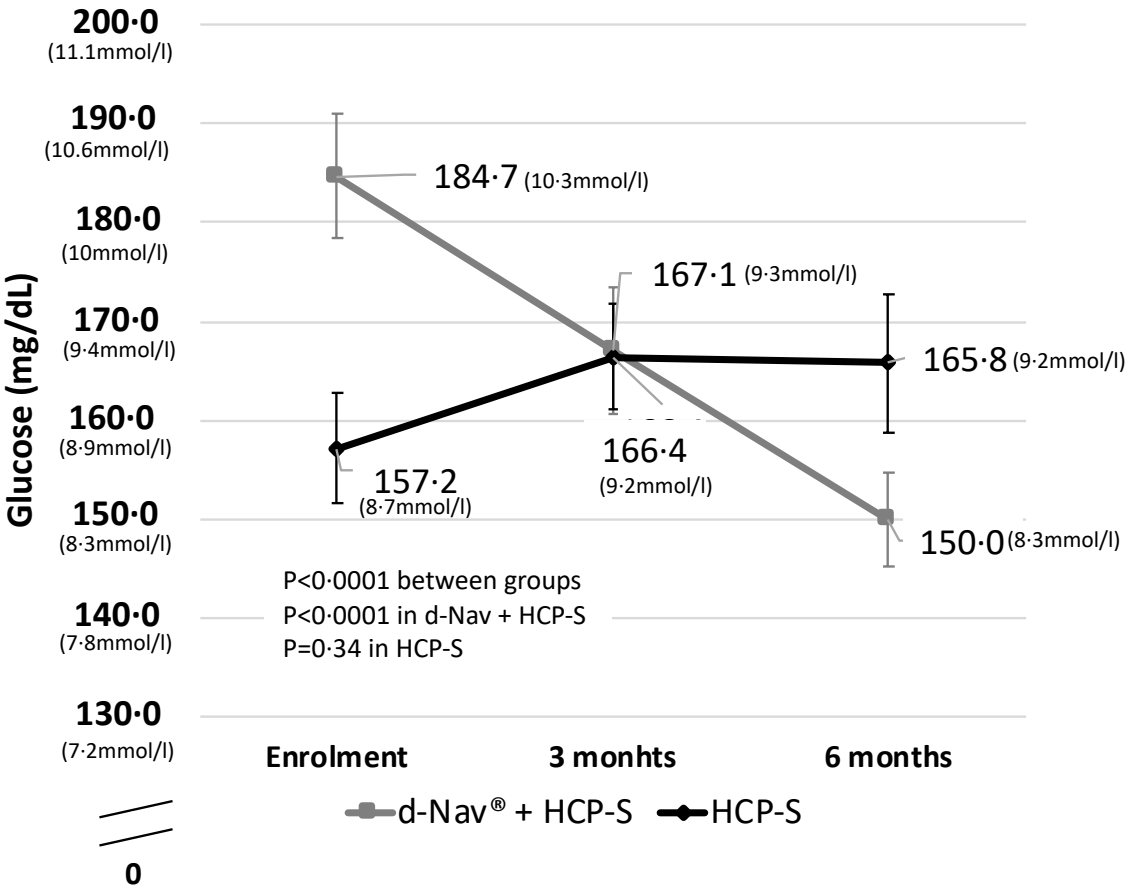
<u>Supplementary Figure 2:</u> Distribution of HbA1c changes during the study.



<u>Supplementary Figure 3:</u> Mean glucose changes during the study.

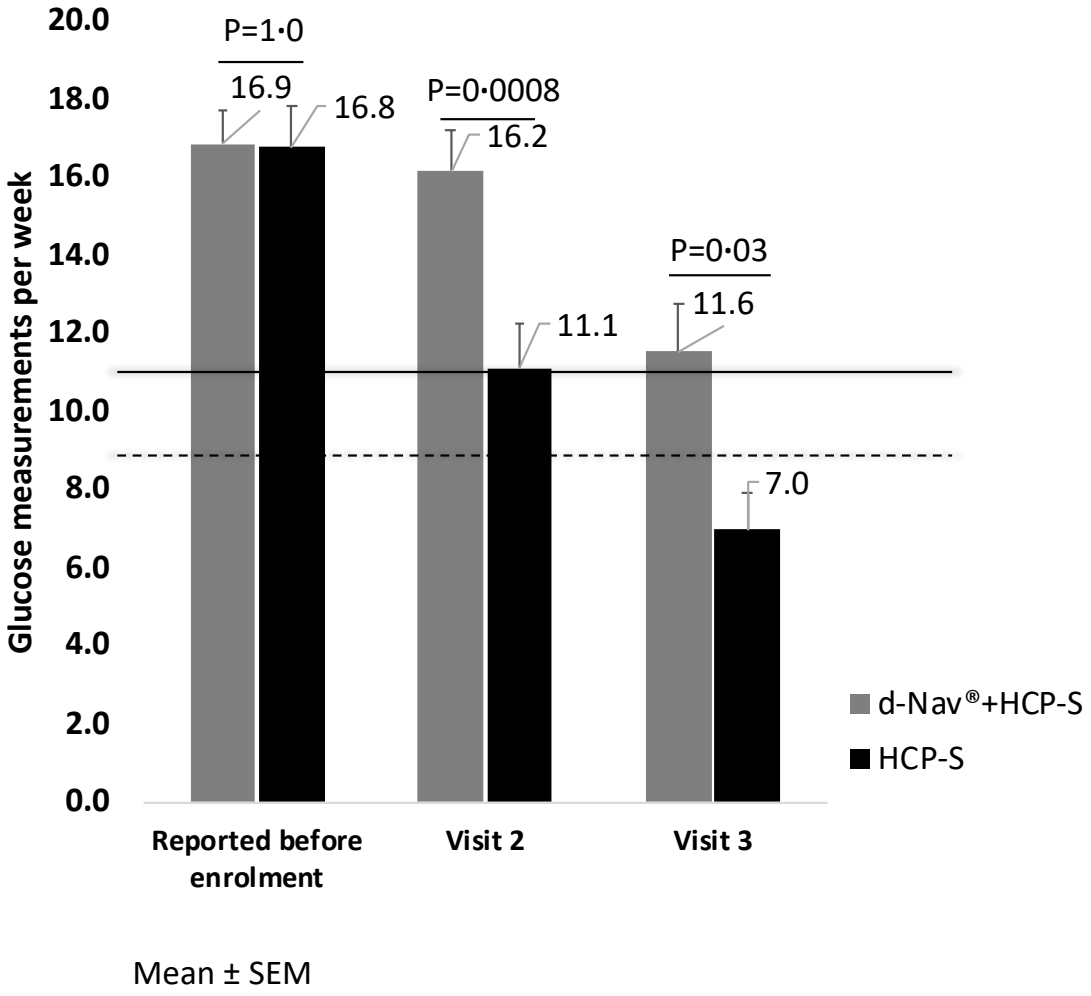


<u>Supplementary Figure 4:</u> Mean fasting glucose changes during the study.



Mean ± SEM

Supplementary Figure 5: **Average number of glucose measurements per week.**



Supplementary tables

<u>Supplementary Table:</u> Key questions in patients questionnaire.

	Answers:		
Questions:	**d-Nav®+HCP-S**	**HCP-S**	**P**
<u>Baseline:</u>			
Is your diabetes primarily treated by an endocrinologist or a primary care provider? (percent of patients)	Endocrinologist: 54·8% Primary care provider: 44·1% Both: 0 No one at this time: 1·1%	Endocrinologist: 46·6% Primary care provider: 50·0% Both: 2·3% No one at this time: 1·1%	P=0·9
How many times during the past year has your insulin dosage been adjusted by your doctor or another health care professional? (percent of patients)	0 times: 18·3% 1 times: 36·6% 2 times: 26·9% 3 times: 14·0% 4 times: 3·2% 5 times: 1·1% ≥6 times: 0	0 times: 18·2% 1 times: 33·0% 2 times: 23·9% 3 times: 17·0% 4 times: 6·8% 5 times: 0 ≥6 times: 1·1%	P=0·9
<u>At 6 months:</u>			
How likely are you to continue to monitor your glucose levels at least 4 times per day (if you are taking 4 shots of insulin) or 2 times per day (if you are only taking 2 shots of insulin)? (percent of patients)	Probably not: 9·5% Maybe: 8·3% Probably: 33·3% Definitely: 48·8% Not available: 9 patients	Probably not: 9·3% Maybe: 14·7% Probably: 33·3% Definitely: 42·7% Not available: 13 patients	P=0·6
During the study were you comfortable with your insulin dosage being adjusted by the d-Nav® rather than your Primary Care Provider or endocrinologist?	Not comfortable: 9·5% Somewhat comfortable:20·2% Comfortable: 31·0% Very comfortable: 39·3% Not available: 9 patients	NA	
How satisfied are you with your diabetes management throughout the study?	Not satisfied: 7·9% Somewhat satisfied: 16·9% Satisfied: 28·1% Very satisfied: 47·2% Not available: 4 patients	Not satisfied: 8·8% Somewhat satisfied: 23·8% Satisfied: 32·5% Very satisfied: 35·0% Not available: 8 patients	P=0·4

Abbreviations: SD=standard deviation; NS=non-significant; NA=not-applicable;
d-Nav®=diabetes navigator; HCP-S=healthcare professional; support.

2014

Prospective, Open-Label, Randomized, Controlled, Multi-Center Study Comparing Efficacy and Safety of Frequently Modified Insulin Therapy Using Dosage Recommending Device to Clinic Based Support of Insulin Titration in Individuals with Type 2 Diabetes

Protocol No PD004

Protocol Amendment 1

Robert J Bard, Esq
Hygieia Research
12/18/2014

Introduction

Hygieia Research seeks to conduct a prospective randomized clinical study involving adult subjects with uncontrolled Type-2 diabetes requiring insulin. The study seeks to demonstrate that the clinical application of the d-Nav will achieve metabolic control in a safe and effective manner.

This is a 6 month prospective, open-label, randomized, controlled, multi-center clinical safety and efficacy study as a single intervention. The study will include 200 subjects with Type-2 diabetes, who are already on insulin therapy, but have inadequate metabolic control.

Background

Diabetes has become a growing epidemic, yet treatment goals are seldom achieved, and subjects endure detrimental complications. Insulin is the only dose-dependent diabetic medication in which most subjects can achieve optimal blood glucose levels when an adequate dosage is prescribed.

Soon after the introduction of home glucose monitoring in the late 1970s, the idea that an algorithm could be used to determine insulin dosage was introduced by Skyler[1]. This was a published table that guided dosage decisions. Later, Albisser developed the Insulin Dosage Computer, a handheld device that helped subjects calculate their insulin dose. The Insulin Dosage Computer was clinically evaluated by several researchers[2-8] although most of these studies report a minimal number of subjects.

During the mid 1980s and early 1990s there was an effort to develop a useful mathematical model for one's metabolic process and use it to predict and to achieve tight Control of glucose level[9-11]. Unfortunately, most efforts did not yield a model accurate enough for diabetes Control purposes[12]. In a meta-analysis study, Balas et al.[13] could not point to a study showing a robust and efficient dosage management algorithm to improve outcomes of insulin treated subjects with diabetes.

Hygieia, Inc. has developed a device called d-Nav™, intended for use by insulin-requiring subjects with diabetes. d-Nav is a pocket-sized, hand-held device, with proprietary algorithmic software that analyzes blood glucose patterns stored in the device's memory captured from the device's integrated glucose sensor. The device analyzes its user's stored glucose readings and periodically moderately adjusts its insulin dosage. The software algorithms are based on the way an endocrinologist evaluates and adjusts insulin dosage in a patient with diabetes. The ability of the d-Nav device to provide insulin dosage adjustments clinically equivalent to dosage adjustments from health care providers was demonstrated using data from two studies conducted in the UK and two clinical studies conducted in the US. (See Results of Prior Investigations Summary Section).

Incidence of Diabetes / Standard of Care

According to the American Diabetes Association (March 2013), there are more than 25.8 million subjects with diabetes and another 79 million considered to be pre-diabetic in the United States (US). Direct costs of diabetes-related complications were $176 billion in 2012 (compared with $58 billion in 2007). Diabetes complications are mainly attributed to uncontrolled glucose levels[14]. Diabetes is the leading cause for blindness among adults, kidney failure, and non-traumatic lower limb amputation[15]. In 2007, the NIH reported that the prevalence of diabetes mellitus diagnosed cases in the U.S. was 17.9 million. This prevalence is expected to reach 44 million by 2034. According to the 2007 National Diabetes Fact Sheet (Center for Disease Control), among people with diabetes, 14% are being treated with insulin only (2.51 million), and 13% with insulin plus oral diabetic medications (2.33 million); thus, at present it is estimated that more than 5 million people in the US are self-administering insulin daily, by injection or an infusion pump. Nevertheless, more than 3 million insulin-treated subjects exhibit poorly Controlled, glucose levels, and therefore are at increased risk to develop long-term disease complications [16, 17].

Insulin treatment requires individual tailoring of dosage to obtain a benefit from the drug. Studies indicate that modifying insulin dosage every 1-2 weeks maximizes treatment utilities [18-26]. However, the current structure of the health care system does not permit such frequent review of glucose data and corresponding timely insulin dosage modification. Simply stated, there are not enough care providers to support subjects with the care level they require.

Rationale

The rationale to support frequent insulin dosage adjustments is based on the fact that the state of metabolism of a given individual varies from time to time, beyond the daily fluctuations in energy balance. In a person with normal insulin reserves, periodic changes in insulin needs keep glucose levels in the normal range. In the case of a patient with diabetes, whose metabolism relies on exogenous insulin, infrequent dosage adjustments will not meet the fluctuating demand (Figure 1). Consequently, it is only when frequently adjusted that insulin therapy exploits the full benefit of the regimen.

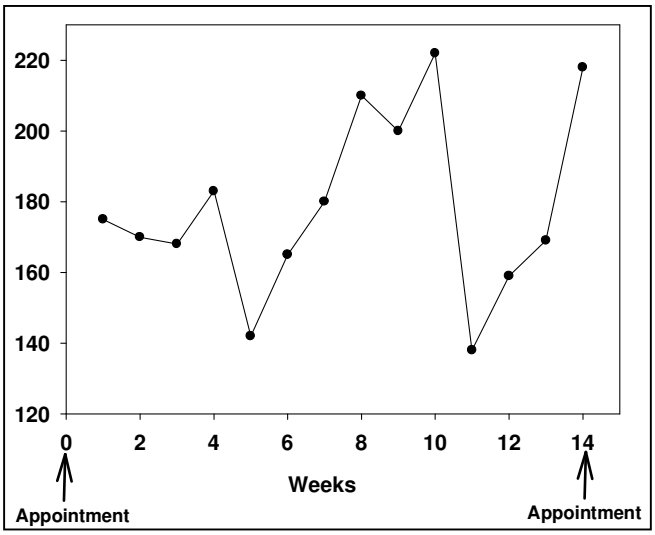


Figure 1: Weekly mean glucose readings between clinic visits (about 15-30 readings per week) of a representative patient with uncontrolled diabetes. Fluctuations in weekly mean glucose levels are noted between visits, demonstrating that dosage adjustments made only at time of clinical visits will be inadequate.

The rationale to conduct this study is that Hygieia hypothesizes that d-Nav will effectively and safely optimize glucose Control in insulin-requiring subjects with Type-2 diabetes. d-Nav was designed to provide safe insulin dosage recommendations.

Results of Prior Investigations Summary

A service evaluating the effectiveness of using the d-Nav (a handheld device that automates the process of insulin dosage titration using Diabetes Insulin Guidance System [DIGS™] device) in achieving glycemia Control was conducted in the UK at the Ulster Hospital, Dundonald, Belfast, Northern Ireland.

An exploratory single-centre pilot evaluation of the use of d-Nav in subjects aged ≥ 21 years with an HbA1c ≥7.0% (53 mmol/mol) who were receiving insulin therapy for at least one year. Subjects were asked to use d-Nav to monitor their blood glucose level before every insulin injection and when they suspected the occurrence of hypoglycemia, to allow d-Nav to adjust insulin dosage. At scheduled 3-monthly clinic visits, HbA1c was measured and information on episodes of hypoglycemia were collected from d-Nav and by patient reporting. Subjects were followed for a minimum of 6 months.

A total of 96 subjects completed the evaluation (active users). The mean (± SD) HbA1c for the active users decreased from 9.2 ± 1.4% (77 ± 15 mmol/mol) at baseline to 7.8 ± 1.2% (62 ± 13 mmol/mol) at the 3–5 month clinic visit and to 7.5 ± 1.2% (58 ± 13 mmol/mol) at the 6–12 month clinic visit. In subjects for whom paired data were available, the decreases were statistically significant at both post-baseline visits (both $p<0.001$). The frequency of minor hypoglycemia (blood glucose ≤3.6 mmol/L) was low and well within the tolerated range.

Original software algorithm studies

Study 1: Using data from a previously completed trial of elderly subjects with uncontrolled Type-2 diabetes requiring insulin therapy[18], Hygieia, Inc. compared the insulin dosage adjustments made by clinical personnel at the University of Michigan to the dosage adjustments recommended by device software. Information (i.e., blood glucose values on the patient's weekly or bi-weekly charts) used by clinical personnel at the University of Michigan to make insulin dosage adjustments was also used as an input to the device software. The device software was developed prior to acquiring the clinical data from the University of Michigan. William H. Herman and his study-team, from whom the data was acquired, were not involved in the development of the device software. Ninety-six percent (96%) of the 2,520 dosage adjustment episodes from device software recommendations yielded insulin dosage recommendations clinically equivalent to the recommendations of the clinical personnel at the University of Michigan. Eight dosage recommendations (0.3%), 7 of which were recorded in a single patient, were considered "Different by 10%-20%". No cases of "Different by >20% were noted.

Study 2: Hygieia, Inc. conducted a prospective clinical study involving adult subjects with uncontrolled Type-1 and Type-2 diabetes. The study demonstrated the efficacy and safety of dosage adjustments based only on self-monitored blood glucose (SMBG) levels, without having direct interaction with subjects. In addition, 99% of the 568 device software recommendations yielded insulin dosages clinically equivalent to the recommendations of Dr. Hodish (study endocrinologist and co-developer of the insulin adjustment software). In sixty-three percent (63%) of the cases, the device software gave "Identical" recommendations to Dr. Hodish; 30% were "within 10%", 6% were "within 10%-20%". A single episode (0.2%) was "different 10%-20%" and due to data discrepancy of the patient's reported SMBG value (94 mg/dl interpreted

as 44). There were no cases of "Different by >20%" noted. There were 3 (0.5%) recommendations categorized as "other".

Study 3:

In a prospective feasibility clinical study {Bergenstal, 2012[27]}, Hygieia Research tested the competence of the DIGS software to independently titrate insulin therapy on a weekly basis in subjects with suboptimally controlled type 1 and type 2 diabetes. The study was funded by the NIH-NIDDK (R41 DK085974-01), conducted at the International Diabetes Center, Minneapolis, Minnesota, USA (clinicaltrials.gov #NCT01170208), and supervised by Richard M. Bergenstal MD. The ability to apply DIGS in an unsupervised manner was assessed by monitoring events in which the study-team decided to over-ride the software recommendations. Efficacy was assessed by reduction in weekly mean glucose levels and A1C and safety was assessed by the frequency of hypoglycemia. Eligible adult subjects with type 1 and type 2 diabetes were enrolled into one of 3 treatment groups which included subjects with: I. suboptimally controlled type 1 diabetes (A1C≥7.4%) treated with basal-bolus insulin therapy and incorporating carbohydrate-counting; II. suboptimally controlled type 2 diabetes (A1C≥7.4%) treated with basal-bolus insulin therapy (without carbohydrate-counting); and III. suboptimally controlled type 2 diabetes (A1C≥7.8%) treated with twice daily biphasic or pre-mixed insulin. During the first 4 weeks subjects continued their pre-enrollment regimens without intervention. During this period subjects were acquainted with weekly submission of a diabetes diary and their current insulin dosage was unaltered. During the remaining 12 weeks, self-measured blood glucose readings reported on subjects' diaries were processed weekly by the DIGS software which recommended a new insulin dosage. Upon review and approval by the study-team, the DIGS software insulin dosage recommendations were communicated to the subjects (see example in Figure-1 on the right). Overall, 46 subjects were enrolled in the study (20 subjects in group-I, 20 in group-II and 6 in group-III), of whom 38 completed the study. The entire study population was cumulatively followed for 12.2 patient-years.

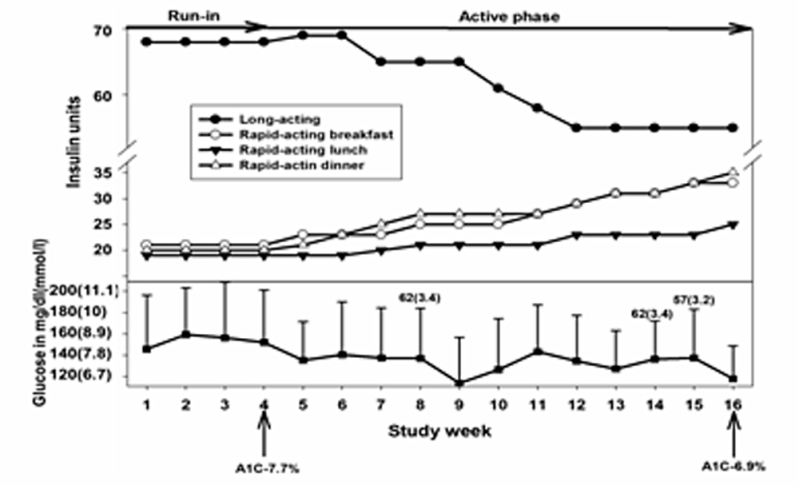


Figure 1 Using DIGS software, Type 2 diabetes, treated with basal-bolus insulin therapy.

In 1,731 out of 1,734 instances, DIGS software recommendations were provided to study participants without study team intervention. Thirty-eight of the 46 subjects enrolled reported

632 episodes of minor hypoglycemia (glucose <65mg/dL) during the study. No episodes of severe hypoglycemia were documented. Compared to the 4-week run-in period when subjects reported 63.5 (±100.6) episodes of minor hypoglycemia per patient-year, during the 12-week active phase (weeks 5 to 16), the frequency of hypoglycemia decreased to 47.5(±73.3) episodes per patient-year, but these differences did not reach statistical significance ($p<0.8$).

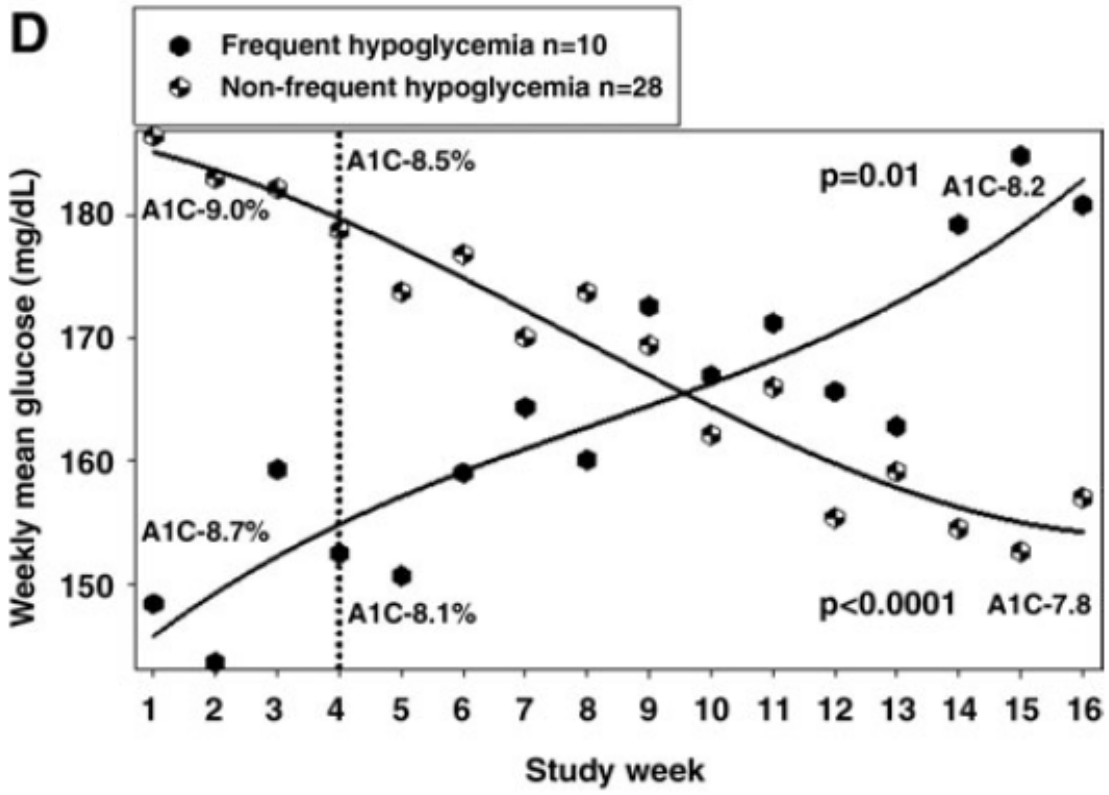
The results indicate that the DIGS software is able to adjust insulin dosage on a weekly basis, in an unsupervised manner, to achieve a superior glucose balance – defined as first avoiding hypoglycemia and second reducing mean glucose to goal.

About one-quarter of the patients exhibited a high frequency of hypoglycemia, which may preclude safe reduction of average glucose and HbA1c, particularly among patients managed in primary care clinics[28]. We sought to separate the study population based on their hypoglycemic frequency. To refrain from partiality, it was essential to identify an exogenous hypoglycemia frequency threshold, unrelated to the study results. A frequency of 85 events of minor hypoglycemia per patient-year was chosen as a cutoff point because it was double the frequency among patients with type 1 diabetes found in a community-based survey[29]. It was thought that such frequency might be considered unsafe or at least excessive by primary care teams for their insulin-treated patients. Based on this threshold, patients were separated into two groups:

i. Ten of the 20 patients enrolled with type 1 diabetes and two of the 26 patients enrolled with type 2 diabetes demonstrated a high rate of hypoglycemia. Ten of these patients completed the study (eight with type 1 diabetes and two with type 2 diabetes). In these patients DIGS insulin dosage adjustments resulted in an increase of mean weekly glucose from 152.5 mg/dL to 180.9 mg/dL (Fig. D), while the frequency of hypoglycemia significantly decreased by 36.3% ($P = 0.047$), from 167.3 to 106.6 events per patient-year. For these patients, HbA1c did not significantly change (8.1% to 8.2%; $P = 0.5$).

ii. Ten of the 20 patients with type 1 diabetes and 24 of the 26 with type 2 diabetes (18 in Group II and six in Group III) did not demonstrate a high rate of hypoglycemia. Clearly, in these cases it was possible to safely increase insulin dosage. Of the 34 patients composing this category, 28 completed the study (six with type 1 diabetes and 22 with type 2 diabetes [18 in Group II and four in Group III]). As shown in Figure D, in this group weekly mean glucose improved from 178. mg/ to 157 mg/dL), meeting the study efficacy end point (> 10% reduction in weekly mean glucose), while maintaining a low and stable rate of hypoglycemia of approximately 25 events per patient-year. During the 12-week

active phase, daily total insulin dosage was increased, and HbA1c decreased from 8.5% to 7.8% (P = 0.0005).



Study Cohorts

Primary cohort: the group that does not have frequent hypoglycemia (no more than 42 glucose readings<65 mg/dl through the course of this 6 month study, (half of the 85 hypoglycemia events per patient year described previously[27]). It is estimated that 90% of patients will be in this cohort.

Secondary cohort: the group that has frequent hypoglycemia (>42 documented glucose readings <65 mg/dl through the course of the study).

Study Objectives

The purpose of this study is to demonstrate that the use of d-Nav (d-Nav group) is superior to titration of insulin dosage relying on data from glucose meters with health care provider support (Control)[1] in the management of insulin treated diabetes, by randomizing 200 insulin treated subjects with type 2 diabetes.

Primary Objective: To demonstrate a greater reduction in HbA1c at 6-months for d-Nav users compared to control patients in the primary cohort.

Secondary Objectives:

- Primary cohort: To determine the difference between the Control and d-Nav group in the percent of participants who achieve A1c < 7.0%, < 8.0%, and >9.0% at 6 months.
- Secondary cohort: To determine the difference between the Control and d-Nav group in the number of glucose readings <70 mg/dl (symptomatic or asymptomatic) utilizing the documented downloaded glucose values at 3 months and 6 months.

Additional analyses include

- To determine change (if any) in rate of hypoglycemia, [on a month-by-month basis], during the study for d-Nav users in the secondary cohort.
- To determine the difference between the Control and d-Nav group in the percent of participants who achieve A1c < 7.0%, < 8.0% without a severe hypoglycemia event at 6 months.
- To determine the difference between the Control and d-Nav group in the number of glucose readings < 50 mg/dL, < 60 mg/dL and < 70 mg/dL (symptomatic or asymptomatic) utilizing the documented downloaded glucose values at 3 months and 6 months.
- To determine the difference between the Control and d-Nav group in the mean fasting glucose utilizing the documented downloaded glucose values) at 3 months and 6 months.

[1] For the purpose of this study, standard of care (Control) is that practice which is the norm for the clinical site. For participants in the control group, no change in treatment is being requested other than the identified visits and laboratory tests. During study visits, insulin adjustments may be made according to clinical site protocol.

- To determine the difference between the Control and d-Nav group in the standard deviation (SD) and Coefficient of Variation (CV) of the mean fasting glucose utilizing the documented downloaded glucose values at 3 months and 6 months.
- To determine the difference between the Control and d-Nav group in Mean Blood Glucose utilizing the documented downloaded glucose values at 3 months and 6 months.
- To determine the difference between the Control and d-Nav group in the number of test strips used at 3 months and 6 months.
- To compare type and frequency of adverse events for d-Nav group vs. Control.

Study Design and Methods

The study is designed as a prospective, open-label, randomized, controlled, multi-center, 6-month study. Male or female adults (21-70 years of age) will be eligible to participate if they have a clinical diagnosis of Type-2 diabetes for at least 1-year; have HbA1c between 7.5% and 11%; use a total daily dose of insulin of 25 units or more (10 units if on Lantus® alone); have been using the same insulin regimen for the previous 3-months; and may be using other diabetes agents (e.g., metformin) at a stable dose for the last 3-months. Subjects will be excluded from the trial if they have a body mass index (BMI) ≥45 kg/m2; severe impairment of cardiac, hepatic, or renal functions; psychological or cognitive impairment; more than two episodes of severe hypoglycemia in the past year; a history of hypoglycemia unawareness; or do not regularly conduct Self-Monitored Blood Glucose (SMBG).

Upon enrollment subjects will be randomized in a 1:1 ratio either to the Control or the intervention groups. One hundred subjects will be enrolled to the intervention group and will receive d-Nav. The remaining 100 subjects will be enrolled to the Control group and will receive insulin dosage adjustment recommendations at study visits. Subjects in both groups will receive free test strips for the duration of the study (co-pay reimbursement for subjects in the Control group). Subjects in the Control group may also receive insulin dosage recommendations from their primary care provider. Insulin dosage will be recorded on the case report forms.

Eligible subjects with Type-2 diabetes will be using one of four insulin regimens, which include:

- **Regimen 1** – subjects treated with a single injection of the long-acting insulin analog Lantus® (Glargine) per day (limited to a daily dose that is no more than 0.7 units per kg of body weight);
- **Regimen 2** – subjects treated with twice daily biphasic insulin (i.e., Humalog® Mix 75/25, NovoLog® Mix 70/30) or pre-mixed insulin (i.e., Humulin® 70/30, Novolin® 70/30);
- **Regimen 3** – subjects treated with a short-acting insulin analog (i.e., Humalog®-Lispro, NovoLog®-Aspart, Apidra®-Glulisine) before each meal and are treated with a single injection of the long-acting insulin analog Lantus® (Glargine) per day and do not utilize an insulin/carbohydrate ratio for calculating their short-acting insulin doses; or

- **Regimen 4** - subjects treated with a short-acting insulin analog (i.e., Humalog®-Lispro, NovoLog®-Aspart, Apidra®-Glulisine) before each meal and a single injection of the long-acting insulin analog Lantus® (Glargine) per day and utilize an insulin/carbohydrate ratio for calculating their short-acting insulin doses.

Because diabetes is a progressive disease, during the conduct of the study, subjects can move between groups per the judgment of their health care providers and/or the clinical study team.

Subject Selection

The following eligibility criteria are designed to select appropriate subjects. All relevant medical and non-medical conditions should be considered when deciding whether the study is suitable for a patient.

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male or female, 21 to 70 years of age
2. If female, must be of non-childbearing potential (e.g., bilateral tubal ligation, hysterectomy, post menopausal or bilateral ovariectomy) or have a negative urine pregnancy test at screening and must agree to use an adequate method of contraception throughout conduct of the study
3. Individual with a clinical diagnosis of Type-2 diabetes for at least 1-year
4. HbA1c 7.5% to 11% inclusive
5. Total daily dose of insulin of 25 units or more (10 units if on Lantus® alone) using one of these insulin regimens:
    a. **Regimen 1** – subjects treated with a single injection of the long-acting insulin analog Lantus® (Glargine) per day (limited to a daily dose that is no more than 0.7 units per kg of body weight);
    b. **Regimen 2** – subjects treated with twice daily biphasic insulin (i.e., Humalog® Mix 75/25, NovoLog® Mix 70/30) or pre-mixed insulin (i.e., Humulin® 70/30, Novolin® 70/30);
    c. **Regimen 3** – subjects treated with a short-acting insulin analog (i.e., Humalog®-Lispro, NovoLog®-Aspart, Apidra®-Glulisine) before each meal and are treated with a single injection of the long-acting insulin analog Lantus® (Glargine) per day and do not utilize an insulin/carbohydrate ratio for calculating their short-acting insulin doses; or
    d. **Regimen 4** - subjects treated with a short-acting insulin analog (i.e., Humalog®-Lispro, NovoLog®-Aspart, Apidra®-Glulisine) before each meal and a single injection of the long-acting insulin analog Lantus® (Glargine) per day and utilize an insulin/carbohydrate ratio for calculating their short-acting insulin doses.
6. Using the same insulin regimen for the previous 3-months

7. May be using other diabetes agents (e.g., metformin) at a stable dose for the last 3-months
8. Evidence of a personally signed and dated informed consent document, which contains Health Information Portability and Accountability Act (HIPAA) waiver information, indicating the patient (or legal representative) has been informed about all of the aspects of the clinical study;
9. Will regularly conduct Self-Monitored Blood Glucose. Subjects must meet the following minimum number of tests during the week prior to being randomized in the study.

   The minimum number of tests required from all subjects is the following:

   - For subjects using basal insulin at least 4 fasting glucose readings per week
   - For subjects using premixed insulin at least 8 readings per week
   - For subjects using basal-bolus insulin therapy at least 16 total readings per week

10. Subjects who are willing and able to comply with the scheduled clinical study activities and glucose testing:
    a. For subjects using basal insulin at least 5 fasting glucose readings per week
    b. For subjects using premixed insulin at least 5 pre-breakfast and 5 pre-evening meal readings per week
    c. For subjects using basal-bolus insulin therapy at least 20 total readings per week which include 5 readings before each of the following time points: breakfast, lunch, evening meal and bedtime.

    Note: All subjects may be asked to test during the night if clinically indicated.
11. Participant must have a primary care provider

Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Have a history of greater than 2 episodes of severe hypoglycemia (see definition below) in the past year, or have hypoglycemic unawareness when glucose levels are less than or equal to 50 mg/dl;
2. Have a significant physical, psychological, or cognitive impairment that would prohibit adherence to the protocol at the discretion of the PI;
3. Splitting Lantus and taking Lantus twice a day
4. Have any severe cardiovascular disease including a history of congestive heart failure (New York Heart Association [NYHA] 3 or 4), unstable angina, myocardial infarction or stroke that occurred within the 6-months preceding enrollment;
5. Have known active anemia with a hematocrit less than 25% in women or 30% in men;
6. Known advanced kidney disease Stage 4 (eGFR < 30 ml/min) and above

7. Have active cancer or cancer in the past 2-years (except non-melanoma skin cancer)
8. Have history of significant liver disease including cirrhosis or elevated liver enzymes (e.g., AST and ALT greater than 3 times the upper limit of normal values).
9. Have a body mass index (BMI) > 45 kg/m^2
10. Are pregnant, plan to become pregnant during the study period, or are breastfeeding.
11. Have a meter that cannot be downloaded.

Randomization

Each study site will be randomized to 50% for the d-Nav test device and Control Participant Blood Glucose Meter.

Clinical Supplies

Subjects participating in this study, who have been randomized to the intervention group, will be provided with d-Nav and an appropriate amount of test strips, Control solution and lancing device. Subjects randomized to the Control group will use their own glucose meters and will receive reimbursement for the co-pay they have for its respective consumables.

Device Description and Utilization

Description

Participant Device

d-Nav analyzes and evaluates the historical blood glucose patterns to support effective diabetes management. d-Nav provides insulin dosage updates weekly – or sooner when needed, similar to the directions physicians provide to subjects as part of insulin therapy dosage adjustment in clinical practice.

d-Nav works with four insulin regimens: [a] once a day basal insulin injection; [b] twice daily biphasic/premixed intermediate- and short-acting or rapid-acting insulin; [c] intensive insulin therapy involving long-acting and rapid-acting insulin; and, [d] intensive insulin therapy involving long-acting and rapid-acting insulin, guided by carbohydrate counting. A healthcare professional sets up the initial regimen and dosage. Subjects use d-Nav to measure capillary glucose before every insulin injection and select the purpose of each glucose reading (e.g., Breakfast) based on the regimen. Following the logic of an endocrinologist, and consistent with guidelines for insulin management[15], d-Nav assesses the subject's response to the current insulin dosage weekly by analyzing glucose patterns, and automatically updates the dosage as needed to improve overall glycemia and limit hypoglycemia. d-Nav does not require any lifestyle

modifications from the user. It simplifies diabetes management for the patient, and does not increase the burden on the already stressed healthcare system.

d-Nav Blood Glucose Test Strips. The d-Nav device uses non-coding test strips. The d-Nav strips are used for quantitatively measuring glucose in capillary whole blood from fingertips. The glucose in the blood sample mixes with special chemicals on the test strip to produce a small electrical current. The d-Nav device detects this electrical current and measures the amount of glucose in the blood sample. d-Nav test strips are intended for self-testing outside the body.

Test Strip Chemical Composition.

- Each *d-Nav* test strip contains the following reagents*:*
- Glucose oxidase: 2.7 units
- Hexaaammineruthenium (III) chloride: 45.7 µg
- Other ingredients: 1.6 µg.

Health Care Professional (HCP) device

d-Nav PRO Scribe™ Setup Module (PRO Scribe) is a software tool used by the site Health Care Professional (HCP) to set up the individual patient d-Nav device with an electronic insulin dosage prescription. The PRO Scribe is only used by Hygieia-trained HCPs for use with only the d-Nav device.

The PRO Scribe is a software package that can be loaded onto a Windows netbook type computer to be used as a single task appliance. It does not log HCP User or other Device setup information. The PRO Scribe does not retrieve any data from the Device. The PRO Scribe does not interface with other types of equipment or products.

Labeling

As required by 21 CFR 812.5 (Labeling of investigational devices), in addition to other labels, the d-Nav device will bear a label with the following information: Hygieia Research LLC, 6276 Jackson Rd, Suite G, Ann Arbor, MI 48103 and the following statement “CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use.”

Each d-Nav device will be provided with user instruction.

Labeling for the d-Nav PRO Scribe Setup Module (PRO Scribe) are provided to study site Investigator or designee.

Labeling for the d-Nav PRO View Follow-up Module (PRO View) are provided to study site Investigator or designee.

Participant Study Compliance

Participant's failure to follow study requirements (e.g., not testing blood glucose.) constitutes a compliance failure. Lack of compliance will occur where the Participant has failed to follow study requirements as described below for 2 consecutive weeks:

- For Participants using basal insulin at least 5 fasting glucose readings per week
- For Participants using premixed insulin at least 5 pre-breakfast and 5 pre-evening meal readings per week
- For Participants using basal-bolus insulin therapy at least 20 total readings per week which include 5 readings before each of the following time points: breakfast, lunch, evening meal and bedtime.

Where a subject is not following the d-Nav recommendations and a gap in dosing has been created, the d-Nav will be reset and the site will work with the subject to get him/her comfortable with following the recommendations. If the subject continues to not follow the d-Nav recommendations, they will be withdrawn from the study.

Diabetes Medications

Oral (e.g., metformin) or injectable agents will be continued during the conduct of the study unless a provider decides to discontinue or change that diabetes medication. Only insulins described in the Inclusion Criteria Section will be allowed during the conduct of this study.

Assessments

Demographics, Medical History, Physical Exam, Vital Signs, and Laboratory

At screening, demographics (e.g., sex, age, race and educational level) and medical history will be obtained. Medical history will include:

- Disease history (e.g., year of diagnosis of diabetes);
- Complications associated with diabetes (e.g., retinopathy, nephropathy, and neuropathy); and
- Co-morbidities (e.g., hypertension, dyslipidemia, cigarette smoking, ischemic heart disease / heart failure, peripheral vascular disease).
- Other clinically significant medical history including allergies.

Subject will also be asked to provide information related to use of medications including prescribed, over the counter medications, and / or nutritional supplements.

A physical exam (to assess each potential participant to determine if s/he is a good candidate) will include height and weight, waist circumference and pregnancy test for female participants and will be performed at screening.

Lab samples will be obtained for A1c and if the following lab tests have not been performed within the previous 12 months, blood will be drawn for testing of hematocrit, creatinine, AST and ALT.

Vital signs will be obtained at all clinic visits. Vital signs will include an average of 2 blood pressures taken 1 minute apart (sitting; after 5 minutes of rest), heart rate, and pulse.

Efficacy Assessments

As in other diabetes studies, treatment efficacy will be determined based on HbA1c and weekly mean blood glucose levels.

- HbA1c - Blood samples for HbA1c will be obtained at screening, Visit 2 (3-months), and Visit 3 (6-months) and sent to an NGSP-certified central laboratory.
- Weekly Mean Blood Glucose – Calculated based on downloaded blood glucose data from Participant d-Nav or glucometer at Visits 2 and 3.
- Frequency of Blood Glucose Testing – Calculated based on downloaded blood glucose data from Participant d-Nav or glucometer at Visits 2 and 3 or, if device memory is full, by extrapolation.

Safety Assessments

Safety will be monitored by frequency and severity of hypoglycemic events (see definition below) as well as reporting of glycemia-related adverse events (AEs).

- Hypoglycemia – Minor hypoglycemia (see definition on page 27) based on downloaded blood glucose data from Participant d-Nav or glucometer at Visits 2 and 3 for the entire memory of the device. Severe hypoglycemia to be summarized based on patient reporting.

Any changes in the health of the Participant will be obtained and reported in accordance with the protocol and good clinical practice.

Participant Questionnaire

A Participant questionnaire (Appendix 2) will be included in this study at Screening and Visit 3. Copies of the completed questionnaires will be provided to Hygieia Research. Information from the completed questionnaires is intended for sponsor information only and will not be entered into the study database.

Study Procedures

At Visit 1, subjects must continue to meet inclusion – exclusion requirements prior to randomization.

Screening – Week -1

Potential Participants will read the informed consent document and will have the benefits, risks and aims of the study explained to them by a designated clinical staff member. The Participants will have time to ask questions prior to signing the consent.

Once the Participant has signed the consent document and has been provided a copy of it, the Participant will have venous blood drawn to determine his/her HbA1c levels (and other lab tests as needed) and have his/her medical history, height, weight and waist circumference obtained and all inclusion/exclusion criteria will be reviewed. Participants will provide a detailed medical history to the study staff, which will include a list of past and current medical conditions and medications, including over the counter medications or nutritional supplements. Types and dosage of the medications including insulin will be recorded.

Visit 1 – Week 0

A provider will review the patient's insulin doses, frequency of SMBG testing, etc. to determine that they have met all inclusion/exclusion criteria and also to review that the patient is a good candidate for the d-Nav if they get randomized to that arm. Qualified subjects will be randomized to either d-Nav or standard of care and given a unique enrollment number.

For Participants randomized to the d-Nav arm, training for the use of the d-Nav will be provided at this visit. The provider will set up the d-Nav with the Participant's insulin regimen and dose.

All Participants will continue to use their current insulin formulations. Participants are encouraged to measure their blood glucose before each insulin injection and importantly, any time they feel symptoms of hypoglycemia. Participants using basal insulin are required to measure fasting glucose at least 5 days/wk; Participants using premixed insulin are required to measure pre-breakfast or pre-dinner glucose at least 10 times/wk; Participants using basal-bolus insulin therapy are required to measure pre-meal and bedtime glucose at least 20 times/wk.

Visit 2 (3-months)

Participant will return to the clinical site to have venous blood drawn to determine his/her HbA1c levels, obtain weight and waist circumference, download their glucometer or d-Nav, report any changes in their health at any time during the study (adverse events), and review concomitant medications. Study staff will review the insulin dose recommendations in the d-Nav and compare it with what the Participant is actually taking to see if the Participant has been following the recommendations. All activities will be handled by the local site study staff. Participants not following recommendations will be retrained.

Visit 3 (6-months)

Participants will return to the clinical site to have venous blood drawn to determine his/her HbA1c levels, obtain weight and waist circumference, download their glucometer or d-Nav, report any changes in their health at any time during the study (adverse events), and review concomitant medications. All activities will be handled by the local site study staff.

Phone visits (weeks 1 and 2 and months 1 and 5)

All subjects will be called at weeks 1 and 2 and months 1 and 5. During phone visits, Participants will be asked how they feel, be reminded about frequency and times of SMBG testing and be asked if there were any issues regarding their devices (d-Nav or meter).

Table 1: Participants Visits

Interval	In-person visit	Telephone visit
Screening Visit	**X**	
Visit 1	**X**	
Phone Follow up - Week 1		**X**
Phone Follow up - Week 2		**X**
Phone Follow up - Month 1		**X**
Visit 2 -Months 3	**X**	
Phone Follow up - Month 5		**X**
Visit 3- Month 6 End of Study	**X**	

At 6 months, the Participants will complete his/her participation in the study and will be instructed to follow-up with their primary care provider (PCP) and continue their diabetes management according to their PCP's guidance.

As provided above, both groups of participants will be interviewed throughout the study either in person or by telephone to ascertain health issues and success level of their device usage. Participants in the Control arm may be advised to make changes in the insulin (dose and type). Both groups may have changes made to other diabetes medications s/he is using if deemed necessary by the PI or primary care provider. Any dosing or medication changes will be recorded. During the study, any dose changes made by the Control participant's primary care provider or the patient on their own will also be recorded.

After Visit 1, when a phone visit with the participant requires more than 15 minutes, the actual amount of time required will be recorded along with the specific issue(s) covered.

Unscheduled Visits

Unscheduled visits may be performed as needed. For example, participants may need to return to clinic for a reset of their d-Nav. All unscheduled visits will be documented.

Follow Up, If Applicable

Any subjects that have Serious Adverse Device Effect (i.e., Serious Hypoglycemia determined to be related to the dosage recommendations from the device) that occurred during the study but not resolved prior to final visit (Visit 3 Month 6) will be followed until the event resolves.

Waist Circumference Procedure

Equipment: The measuring tape should be made of material that is not easily stretched such as fiberglass.

Procedure:

1. The waist circumference is taken with the subject standing and recorded to the nearest 0.1 centimeter.

2. Measure the waist circumference (WC) once. To the extent possible WC should be taken with the help of an assistant.

3. Waist (minimum) circumference should be measured at the smallest point between the 10th rib and the iliac crest over bare skin. Check to see that the tape is level front and back and record the value in the source documentation and on the annual physical exam form.

Patient Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, compliance, or administrative reasons. If a patient does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved serious adverse device effects.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations shall be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Definition of Hypoglycemic Event

- Minor hypoglycemia is defined as recorded capillary blood glucose level less than 70 mg/dl, which the patient has been able to self treat.

Severe hypoglycemia is defined as a hypoglycemic episode requiring assistance of another person to actively administer carbohydrates, glucagon, or other resuscitative actions. The episodes may be associated with symptoms of memory loss, confusion, seizures, irrational behavior, unusual difficulty in awakening, loss of consciousness, or suspected seizure that the patient was unable to self treat, or in the absence of a blood glucose determination, these symptoms are reversed with the administration of oral carbohydrate, glucagon, or intravenous glucose by someone else.

Adverse Events

Safety monitoring will include the collection of adverse events (AEs). As used in this protocol, an Adverse Event will be considered synonymous with Adverse Effect. An adverse event is any untoward medical occurrence in a patient during the conduct of a clinic study, regardless of the causal relationship of the event to the dosage recommendations from the device. All adverse events will be indicated on the source documentation for the study and reported using the adverse event reporting form. The following information related to each adverse event will be collected:

- Onset and resolution[2];
- Action taken (e.g., none, referral to MD, start or increase concomitant medication)
- Causality assessment or attribution of the event;
- Severity assessment; and
- Seriousness.

The PI and the study-team will determine the causality, severity, and seriousness of the event, and will monitor severe event until its resolution[2].

Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious) and completed in a timely manner. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the dosage recommendations from the device caused or contributed to an adverse event.

If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on trial records and will not require reporting to the IRB.

The reporting period for this study begins at baseline (Visit 1) and ends at month 6 (Visit 3). Adverse events determined to be related to the device will be followed until the event is resolved (restored to the normal state after the Adverse Event) or stabilizes at a level acceptable to the investigator-sponsor

Severity Assessment

[2] The subsiding or termination of an abnormal condition, such as a fever or an inflammation.

The assessment of severity must be provided for all adverse events. For purposes of consistency, the intensity grades are defined as follows:

- MILD - Does not interfere with patient's usual function.
- MODERATE - Interferes with patient's usual function.
- SEVERE - Interferes significantly with patient's usual function.

Seriousness

A serious adverse event (SAE) is any event that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

A serious adverse event which has been determined to be related to the device must be reported by the clinical investigator to the sponsor and, if required, the IRB within 24 hours of the investigative personnel's knowledge of the event. The initial report will be conducted by phone, e-mail or fax. This initial contact will later be followed by a written report.

Expectedness of Adverse Event

Hypoglycemia is the only expected adverse event in this study.

Unanticipated Adverse Device Effects

Unanticipated Adverse Device Effects (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

UADEs must be reported by the clinical investigator to the sponsor and the IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to the FDA (form 3500), IRB(s), and participating investigator(s) within 10 working days after the sponsor receives notification of the effect.

Reporting Period

The reporting period for this study begins at baseline (Visit 1) and ends at month 6 (Visit 3). Adverse events determined to be related to the device will be followed until the event is resolved (restored to the normal state after the UADE) or stabilizes at a level acceptable to the investigator-sponsor.

Data and Safety Monitoring

In June 1998, the National Institutes of Health (NIH) issued a policy on data and safety monitoring that requires oversight and monitoring of all intervention studies to ensure the safety of participants and the validity and integrity of the data. The policy further elaborates that monitoring should be commensurate with risks and with the size and complexity of the trials.

For the purpose of this study, a Data Safety Monitoring Board (DSMB) member has been appointed by the investigator(s) to provide data and safety monitoring. A data and safety monitoring plan has been prepared and approved by NIH.

Data Analysis and Statistical Methods

Study Design and Sample Size Determination

Patients will be randomized in a 1:1 ratio between the d-Nav and control arms. Randomization will be stratified by study site (3 sites) and will be blocked to ensure approximately equal distribution of treatment groups within each site.

The primary aim is to demonstrate a greater reduction in HbA1c at 6-months for d-Nav users compared to control patients. The standard deviation of the within subject changes in HbA1c is expected to be 1.1. The study was powered to detect a mean difference of 0.5 between treatment groups. Based on a 0.05 level two-sample t-test, 77 patients per group will give 80% power. To allow for up to 15% of patients lost to follow-up and 10% of patients with high frequency of hypoglycemia (who will be excluded from primary analysis), 100 patients per group will be randomized in a 1:1 ratio for a total of 200 patients.

Data Analysis & Interpretation

General Statistical Items:

Descriptive statistics for each variable will be calculated which will include measures of central tendency, variation, a frequency histogram and a count of the number of missing values. When the arithmetic mean is found not to be an appropriate measure of central tendency, alternative statistics will be considered (e.g. median). When the distribution of a variable does not support

the use of parametric statistics, nonparametric approaches or data transformations may be implemented. If data transformations are used they will be specified in the final clinical report.

Assessment of the Comparability of Randomized Groups and Poolability of Investigational Sites

The d-Nav and Control groups will be compared with respect to the following parameters to assess their comparability: age, sex, HbA1c, educational level, race, frequency of hypoglycemic events and insulin sensitivity. Any of the variables that are significant at $\alpha=0.10$ will be included as covariates in the statistical models used to evaluate the objectives, as appropriate. This adjustment ensures that similar patients in each group will be compared. The investigational sites will be tested for differences in the endpoints. If there are any investigational site effects (i.e., statistically significant results at $p<.10$), the investigational sites that have similar results will be grouped using the Least Significant Difference (LSD) method. Then, indicator variables for the grouped centers will be included in the model to adjust for investigational site differences. If there are no differences, all data from all investigational sites will be pooled for the analyses.

Primary Objective: To demonstrate a greater reduction in HbA1c at 6-months for d-Nav users compared to control patients in the primary cohort.

The change in HbA1c from baseline to 6 months (HbA1c at 6 months – HbA1c at baseline) will be calculated for each patient. This within subject change will be compared between treatment groups in a linear regression model with terms for treatment as well as site, insulin regimen or any other covariates identified as described above. A t-test will be used to test for a significant treatment effect at a 2-sided .05 level.

Secondary Objectives:

- Primary cohort: To determine the difference between the Control and d-Nav group in the percent of participants who achieve A1c < 7.0%, < 8.0%, and >9.0% at 6 months
- Secondary cohort: To determine the difference between the Control and d-Nav group in the number of glucose readings <70 mg/dl (symptomatic or asymptomatic) utilizing the documented downloaded glucose values at 3 months and 6 months.
- To determine change (if any) in rate of hypoglycemia, [on a month-by-month basis], during the study for d-Nav users in the secondary cohort.
- To determine the difference between the Control and d-Nav group in the percent of participants who achieve A1c < 7.0%, < 8.0% without a severe hypoglycemia event at 6 months.
- To determine the difference between the Control and d-Nav group in the number of glucose readings < 50 mg/dL, < 60 mg/dL and < 70 mg/dL (symptomatic or asymptomatic) utilizing the documented downloaded glucose values at 3 months and 6 months.

- To determine the difference between the Control and d-Nav group in the mean fasting glucose utilizing the documented downloaded glucose values) at 3 months and 6 months.
- To determine the difference between the Control and d-Nav group in the standard deviation (SD) and Coefficient of Variation (CV) of the mean fasting glucose utilizing the documented downloaded glucose values at 3 months and 6 months.
- To determine the difference between the Control and d-Nav group in Mean Blood Glucose utilizing the documented downloaded glucose values at 3 months and 6 months.
- To determine the difference between the Control and d-Nav group in the number of test strips used at 3 months and 6 months.
- To compare type and frequency of adverse events for d-Nav group vs. Control.

All but one of the secondary objectives involves a comparison of outcome between the two treatment groups. Outcomes will be summarized by treatment group using descriptive statistics appropriate for the distribution of the outcome. For binary outcomes (e.g. achievement of A1c < 7.0%) proportions with 95% confidence intervals will be utilized. For continuous outcomes (e.g. mean fasting glucose) the mean with associated standard error and 95% confidence intervals, min, max and median will be reported for each group. Regression models will be utilized to test for significance differences in outcome between treatment groups. Logistic regression models will be utilized for binary endpoints while normal linear regression models will be utilized for continuously distributed outcomes. In addition to treatment, regression models will include terms for site, baseline insulin regimen or other covariates found to differ significantly between the treatment groups, in order to perform covariate adjusted analyses.

One of the secondary objectives is to determine change in rate of hypoglycemia, [on a month-by-month basis], during the study for d-Nav users in the secondary cohort. The 'data' consists of the presence/absence of a hypoglycemic event on each on study day. These longitudinal binary outcomes will be modeled in a mixed logistic regression model with term(s) for time on study. Time here might be modeled continuously (e.g. using linear and quadratic terms for day) or more discretely (e.g. month on study). A random intercept and slope will be included for each subject to accommodate within subject, over time correlation.

To compare variability of glucose readings between treatment groups, we will calculate standard deviations over time for each subject and then compare the mean of these log-transformed standard deviations between treatment groups using standard linear regression models.

Exploratory analyses:

Whereas the study is powered to support analysis within each insulin regimen group, exploratory analyses will also assess the treatment effect separately in each of these groups . This primary population, based on the intent-to-treat principle, will include all subjects enrolled

and with the requisite six (6) months of data. In the case of study discontinuation or required administration of new diabetes therapy to a patient during the study, efforts will be made to get final measurements of the efficacy variables (prior to discontinuation or new administration) and these measurements will be substituted in the primary analyses (LOCF – last observation carried forward).

Safety Analysis

Safety will be reported as the incidence of hypoglycemic events (minor or severe, and/or serious), including causality (related; not related to the dosage recommendations from the device). The frequency of minor and severe hypoglycemic events will be compared to that reported in other studies [18, 26].

Quality Control and Quality Assurance

During study conduct, Hygieia Research or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitor(s) may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow monitor(s) and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Hygieia Research, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Protocol Violations / Deviations

The following protocol violations and deviations will be tracked by the study site.

- Inclusion / Exclusion Criteria Violation
- Missed Procedure Deviation
  - Not following the visits schedule
  - Not following the phone visits schedule
- Unreported SAE / UADE

Data Handling and Recording

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

Case report forms are required and must be completed for each patient enrolled. The completed original case report forms are the sole property of Hygieia Research and shall not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities (e.g., US FDA), without written permission from Hygieia Research.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Patient source documents are the physician's patient records maintained at the study site (clinic charts). In most cases, the source documents will be the clinic's record. In cases where the source documents are the clinic's record, the information collected on the CRFs must match those records.

In some cases, the CRF may also serve as the source document. In these cases, Hygieia Research and the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document

Data shall be recorded on the CRF within 3-days of obtaining the information.

Record Retention

To enable evaluations and/or audits from regulatory authorities or Hygieia Research, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition.

The investigator or sponsor shall maintain the records during the investigation and for a period of 2 years after the latter of the following two dates: 1) The date on which the investigation is terminated or completed, or 2) the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.[3]

Ethics

[3] The Clinical Site shall maintain documents for a minimum of 6 years in compliance with HIPAA requirements.

Institutional Review Board

An appropriate Institutional Review Board (IRB) will review the protocol and all addenda for this study in compliance with institutional requirements and 21 CFR 56.

IRBs must have standard operating procedures that explain how the IRB makes significant risk (SR) and non significant risk (NSR) determinations and that the decision shall be documented. FDA considers this determination to be part of the IRB's responsibilities for conducting its initial review of a study (21 CFR 56.108).

In addition to documenting approval of the study and related documents (e.g., Informed Consent Form), the IRB shall document its SR/NSR determination in the IRB meeting minutes.

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB. All correspondence with the IRB shall be retained in the Investigator File. Copies of IRB approvals shall be forwarded to Hygieia Research.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate harm to the patient(s). In that event, the investigator must notify the IRB/IEC and Hygieia Research in writing immediately and in no case more than 5 working days after the implementation.

Ethical Conduct of the Study

The study will be conducted in accordance with all applicable guidelines for the protection of human subjects for research as outlined in 45 CFR 46 (for government funded studies), 21 CFR 11, 21 CFR 50, 21 CFR 56, 21 CFR 812.

Patient Information and Consent

The informed consent form template must be approved by the IRB, agreed to by Hygieia Research, and must be in compliance with 21 CFR 50 and 45 CFR 46 (for government funded studies).

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and Hygieia Research before use. The investigator will retain the original of each patient's signed consent form.

No subjects can enter the study before his/her informed consent has been obtained. The investigator is further responsible for obtaining a HIPAA waiver / authorization from each patient participating in the study.

Sponsor Discontinuation Criteria

Premature termination of this clinical study may occur because of a regulatory authority decision, change in opinion of the IRB (e.g., new safety information, compliance), or at the discretion of Hygieia Research.

If a study is prematurely terminated or discontinued, Hygieia Research will promptly notify the investigator. After notification, the investigator must contact all participating subjects within 5 days. As directed by Hygieia Research, all study materials must be collected and all CRFs completed to the greatest extent possible.

Publication of Study Results

Publication or presentation of study results will be reviewed by Hygieia Research, LLC as described in the Clinical Trial Agreement.

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