

PROTOCOL

Title: diEtitiaNs Helping pAtieNts CarE for Diabetes (ENHANCED)

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1. Study Synopsis:

This will be a randomized-controlled trial to examine the impact of a Registered Dietitian (RD) led telemedicine program on diabetes outcomes for adults with type 2 diabetes. Two groups will be compared over one year; an intervention group who receives the telemedicine program versus a control group who receives usual diabetes care. Specifically, we will assess the ‘D5,’ which is a set of five treatment goals that when reached together, represent the gold standard for managing diabetes. D5 outcomes includes the proportion of participants in each group who achieve goal levels for blood glucose, blood pressure, tobacco use, statin use, and aspirin use.

2. Background:

Diabetes is a progressive, complex disease that requires frequent follow-up and ongoing care. Five key metrics—blood glucose, blood pressure, tobacco use, statin use, and aspirin use – commonly referred to as the “D5” are targeted in individuals with diabetes to reduce the risk of health complications¹. A recent review found that some risk factors were generally improving in U.S. adults with diabetes (e.g. blood glucose, LDL cholesterol), but 30-50% still did not meet individualized targets for glycemic control, blood pressure, or lipid control, and more than 20% remained smokers².

Poor diabetes control is also evident at local levels, particularly where access to diabetes care and education is more limited. In Hutchinson, MN, a rural region about 60 miles west of the Minneapolis metropolitan area, diabetes care quality is below the state average. The same is true for New Ulm Medical Center (NUMC). According to Minnesota Community Measurement, 30% of Hutchinson Health’s diabetes population is at goal on all D5 measures and 39% for NUMC. The breakdown of individual D5 measures for diabetes patients in Hutchinson and NUMC, respectively include:

- Blood pressure <140/90 mmHg (81%, 87%)
- Statin use (83%, 64%)
- Glycated hemoglobin (A1C) <8% (46%, 68%)
- Not using tobacco (86%, 88%)
- Taking daily aspirin as appropriate (99%, 99%)

Most diabetes care in the U.S. is delivered by primary care providers (PCPs), although it is well documented that PCPs face significant time constraints to address all health issues adequately. The National Standards for Diabetes Self-Management Education³ emphasize the importance of a multidisciplinary clinical care team, which includes a registered dietitian (RD), to reduce disease risks. The role of the RD is well established for nutrition, physical activity, and behavior change education with high risk patients, but the involvement of RDs in other aspects of diabetes care is more limited, particularly as it relates to medication management. The few studies in this area have found encouraging results. Robinson and colleagues demonstrated that RDs who followed a lipid-titration algorithm were able to double the number of patients meeting lipid goals⁴.

Worth and Davies found that RDs who recommended, monitored, and titrated lipid-lowering therapies were able to achieve significant improvements in both total cholesterol and triglycerides⁵.

Innovative models are clearly needed to complement usual diabetes care. Achieving blood pressure, lipid, and glucose goals in adults with diabetes requires extensive lifestyle counseling, patient education, and pharmacological therapy, with frequent follow-ups to address challenges as they arise. This study will examine the impact of an RD-led, primary care integrated, telemedicine program on the D5 measures over one year as compared to a usual care group that will receive usual care only during this timeframe.

3. Specific Aims

The specific aims of this study are to:

1. Compare individual and composite D5 optimal care measures between patients in the intervention group vs. those in the usual care group.
2. Analyze changes in secondary outcomes including nutrition, physical activity, body mass index, medication adherence and gender.

Methods

4. Subjects and Setting:

Sample. We will seek to recruit 144 participants for this trial. Patients will be recruited from Hutchinson Health in Hutchinson, MN and New Ulm Medical Center in New Ulm, MN in order to reach our recruitment goal. Hutchinson Health is an independent hospital/clinic that contracts with Allina Health to use their EHR. New Ulm Medical Center is part of the Allina Health system. Eligible patients will be identified by Allina Health informatics personnel based on the most recent available information contained in the EHR. Only EHR data from the previous 2 years will be considered to determine eligibility. Data will be extracted from the EHR system to identify individuals who are seemingly eligible for this study based on the criteria listed below. Each individual's most recent value for each measure from the previous 2 years will be considered. Values greater than 2 years old will be considered missing. Inclusion criteria will be:

- Diagnosis of type 2 diabetes
- Meeting 0-3 of the D5 measures
- Individuals meeting 0 of the D5 measures and have no more than two missing measures
- Individuals meeting 1 of the D5 measures and have no more than one missing measure

- Age 40-75 years
- ‘Homed’ in the Hutchinson Health clinic. This is defined as having at least one ambulatory care visit at the Hutchinson Health clinic in the last 2 years.
- ‘Homed’ at the New Ulm Medical Center. This is defined as having at least one ambulatory care visit at NUMC in the last 2 years.

Exclusion criteria:

- Individuals meeting ≥ 4 D5 measures
- Individuals meeting ≥ 2 D5 measures with any missing measures
- Type 1 diabetes
- Chronic kidney disease (GFR <30)
- HIV
- Institutional residence
- Major cognitive or language barrier (as determined by program enrollment staff)
- Other active end-stage disease (e.g., late stage cancer or pulmonary disease)
- Actively receiving cancer treatment
- Pregnant

Study Recruitment

Recruitment will be conducted over a four to six month timeframe beginning in late 2015 and will start with Hutchinson Health. Once recruitment efforts are exhausted in Hutchinson, the same process will occur at New Ulm Medical Center. Contact information for study-eligible individuals will be extracted from the Hutchinson Health and New Ulm Medical Center/Allina Health EHR. A random sample of these enumerated individuals will be drawn and an initial letter will be mailed, signed by their PCP that contains a description of the study and an invitation to contact the study team by phone for eligibility screening. Up to three additional outreach attempts by phone will be made until a response is received. The screening phone call will confirm study eligibility and the baseline study (enrollment) visit will be scheduled with a study team member. Patients will be instructed to fast prior to their baseline visit in order to obtain accurate lab values.

Baseline study visit

- At the baseline visit, patients will be provided with study related information and have an opportunity to ask questions. Study personnel will verify inclusion/exclusion criteria to confirm eligibility. If subjects meet study criteria, they will be consented to participate in the study. The baseline visit will be completed in-person for all participants and will be led by a study coach with the assistance of lab personnel. They will last 30-45 minutes and include detailed study explanation and consent, completion of baseline lifestyle survey, measurement of anthropometrics, and a blood draw (described further below). In addition, a brief education session with a study coach will be conducted and focused on optimal diabetes measures and basic diabetes nutrition and physical activity recommendations. Individuals will also receive a diabetes basics booklet from the International Diabetes Center. Randomization will take place at the end of the visit using a 5 block envelope; an equal number of participants will be randomly assigned to the intervention and control groups. For those randomized to the intervention group, the first phone appointment will be scheduled upon completion of the baseline visit.

Measures. The primary outcomes will include changes in the D5 measures (A1C <8%, blood pressure <140/90 mmHg, not using tobacco, taking a statin and aspirin use as appropriate). These measures will be ascertained at baseline and 12 months after study enrollment. Interim D5 measures and those unavailable at follow-up will be extracted from Hutchinson Health and NUMC's EHR where possible. Secondary outcomes will include nutrition, physical activity, body mass index, medication adherence, confidence and satisfaction with diabetes management and gender. Specifically:

- Height
- Weight
- Waist Circumference
- Blood pressure
- Labs: A1c, fasting glucose, lipids
- Lifestyle questionnaire (see attachments)

Phone coaching

Phone visits will occur monthly over the course of one year, with some variability as needed such as more frequent phone contacts when a medication is started. They will be conducted by study coaches and last approximately 30 minutes. Topics will include:

- Brief lifestyle & medication assessment
- Nutrition coaching regarding appropriate choices (e.g. carbohydrate choices at meals/snacks, healthy fats, portion control).
- Physical activity recommendations
- If needed, medication initiation/titration for blood pressure, cholesterol or blood glucose

12-month/Final visit

The study follow-up visit will be similar to the baseline visit and occur at the Hutchinson Health clinic about 12 months later. The study follow-up visit will occur at NUMC for those patients identified from New Ulm. This will again be in-person and conducted by study coaches and lab personnel. The same measures will be taken as at baseline.

5. Study Procedures & intervention:

At the baseline visit, study participants will be randomized into the intervention or control group by computer using block randomization (block size 5).

Coaches in this study will be registered dietitian/certified diabetes educators trained to address the D5 optimal care measures. They will also be trained in the use of a medication protocol that permits initiation and titration of blood glucose, lipid, and/or blood pressure medications (attachment). All coaching aside from the baseline and final visits is done via telephone and participants will generally receive a minimum of one call per month. The intervention is designed to complement to usual clinic-based primary care, with coaches documenting lab, biometrics, and medication adjustments in the EHR, along with documenting phone encounters and communicating directly with patients' PCPs as needed.

Documentation in the EHR uses an order created specifically for the study indicating the patient's research status; "opt-in" for those who choose to enroll.

To answer outcome evaluation questions, all individuals with a diabetes research study order will be extracted from the EHR along with baseline and 12 month D5 measures collected during respective visits. For comparisons between the intervention and usual care patients, the analysis

will examine mean changes in biometric risk factors and the percentage of patients meeting recommended levels for the D5 measures at baseline and after the one year intervention period. Medication changes will also be examined and compared between the two groups.

Study procedures will be approved in advance by the Allina Institutional Review Board.

Analysis

Analyses and power. A moderate effect size is expected of at least (Cohen's $w=0.25$) in this trial. Over one year, this translates into about 30% of the intervention group experiencing improvement in ≥ 1 D5 measure vs. 10% of usual care participants. Under the assumptions of 85% power, an alpha-level of 0.05, and a one degree of freedom test, 144 total participants (72 in each group) will be needed for this study. Mixed regression models will be used to compare D5 outcomes between the two study groups over time. Similar analyses will be conducted on secondary outcomes as well. An intent-to-treat framework will be used that will include all randomized participants.

6. Risk/ Safety information

This study is minimal risk because the only risks associated with this study are: 1) Potential identification of individuals; 2) Individuals may be uncomfortable answering certain questions in the questionnaire; and 3) Potential risk associated with venipuncture at baseline and 12 month visit; 4) patient may experience adverse side effect from being started on a blood pressure, statin, or diabetes (blood glucose) medications. However, all of the medications on the protocol are currently used in diabetes care standards of practice (none are investigational).

1. To mitigate this risk, the study personnel with access to this data already have access to similar types of data for their work and have procedures in place to limit access to this identifying information. Data is stored in a secure folder at Allina, and patient identifiers will be eliminated from data sets after appropriate analysis is done.
2. Study participants can choose not to answer any questions in the questionnaire that may make them uncomfortable.
3. Venipuncture: There are minor risks associated with drawing blood. Participants may feel brief pain, develop a bruise, become lightheaded, or faint. In rare cases, an infection may occur.
4. Medication protocol: Any medications prescribed by the RD/Phone coach will require a co-signature by the patient's primary care provider or medical director. This intervention poses no more risk than going to a primary care provider for diabetes care management. The protocol also has indications for assessment and action for those who experience side effects (see Diabetes Medication Protocol appendix).

7. Monitoring / Reporting of AE/ SAE

We believe this study poses no more than minimal risk and as such do not expect any safety events. The main risk with this type of study is potential identification of individuals included in the study, risk associated with venipuncture or an adverse reaction to a medication. Only individuals on the study research team will see the individual level data in this study. If there is a breach of confidentiality, those people will work together to report it to the compliance office and IRB and follow the appropriate procedures. However, we will follow all standard procedures to ensure data privacy is maintained by storing data in a limited access folder that is on the Allina servers.

8. Study Oversight

We do not foresee any conditions under which this study would be prematurely terminated as the risks associated with participating in the diabetes research project are minimal and include no more risk than usual care. If the study is prematurely terminated, the study will be made available for monitoring, auditing, IRB review and regulatory inspection by providing direct access to study related source data.

9. Data Management

The diabetes research study database will be maintained by the MHIF team and a final research data set will be created which will be managed by team members from Allina Health who maintain this data as part of their routine job responsibilities. All analysis will be done in SPSS by members of the research team. Data will be maintained in a limited access folder on Allina Servers.

10. IRB Review/ Ethics/ Informed Consent

The protocol and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB prior to being used. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with applicable regulations, applicable laws and the IRB requirements. The Sponsor must submit any change to the protocol to the IRB for review and approval before implementation.

11. Confidentiality

Only 5 people will have access to identifying data through this study. Two are Allina employees who work with patient data for research purposes as part of their job and as such will follow standard procedures for protecting data privacy. The other three are employees of the Minneapolis Heart Institute Foundation who oversees the HBC program. Through a contractual agreement between Allina and MHIF, this person

has access to the Allina EHR and has access to patient data related to the HBC program. Data is stored in a secure folder at Allina with access limited to the people doing analysis and the health informatics person pulling data out of the EHR, and patient identifiers will be eliminated from data sets after data cleaning and analysis is done. All study records identifying the subjects will be kept confidential and will not be made publicly available or presented in any publications.

The IRB could review records if determined necessary.

12. Intended Use of the Data

The data is intended to measure changes in D5 measures among study participants who receive a phone coaching intervention compared to a usual care group. A manuscript will be prepared based on the information obtained from the study.

References

1. The D5: Five Goals for Living Well with Diabetes. www.mnhealthscores.org. Accessed June 12, 2015.
2. Mohammed KA, et al. Achievement of Goals in U.S. Diabetes Care, 1999–2010. *NEJM*. 2013; 368:1613-1624.
3. Funnell, MM, et al. National Standards for Diabetes Self-Management Education. *Diabetes Care*. 2008; 31: S97-S104.
4. Robinson, JG, Controy, C, Wickemeyer, WJ. A novel telephone-based system for management of secondary prevention to a low-density lipoprotein cholesterol \leq 100 mg/dl. *Am J Cardiol*. 2000;85:305-308.
5. Worth, JM, Davies, RR, Durrington, PN. A dietitian-led lipid clinic is effective. *Prac Diabet Int*. 2006;23(5):221-228.

Primary and Secondary Outcome Measures of the ENHANCED Study

Primary and Secondary Outcome Measures of the ENHANCED Study		
	Measures	Description
Lifestyle (self-report survey)	Tobacco use	Self-reported; single item indicating current, former, or never used tobacco
	Secondhand smoke	Self-reported; single item indicating weekly smoke exposure ¹
	Alcohol consumption	Self-reported; modified version of screener developed for World Health Organization ² ; 2 items; frequency and indicating ‡ 15, 8–14, 1–7, or 0 drinks/wk; categorized as high (> 14 [men] or > 7 [women]), moderate (1–14 [men] or 1–7 [women]), or none (0) per the EPIC-Norfolk study
	Physical activity	Self-reported; screener developed for the Behavioral Risk Factor Surveillance System ³ ; 2 items; moderate physical activity reported in days/week and minutes/day
	Breakfast	Self-reported; single item; frequency ⁴
	Fruit, vegetable and whole grain intake	Self-reported; 3 items modified from AHA Simple 7 ⁵ ; daily intake of fruits, vegetables and whole grains
	Sodium intake	Self-reported; 4 items modified from AHA Simple 7 ⁵ (tracking, eating out, pre-packaged foods and added salt)
	Meal planning	Self-reported; 4 items; frequency of carbohydrate counting and using portion control strategies
	Sugar-sweetened beverage intake	Self-reported; single item modified from AHA Simple 7 ⁵ ; weekly intake
	General health	Self-reported; single item; rate poor to excellent ⁷
	Intention to improve lifestyle	Self-reported; single item indicating yes, maybe, or no intention to improve lifestyle habits over the next 6 months

	Confidence in managing diabetes	Self-reported; single item modified from Kettering Health Network and Joslin Diabetes Center Diabetes Self-Management Questionnaire ⁶ ; degree of confidence
	Satisfaction with diabetes care	Self-reported; single item; degree of satisfaction ⁷
	Social and emotional support	Self-reported; single item; frequency ⁷
General diabetes care (self-report survey)	Diabetes education	Self-reported; 3 items; last diabetes class ⁷ , last visit with diabetes nurse educator ⁸ , and last visit with dietitian ⁸
	Aspirin use	Self-reported; single item indicating daily aspirin or every other day use ⁹
	Medication adherence (statin, blood pressure, and diabetes)	Self-reported; 15 items; The MMAS ¹⁰ is a generic self-reported, medication-taking behavior scale in which the specific health issue (high blood pressure, diabetes, elevated cholesterol, HIV, contraception, etc.) is inserted for the "health concern." The MMAS consists of four items with a scoring scheme of "Yes" = 0 and "No" = 1. The items are summed to give a range of scores from 0 to 4.
	Blood glucose monitoring	Self-reported; 2 items; frequency ^{4,7}
	Hypoglycemia	Self-reported; single item; frequency ¹¹
Anthropometrics (staff measured)	Blood pressure	Staff measured; participants sit for 5 min prior to 3 pressures taken 1 min apart using auto sphygmomanometers (mean of last 2 measures recorded)
	Body mass index	Staff measured; calculated by dividing weight (measured with digital scale, in light street clothes and no shoes) in kg by height (measured using with a stadiometer and no shoes) in meters squared; categorized as obese (≥ 30.0), overweight (25.0–29.9), or not obese/overweight (< 25.0) per national guidelines
	Waist circumference	Staff measured; distance around the body at the superior border of the iliac crest; categorized as obese (≥ 30.0),

		overweight (25.0–29.9), or not obese/overweight (< 25.0) per national guidelines	
Biometrics (laboratory)	Total cholesterol	Venipuncture following request of 12-hour fast; standard Hutchinson Health medical laboratory blood collection and processing procedures	REFERENCE 1. Prochaska JJ, Grossman W, Young-Wolff KC, Benowitz NL. Validity of self-reported adult secondhand smoke exposure. <i>Tob Control</i> . 2015 Jan; 24(1): 48–53. 2. Saunders JB, Aasland OG, Babor
	HDL cholesterol		
	LDL cholesterol		
	Triglycerides		
	Blood glucose		
	A1c		

- TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction*. 1993;88:791–804.
3. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System Survey Questionnaire. Atlanta, GA: US Department of Health and Human Services; 2009.
 4. Stanford Patient Education Research Center. Diabetes Questionnaire. Available from <http://patienteducation.stanford.edu/research/breakfast.html>. Accessed 26 October 2015.
 5. American Heart Association. My Life Check™ Simple 7™ Assessment. Available from http://mylifecheck.heart.org/AssessmentTools2/main_en_US.html. Accessed 26 October 2015.
 6. Kettering Health Network and Joslin Diabetes Center. Diabetes Self-Management Questionnaire. Available from <http://www.ketteringhealth.org/diabetes/pdf/questionnaireKett.pdf>. Accessed 26 October 2015.
 7. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System Survey Questionnaire. Atlanta, GA: US Department of Health and Human Services; 2014.
 8. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES). Atlanta, GA: US Department of Health and Human Services; 2014.
 9. Centers for Disease Control and Prevention. Behavioral Risk Factor Surveillance System Survey Questionnaire. Atlanta, GA: US Department of Health and Human Services; 2013.
 10. Morisky DE, Green LW, Levine DM. Concurrent and Predictive Validity of a Self-Reported Measure of Medication Adherence and Long-Term Predictive Validity of Blood Pressure Control. *Med Care*. 1986; 24:67-74.
 11. University of Louisville Health Behavior Change Research Lab. Personal Diabetes Questionnaire. Available from <http://louisville.edu/psychology/stetson/lab/personal-diabetes-questionnaire>. Accessed 26 October 2015.