Effectiveness of a diabetes focused discharge orderset among poorly controlled hospitalized patients transitioning to glargine U300 insulin.

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Introduction:
Diabetes is present in 25% of hospitalized patients; yet effective hospital discharge programs for patients with diabetes are understudied.[1] In particular, patients who are initiating or intensifying insulin therapy have the most to benefit in terms of glycemic control.[2,3] However, these patients are also particularly vulnerable to poor transitions of care for a variety of reasons, including the complexity of therapy, inadequate patient education, differences in patient and provider expectations, and insufficient resources.[4,5,6] Disruption of insulin therapy following hospitalization is associated with higher HbA1c, shorter survival, and increased readmissions and medical costs.[7] In a recent Society of Hospital Medicine Survey, only one fourth of hospitals were supported with written protocols to standardize medication, education, equipment, and follow-up instructions.[8] However, discharge order sets have largely been limited to the inpatient setting and have not been utilized to guide insulin use at hospital discharge.[9,10,11,12,13] This study will assess whether a nurse supported diabetes focused inpatient discharge order set (DOS) can improve post-discharge outcomes among hospitalized patients with poorly controlled insulin-requiring diabetes.

Primary Aim: Evaluate the efficacy of a diabetes focused inpatient discharge order set (DOS) on reducing HbA1c at 24 weeks compared to enhanced standard care (ESC) among hospitalized basal insulin requiring patients with uncontrolled diabetes.

Secondary Aims:
- Evaluate the efficacy of a diabetes focused DOS on reducing HbA1c at 12 weeks compared to ESC among hospitalized basal insulin requiring patients with uncontrolled diabetes.
- Evaluate the efficacy of a diabetes focused inpatient discharge order set (DOS) on change in fasting plasma glucose from baseline to 12 and 24 weeks.
- Evaluate the efficacy of a diabetes focused inpatient discharge order set (DOS) on % of subjects reaching HbA1c <7.0% or <6.5% at 12 and 24 weeks.
- Determine whether the DOS in conjunction with nurse supported self-titration of basal insulin glargine U300 is associated with improved persistence with insulin therapy, adequate dose titration, and use of self-monitored blood glucose.
- Determine whether the DOS is associated with improved discharge instructions and processes of care for insulin-requiring patients. This will be measured in terms of clarity of instructions, adequacy and completeness of prescriptions for insulin and diabetes supplies, and follow-up plan.

Study Design: In this 24 week randomized controlled trial, hospitalized insulin-requiring patients with type 2 diabetes and poor glycemic control (HbA1c >8.5%) will receive glargine U300 plus additional background therapy (non-insulin and prandial insulin therapies) with or without a diabetes focused discharge order set and follow-up communication to facilitate insulin titration and outpatient follow-up. Patients in the control group will receive traditional standard of care with the support of a patient care resource manager.

Study Population: Hospitalized patients with type 2 diabetes (HbA1c >8.5%) who are receiving basal insulin at least 10 unit per day and are able to provide informed consent will be approached. Patients must have access to some form of communication (phone, electronic patient messaging) post discharge and be willing to obtain HbA1c at follow-up. Patients will be identified through daily screening of the inpatient medical and surgical services throughout the institution.

Intervention: For the DOS group the primary team will be contacted to review the discharge order set, which will be pre-populated into the electronic discharge navigator. Patients in both groups will receive survival skills education by a dedicated nurse and study drug throughout the study. The study nurse will contact the patient at 2 weeks and 6 weeks to confirm titration and hospital follow-up in the DOS group, and study coordinator will contact patients to obtain data at similar time points in the ESC group. At 12 and 24 weeks, HbA1c is measured and the staff will assess outpatient follow-up, hospital readmission or emergency department visit,

adherence to insulin and glucose monitoring, hyperglycemic and hypoglycemic events, and perform the DES-SF in person at CarePoint East or McCampbell Hall.

Study Drug: Patients will be provided standard of care insulin therapy including FDA-approved basal insulin (TOUJEO® U300, insulin glargine) plus additional background therapy (non-insulin and prandial insulin therapies) based upon discharge team preference. The starting dose will be determined during hospitalization from the dose of glargine/detemir U100 in a 1:1 dose conversion. Upon discharge, standard titration instructions (every 4 days) will be implemented in the DOS group but will be left to the discretion of the discharge team in the ESC group. **Endpoints:**
Primary: Change in HbA1c from baseline to 24 weeks (+/-2 weeks) post-discharge
Secondary:

- Change in HbA1c from baseline to 12 weeks (+/-2 weeks) post-discharge
- Change in fasting plasma glucose (FPG) from baseline in DOS vs ESC
- % of patients achieving HbA1C 7% in DOS vs ESC
- % of patients achieving HbA1C 6.5% in DOS vs ESC
- % of patients achieving individualized HbA1c target in DOS vs. ESC: HEDIS HbA1c target (<8% if age ≥ 65 years or known history of ischemic vascular disease, heart failure, advanced kidney disease [eGFR <30], dementia, proliferative retinopathy/blindness, advanced neuropathy [history of ulcer or amputation] or history of severe hypoglycemia; otherwise goal is <7%)
- Proportion of patients with accurate and complete discharge orders for insulin and related supplies.
- Adherence to glargine U300 (>80% of doses) at 2, and 24 weeks
- Proportion of patients who remain on glargine U300 at 24 weeks
- Mean dose of glargine U300 at 2 and 24 weeks
- Proportion of patients who follow up with their primary care provider within 2, 6 weeks of discharge
- Incidence of documented symptomatic (BG <54 mg/dl) hypoglycemia

Analysis: Outcomes will be further analyzed by type of diabetes, pre-admission therapy, and bolus insulin requirements.

B. Background

Long-term glycemic control reduces the frequency of microvascular complications in patients with diabetes,[14,15] but is frequently difficult to achieve.[16] Diabetes is associated with intense resource utilization; medical costs are estimated at 2.3 times that of a patient without diabetes, and the largest expenditure is inpatient care.[17,18] A large proportion of hospital costs are accumulated by a small percentage of patients, particularly those with chronic medical conditions,[19,20] largely due to repeated hospitalizations.[21] Prevention of unplanned hospital readmission has received attention as a way of reducing hospital costs.[22,23,24] Diabetes is present in 25% of hospitalized patients; yet effective hospital discharge programs for patients with diabetes are understudied.[25]

Transitions of care among hospitalized insulin requiring subjects

A report from the Health Care Utilization Project of the Agency for Health Care Research and Quality highlights the need for careful monitoring of recently hospitalized patients with diabetes and suggests enhanced interventions for vulnerable populations with diabetes.[26] While inpatient glycemic control has improved over time,[27] there is little indication that this translates automatically to better outcomes following discharge. In a recent Society of Hospital Medicine Survey, only one fourth of hospitals were supported with written protocols to standardize medication, education, equipment, and follow-up instructions.[28]

Traditional efforts to improve transitions of care have focused on the primary reasons for hospital admission.[29] Unfortunately, most studies do not target diabetes specifically. Failure to acknowledge diabetes at discharge is associated with increased 30 day readmissions.[30] Although the current recommendation for discontinuation of pre-admission diabetes therapies (other than insulin) is sound in principle,[31] it can add to confusion and lapses in care of diabetes at discharge.

Few published data exist for interventions targeting improved discharge care in patients with diabetes. Several strategies have demonstrated potential but require larger, more scientifically rigorous studies.[32] There is some evidence supporting individualized discharge planning for decreasing readmissions in undifferentiated hospitalized patients. Successful programs utilize multiple approaches (e.g., a nurse discharge advocate, pre-arranged follow-up appointments, medication reconciliation, patient education, and primary care provider communication).[29] A Cochrane Review suggested that nurse or pharmacist follow-up calls alone had favorable effects for some outcomes, but did not decrease readmissions.[30] However, conclusions were limited due to low methodological quality and heterogeneity of studies. In addition, these studies did not target diabetes specifically.

In particular, patients who are initiating or intensifying insulin therapy at discharge have the most to benefit in terms of glycemic control.[2,3] However, these patients are also particularly vulnerable to poor transitions of care for a variety of reasons, including the complexity of therapy, inadequate patient education, differences in patient and provider expectations, and insufficient resources.[6,33,34] Disruption of insulin therapy following hospitalization is associated with higher HbA1c, shorter survival, and increased readmissions and medical costs.[35]

Role of the Electronic Medical Record (EMR)

The implementation of comprehensive electronic medical records (EMR) has led to improvement in achieving recommended standards of glycemic control and intermediate outcomes in the ambulatory setting.[36,37] In the hospital, the EMR has added many benefits including computerized decision support, medication reconciliation, and facilitation of communication between providers. Studies in undifferentiated populations have reported that while medication reconciliation using the EMR can reduce medication errors at discharge,[38] a multifactorial approach that includes the patient, primary care provider and the inpatient team is desirable.[39] In a non-randomized study of 283 patients before and after implementation of a pharmacist and nurse driven electronic discharge system featuring systematic medication reconciliation, patients had greater understanding of their medications and were more likely to adhere to them following the intervention.[40]

However, diabetes specific discharge order sets have largely been limited to the inpatient setting and have not been utilized to guide insulin use at hospital discharge.[41,42,43,44,45] EMR systems inadequately support complexities in certain prescriptions including insulin therapy, and fail to assure accurate, and reasonable

medication reconciliation.[46] Insulin, in particular, is not easily ordered using the electronic fields provided for other medications, incentivizing prescribers to resort to copying and pasting medical jargon or typing in free text, both of which reduce accuracy and clarity, or providing instructions outside of the EMR. [47]

This study will assess whether a nurse supported diabetes focused inpatient discharge order set (DOS) can improve post-discharge outcomes among hospitalized patients with poorly controlled insulin-requiring diabetes.

Insulin Titration in the era of Longer-acting Basal insulins
Previous studies indicate that patients beginning either basal or prandial insulin achieve the greatest benefit from inpatient education following hospital discharge.[2,3] These patients often undergo optimization of the insulin dose prior to discharge. Most previous inpatient studies have utilized daily titration algorithms.[48,49] Insulin stacking has not been a significant concern, since higher treatment targets are generally implemented and only small adjustments (10-20%) in the total daily dose are made. In contrast, daily titration may not be appropriate for newer longer-acting insulins, even at higher treatment targets. For example, glargine U300 (Toujeo) is a concentrated formulation of glargine with a longer duration of action than glargine U100 (Lantus). Therefore, titration is not recommended more frequently than every 3-4 days. In addition, patients receiving glargine U100 in the hospital who are transitioned to glargine U300 at discharge will require approximately 11-17.5% more insulin to maintain equivalent glycemic control.[50] This is further complicated by changing insulin requirements in the setting of resolution of illness and glucotoxicity as well as changes in diet and activity following discharge. As a result, additional titration will be necessary following discharge for many patients. Finally, while numerous studies support patient self-titration of insulin, these studies are generally conducted among highly motivated ambulatory patients. It is unclear whether patient self-titration is feasible in recently hospitalized patients.

Glargine U300 (300 units/mL) is 3-fold more concentrated than traditional insulin glargine U100. It has a smaller depot surface area, thereby reducing the rate of absorption.[51,52] As a result, glargine U300 provides flatter and more prolonged pharmacokinetic and pharmacodynamic profiles compared to standard insulin glargine. Its duration of action is ≤36 hours, and its half-life is approximately 23 hours.

In major clinical trials (EDITION 1, 2 and 3), the efficacy and safety of glargine U300 was compared to insulin glargine.[53,54,55] These studies included patients not adequately controlled with basal and mealtime insulin, patients who had previously received basal insulin in combination with oral antidiabetic drugs, and insulin-naïve patients. A meta-analysis that pooled data from all 3 studies reported comparable glycemic control with both glargine formulations, as well as similar rates of adverse events.[56] However, glargine U300 was associated with a significantly lower overall risk of hypoglycemia (-14%) over 6 months of treatment, and a 31% lower rate of nocturnal hypoglycemia.

C. Approach

C.1. Investigative Team
Dr. Dungan and colleagues have been successfully conducting inpatient diabetes research studies for the past 8 years through collaboration with clinical and research staff at multiple levels, including administration, quality improvement, nursing, physician, physician extender, and pharmacy interactions.

C.2. Preliminary Studies

C.2.a. Study 1: Predictors of Readmission in Patients with Poorly Controlled Diabetes
Among hospitalized patients with an HbA1c >9%, fewer patients who were readmitted at 30 days had a diabetes education consultation than those with no readmission (32 vs. 44%, p<0.0001, Table 1).[57] This relationship persisted (OR 0.68, 95% CI 0.52-0.89, p=0.006) after adjusting for

Table 3: Predictors of 30-day Hospital Readmission

	Readmitted N=293	Not Readmitted N=2028	P-value^
Age	52 (14.9)	51 (14.4)	0.38
Male	138 (47%)	1075 (53%)	0.06
Caucasian	163 (56%)	1090 (54%)	0.57
Married	94 (32%)	682 (34%)	0.64
HbA1c	10.8 (9.7-12.3)	11 (9.9-12.6)	0.05
Income	34,559 (29,573-41,713)	35,006 (30,716-43,216)	0.17
Physician consult	140 (48%)	922 (45%)	0.49
Education consult	93 (32%)	900 (44%)	**<0.0001**
Hyperglycemic emergency	17 (5.8)	145 (7.2)	0.46
Non-surgical service	215 (81%)	1615 (86%)	**0.04**

Data are reported as number (%) for binomial variables and mean (standard deviation) or median (interquartile range) for normally and non-normally distributed variables respectively. ^P-value obtained from unpaired t-test, Wilcoxon Rank-Sum, and Fisher's Exact Test for variables with normal, non-normal, and binomial distributions respectively.

demographics, income, marital status, physician consultation, insurance, length of stay, need for critical care, HbA1c, and year of admission. While attenuated, the relationship persisted for 180 day readmissions. Readmissions were more common than previously reported (30% at one year vs. 32% at 6 months in this study).[27] Thus, we have identified a higher risk population than previously recognized.

C.2.b. Study 2: Hospital Discharge Program for Patients with Poorly Controlled Diabetes

This pilot program incorporated individualized education with phone follow-up at one week following discharge and then monthly.[2] Patient characteristics are summarized in Table 2. HbA1c was reduced 1.5% overall (p=0.04). Patients with type 1 diabetes had no change in HbA1c (0%, *p*= 0.96), while patients with type 2 diabetes experienced a 2.8% mean reduction in HbA1c (*p*<0.0001 within type 2 diabetes, *p*= 0.0001 between type 1 and 2 diabetes groups). Both patients who were newly diagnosed (−4.5 ± 3.8%, *p* =0.02, n = 7) and patients with established diabetes (−1.5 ± 2.1, *P* =0.0002, n = 34), had a significant HbA1c reduction (*p* =0.08, between groups). In multivariable analysis, independent predictors of reduction in HbA1c included older age, higher body mass index, shorter duration of diabetes, higher baseline HbA1c, insulin naïve at admission, and education prior to the day of hospital discharge (Table 3, 4). In this sample, patients who were discharged new to insulin, new to basal insulin, or new to bolus insulin had significant HbA1c reductions.

Table 2. Baseline Characteristics Among Hospitalized Patients with HbA1c >9.0% Undergoing Education

	T1DM (n = 19)	T2DM (n = 58)	P value
Male	10 (53%)	29 (50%)	>.99
Race			
White	12 (67%)	36 (63%)	>.99
AAr	6 (33%)	19 (33%)	
Age (years)	37 (11)	47 (11)	.001
Diabetes duration	12 (6.5-23)	6 (1.3-12.8)	.07
BMI (kg/m²)	27 (8.7)	37 (9.8)	.0003
Insurance	10 (53%)	45 (76%)	.046
Reason for admission			
Cardiovascular	0 (0%)	19 (33%)	.0006[b]
Gastrointestinal	2 (11%)	5 (8.8%)	
Infectious disease	2 (11%)	15 (26%)	
Other	2 (11%)	7 (12%)	
Admit Hyperglycemia	12 (63%)	11 (19%)	.0009
Length of stay (days)	3.0 (2-4.0)	4 (3-7)	.12
Discharge instructions	19 (100%)	55 (95%)	.58
DES (n = 40)	37 (36-38)	36 (33-38)	.07
Health literacy (n = 35)	4 (4-5)	4 (1-5)	.47
Any insulin on admission	18 (95)	26 (45)	.001
Discharge regimen			
Any insulin	19 (100%)	48 (83%)	.06
Multiple dose injection	14 (74%)	48 (83%)	.50
New to insulin	1 (5.3%)	22 (38%)	.008
New to bolus insulin	4 (21%)	27 (47%)	.06
Follow-up			
Any phone follow-up	13 (68%)	37 (64%)	.79
PCP at institution (n = 78)	10 (53%)	23 (42%)	.44
Outpatient diabetes follow-up 1 month (n = 68)	7 (35%)	13 (23%)	.37
Readmission			
1 month	3 (16%)	7 (12%)	0.70
3 months	4 (21%)	16 (26%)	0.77
HbA1c			
Baseline	10.5 (9.5-12.5)	11.3 (10.1-12.6)	0.28
Change (n = 41)	0.018 (1.31)	–2.76 (2.72)	.0001

Abbreviations: AA, African American; BMI, body mass index; CDE, certified diabetes educator; DES, Diabetes Empowerment Scale; DM, diabetes mellitus; PCP, primary care physician; T1DM, type 1 DM; T2DM, type 2 DM. [a] Data reported as (%), mean (SD) or median (25-75%). [b]Across all categories, including admission for diabetes.

Of this sample, functional health literacy was limited (median score 4/5, IQR 3-5), but Diabetes Empowerment Scores (DES) were relatively high (median 36, IQR 34-38). The literacy score predicted patients who were ultimately discharged with flexible mealtime insulin dosing using carbohydrate counting (median literacy score 5 [4-5] vs. 3 [1-4], *p* =0.001) and thus may be an effective screening tool for targeting patients for appropriate modalities and intensity of therapy.[8] Hospital follow-up was associated with higher income as well as higher DES. In addition, earlier education was associated with better HbA1c reduction and patient-follow-up.

Table 3. Univariable Predictors of Change in HbA1c

	Estimate	SE	*P* value
Age	–0.09	0.03	**0.009**
Male	-0.19	0.42	0.65
AA	0.32	0.46	0.49
BMI (kg/m^2)	–0.093	0.037	**0.02**
T2DM	–1.39	0.43	**0.003**
Duration of DM	0.10	0.047	**0.046**
Any insurance	–0.86	0.47	0.07
Admit severe hyperglycemia	0.26	0.44	0.56
Phone follow-up	–0.07	0.47	0.89
Readmission 1 month	0.91	0.79	0.26
HbA1c baseline	–0.64	0.22	**0.006**
Any goal adherence	0.49	0.43	0.26
DES score	–0.16	0.35	0.65
Literacy	–1.46	0.71	0.06
Outpatient diabetes follow-up at 30 days	0.25	0.43	0.57
First education day of discharge	1.04	0.40	**0.01**
Any Insulin on admission	0.95	0.40	**0.02**
Any insulin on discharge	0.23	0.56	0.69
Discharge basal insulin	–1.22	0.61	0.05
Discharge bolus insulin	0.27	0.56	0.63
New to insulin	–1.51	0.45	**0.002**
New to bolus insulin	–0.99	0.43	**0.03**

Abbreviations: AA, African American; BMI, body mass index; DES, Diabetes Empowerment Scale; DM, diabetes mellitus; T2DM, type 2 DM

Table 4. Multivariable Predictors of Change in HbA1c

Model 1	Estimate	SE	*P* value
Original Model			
Intercept	25.3	5.4	**<0.0001**
Age	–0.086	0.028	**0.004**
T2DM	–0.43	0.35	0.23
Log(HbA1c baseline)	–9.82	2.00	**<0.0001**
New to basal insulin	–1.17	0.32	**0.0008**
Final Model			
Intercept	24.7	5.3	**<0.0001**
Age	–0.087	0.026	**0.002**
Log(HbA1c baseline)	–9.61	2.00	**<0.0001**
New to basal insulin	–1.10	0.32	**0.002**
Model 2	**Estimate**	**SE**	***P* value**
Final Model			
Intercept	22.5	5.19	**0.0001**
Age	–0.081	0.025	**0.003**
First education day of discharge	0.59	0.29	**0.047**
Log(HbA1c baseline)	–8.86	1.95	**<.0001**
New to basal insulin	1.03	0.31	**0.002**

Abbreviations: HbA1c, glycated hemoglobin; T2DM, type 2 diabetes mellitus

C.2.c. Study 3: Clarity and effectiveness of EMR based discharge procedures in patients with stress hyperglycemia: role of the diabetes consult service

Patients without prior diagnosis of diabetes (HbA1c <6.5% without pre-admission glucose lowering therapy) who were discharged on any anti-diabetic medication following cardiac surgery were identified and individual chart reviews were performed.[47] Outcomes of interest included discharge and follow-up medications as well as clarity of discharge instructions, stratified by electronic medical record (EMR) and diabetes consult service (DCS) status.

A total of 125 patients were identified (Table 5). Patients had a baseline HbA1c of 5.8 +/- 0.41% and admission (random) glucose of 7.6+/-2.3 mmol/L. At discharge, 76, 31, and 33% of patients received oral agents, bolus insulin, or basal insulin respectively. EMR discharge instructions were clear in 67% of patients overall, including 83, 54, and 20% of patients receiving oral agents, basal insulin and bolus insulin respectively. At the 6 week post-operative follow-up visit, 44, 9 and 6% still had these respective therapies listed. DCS involvement was less frequent following conversion to an inpatient EMR but was associated with better glucose control (similar admission glucose but lower peak and a trend for higher trough glucose levels). Patients with diabetes consults were more frequently discharged on oral agents as opposed to insulin, and had greater frequency of clear discharge instructions (Table 5).The most common reason for unclear discharge instructions was medical jargon prior to the EMR, while it was conflicting instructions (either with the consult notes or within the prescription itself, typically because insulin regimens require “free text” rather than direct entry of dosing fields, Figure 1).

Conclusion: The need for glucose lowering therapies at discharge may represent prediabetes or unrecognized type 2 diabetes, but requirements generally decline over time. The data illustrate the extent of unclear EMR based discharge instructions, particularly for patients requiring insulin. A systematic, multidisciplinary team approach may improve processes of care at discharge.

Table 5. Baseline and Hospital Information Stratified by Diabetes Consult Service Involvement

	Overall	No Diabetes Consult (N=19)	Diabetes Consult (N=106)	p-Value
Age (Year)	61+/-13	67+/-14	60+/-12	0.07
Male	93 (74%)	9 (47%)	84 (79%)	0.008
Race				
Caucasian	113 (90%)	15 (13%)	98 (87%)	
African American	10 (8.0%)	3 (30%)	7 (70%)	
Other	2 (2%)	1 (100%)	1 (100%)	0.07[1]
Chronic kidney disease	6 (4.8%)	2 (10.5%)	4 (3.8%)	0.23
Type of Procedure				
CABG	69 (55%)	9 (47%)	60 (57%)	0.47
Valve surgery	51 (41%)	8 (42%)	43 (41%)	>0.99
Aortic root/AA Repair	14 (11%)	3 (16%)	11 (11%)	0.45
Other	19 (15%)	3 (16%)	16 (15%)	>0.99
Body Mass Index	32 +/-9.8	26+/-6.8	35+/-9.7	0.002
Hemoglobin A1c (%)	5.8 +/-0.41	5.7+/-0.56	5.8+/-0.38	0.52
Glucose (mmol/)				
At admission	7.6+/-2.3	7.3+/-3.2	7.6+/-2.2	0.69
Peak	12.4+/-2.7	13.9+/-3.2	12.2+/-2.4	0.03
Trough	1.6+/-2.8	4.1+/-0.7	4.4+/-0.7	0.06
Peak difference	6.3+/-1.0	9.9+/-4.4	7.8+/-2.6	0.01
Discharge morning	6.3+/-1.0	6.3+/-0.7	6.3+/-1.1	0.60
Estimated glomerular filtration rate[2]	46+/-10	45+/-15	48+/-7.0	0.80
Length of stay (day)	10 (8-14)	14 (11-25)	9 (7-13)	0.0002
Total daily insulin 24 hour prior to discharge[3]	10 (0-25)	12.5 (4.5-23)	1 (0-26.5)	0.13
Discharge to Facility	37 (30%)	15 (79%)	22 (21%)	<0.0001
Post-EMR conversion	37 (30%)	12 (63%)	25 (24%)	0.002
Post-operative Follow-up	109 (88%)	13 (72%)	96 (91%)	0.04
Discharge Instructions Clear	84 (67%)	7 (37%)	77 (73%)	0.004
Discharge medication				
Oral	95 (76%)	6 (32%)	89 (84%)	<0.0001
Any insulin	62 (50%)	13 (68%)	49 (46%)	0.09
Bolus insulin	39 (31%)	13 (68%)	26 (25%)	0.0003
Basal insulin	41 (33%)	1 (5%)	40 (38%)	0.006
Follow-up medication				
Oral	44 (44%)	3 (21%)	41(43%)	0.15
Any insulin	15 (23%)	5 (36%)	11 (11%)	0.03
Bolus insulin	10 (9%)	5 (36%)	5 (5%)	0.003
Basal insulin	7 (6%)	0 (0%)	7 (7%)	0.59

Data are reported as mean +/- SD or median (IQR) for continuous variables and number (%) for dichotomous variables. [1]Fisher’s exact test used due to 20% of cells with expected count less than 5. [2] Modification of Diet in Renal Disease equation. [3]Insulin doses were only available following electronic medical record upgrade, N=37. EMR=electronic medical record.

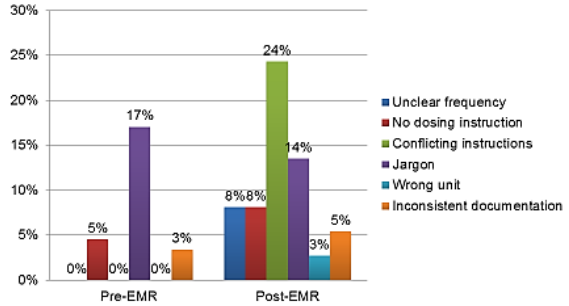

Figure 1. Reason for Unclear Discharge Instructions before or after Electronic Medical Record (EMR) Upgrade

C.2.d. Application to proposed study: The retrospective data (Study 1) as well as the pilot program (Study 2) used an intensive yet individualized education approach within an ADA accredited program; however, in both cases discharge support was often provided to providers through reminders of the scope of prescriptions and supplies needed, direct entry of discharge orders, and facilitation of hospital follow-up. Study 3 illustrates how implementation of an EMR does not guarantee better outcomes and in fact may introduce new problems that were not previously anticipated. In particular, the ease of carrying forward prescriptions through the medication reconciliation process may actually facilitate suboptimal use of insulin or unclear instructions. The current proposal will address these discharge problems through implementation of an insulin-specific orderset within the most commonly utilized EMR nationwide, Epic.

D. Research Design & Methods

D.1 Aims

D.1.a Primary Aim: Evaluate the efficacy of a diabetes focused inpatient discharge order set (DOS) on reducing HbA1c at 24 weeks compared to enhanced standard care (ESC) among hospitalized basal insulin requiring patients with uncontrolled diabetes.

D.1.b. Secondary Aims:

- Evaluate the efficacy of a diabetes focused inpatient discharge order set (DOS) on reducing HbA1c at 12 24 weeks compared to enhanced standard care (ESC) among hospitalized basal insulin requiring patients with uncontrolled diabetes.
- Determine whether the DOS in conjunction with nurse supported self-titration of basal insulin glargine U300 is associated with improved persistence with insulin therapy, adequate dose titration, and use of self-monitored blood glucose.
- Determine whether the DOS is associated with improved discharge instructions and processes of care for insulin-requiring patients. This will be measured in terms of clarity of instructions, adequacy and completeness of prescriptions for insulin and diabetes supplies, and follow-up plan.

D.2. Research Design

D.2.a Study Design: In this 24 week randomized controlled trial, hospitalized insulin-requiring patients with type 2 diabetes and poor glycemic control (HbA1c >8.5%) will receive standard of care insulin therapy including basal insulin glargine U300 (TOUJEO®) plus additional background therapy (non-insulin and prandial insulin therapies) with either a diabetes focused discharge order set (DOS) and follow-up communication to facilitate insulin titration and outpatient follow-up or enhanced standard care (ESC).

D.2.b Study Population: 222 patients (type 2 diabetes) will be recruited. Inclusion/exclusion criteria appear in Table 6. Hospitalized patients with type 2 diabetes (HbA1c >8.5%) who are receiving basal insulin at least 10 unit per day and are able to provide informed consent will be approached. Patients must have access to some form of communication (phone, electronic patient messaging) post discharge and be willing to obtain HbA1c at follow-up. Patients will be identified through daily screening of the inpatient medical and surgical services throughout the institution.

Table 6: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Diagnosis of diabetes, type 2 ≥3 months duration HbA1c >8.5% Ages 25-75 years Phone or electronic media availability Receiving basal insulin >10 unit/day	Sensitive admissions: Prisoners Pregnancy Unable to consent or follow study directions in English Expected nursing facility stay longer than 2 weeks

D.2.c. Recruitment

Participants will be identified from the diabetes consult, medicine and surgery ward services at the main OSU Hospital System and OSU East hospital. OSU East is a community hospital with a high percentage of indigent and minority patients. An efficient system is already in place for screening patients for inpatient diabetes studies. Each morning, the research assistant screens services through the electronic medical record, initially

filtering by insulin use and then HbA1c. Permission will be obtained from the attending physician of the admitting inpatient service to contact the patient. Current annual inpatient diabetes physician and educator consults at OSU main and OSU East are roughly 3000 per year, but there are approximately 13,000 admissions with a diagnosis code for diabetes each year. Approximately 1000 admissions per year have an HbA1c >9%. Diabetes nurse practitioners and certified diabetes educators are available weekdays at both sites.

D.2.d. Enrollment and Randomization
Enrollment is expected at a rate of approximately 3 patients per week with the last patient enrolled within 18 months to allow completion and analysis of all data within 3 years. The study and all study-related documents will be approved by the OSU IRB. Written informed consent will be obtained. Patients will be stratified by pre-admission insulin therapy (yes/no) and randomized using a random number generator program.

D.2.e. Initial Assessment: Trained interviewers will perform initial data collection.
- Contact information, including email address, best times to reach the patient, contact information for 2 additional individuals, and PCP.
- Type of diabetes, duration, complications, reason for hospital admission
- Age, gender, race and ethnicity, education level, marital status, work status, home ownership, insurance coverage, medical history, concomitant medications, weight, height, BMI, standard of care lab results
- Social support is an environmental factor that is associated with readmissions[58], determines behavior in SCT and influences self-efficacy.[59] It will be measured using the Multidimensional Scale of Perceived Social Support (PSSS).[60]
- Health literacy is a determinant of hospital readmissions[61] and will be assessed using the Newest Vital Sign.[62]
- Diabetes Empowerment Scale Short-Form (DES-SF) measures perceived self-efficacy and predicts adherence to a therapeutic plan. The DES-SF[63] is has been shown to have acceptable reliability (α=0.84).
- Comorbidity is key determinant of readmission; it is measured with the Charlson comorbidity index.[64]
- It is anticipated that nearly all patients who are hospitalized with an HbA1c >8.5% will go home on insulin therapy. The complexity of the discharge regimen will be assessed as number of injections per day, total units per day, and number of glucose checks per day.

D.2.f. Retention
Staffing will be funded by the study to reach patients after hours. Incentives will be provided for completing the follow-up HbA1c at the 12 and 24 week visits. Patients will be contacted at pre-arranged times, with up to 3 attempts during the week of the encounter. In the event of failure to contact, a letter/email will be sent and staff will then reach out to the patient designated secondary contacts. The medical records will be monitored at OSU and queries to the patient's designated primary care physician will be made up to 24 weeks following enrollment.

D.2.g. Program Completion
Participants will receive an order to complete the HbA1c at 12 and 24 weeks at any OSU lab. A reminder letter will be sent 1 week prior to the date and a phone call reminder will occur 2 days before the visit. Study team will complete the 12 week and 24 week call and search the electronic medical record and primary provider's chart for HbA1c and healthcare utilization at 12 and 24 weeks.

E. Study Drug: Patients in both groups will be provided standard of care insulin therapy throughout the study, includinginsulin glargine (TOUJEO® U300) plus additional background therapy (non-insulin and prandial insulin therapies), based upon discharge team preference. The starting dose will be determined during hospitalization from the dose of glargine/detemir U100 in a 1:1 dose conversion. Upon discharge, standard titration instructions (every 4 days) will be implemented in the DOS group but will be left to the discretion of the discharge team in the ESC group.

Table 7. Intervention procedures

	Enhanced Standard Care	Discharge Order Set
Diabetes Education	Basic survival skills	Basic survival skills
Discharge orders	Per primary team: medication reconciliation, prescriptions and instructions, follow-up appointments	Discharge order set in addition to primary team
Patient Care Resource Manager	Yes	Yes
U300 glargine at discharge	Yes	Yes
U300 glargine titration	Per primary team	Yes
Follow-up	Coordinator call to assess adherence, outcomes	Nurse call to confirm titration

F. Intervention

F.1 Enhanced Standard Care

F.1.a. Discharge

In the enhanced standard care arm, the discharge regimen will be determined by the primary team with input from the diabetes service if requested. All patients will receive standard discharge instructions using the electronic medical record as per usual practice. Hospital discharge is coordinated by the primary team and existing patient care resource manager who arranges follow-up prior to discharge. A discharge summary is sent to the primary provider per routine practice. Patients are instructed to maintain a glucose and insulin diary. Patients will receive survival skills education by a dedicated nurse.

F.1.b. Follow-up Encounters

Study staff will conduct phone calls or email communications at 2 and 6 weeks to confirm contact information and inquire about discharge follow-up. Patients will be given an appointment day and time prior to discharge for the first phone contact at 2 weeks. Any specific medical concerns reported during any call will be forwarded to the primary provider. At 12 and 24 weeks, HbA1c is measured and the staff will assess outpatient follow-up, hospital readmission or emergency department visit, adherence to insulin and glucose monitoring, hyperglycemic and hypoglycemic events, and perform the DES-SF.

F.2 Discharge Order Set group

F.2.a Discharge

As with the ESC group, the discharge regimen will be determined by the primary team with assistance from the diabetes service if requested. Hospital discharge is also coordinated by the primary team and existing patient care resource manager who arranges follow-up prior to discharge. A discharge summary is sent to the primary provider per routine practice. Patients are instructed to maintain a glucose and insulin diary. Patients will receive survival skills education by a dedicated nurse.

In addition to these elements, for the DOS group the primary team will be contacted to complete the Diabetes Discharge order set, which will be pre-populated into the electronic discharge navigator. The discharge order set contains a variety of elements that are intended to ensure a clear/complete communication to the patient and outpatient provider (summarized in Table 8, detailed mock-up provided in Appendix 1). In particular, the instructions facilitate identifying an appropriate diet, establishing timely and effective follow-up and ordering clear and complete prescriptions. The standardized instructions provide guidance to the patient for monitoring and interpreting glucose levels as well as a basic summary of survival skills.

Table 8. Diabetes Order Set Summary

Standard Elements		
Code Status Activity Wound/Drain//Tube/Catheter Care DME Orders		
Diabetes-specific elements	**Detail**	**Prescriber Guidance**
Diet	Choice of consistent (defaults to 45 or 60 gram/meal) or flexible carbohydrate	Selection criteria for flexible carb diet.
Follow-up and referrals	Choice of primary care or endocrinology (call for appointment for *** weeks, appointment has been made for ***) Diabetes education (general education or survival skills)	Only local patients should be referred to OSU.
Patient instructions	Call provider for hypoglycemia Call provider for hyperglycemia Bring glucose log to appointment Glucose targets Home diabetes management attachment	Identification of glucose targets
Insulin prescriptions	Each insulin is presented as a panel, linked to pen needle or syringe as appropriate Each insulin Rx defaults to 3 pen or 1 vial with 1 refill Insulins categorized by basal, prandial set meal dose with correction, or prandial flexible meal dose with correction	Number of units per pen or vial Syringe size Titration options for basal insulin Selection criteria for flexible meal dosing Correction dosing from pick list of low, standard, or high doses
Glucose Monitoring supplies	Panels categorized by frequency of monitoring Each panel contains glucometer, test strips, lancets, alcohol wipes Prescriptions default to dispense appropriate number of supplies with 1 refill	Guidance on monitoring frequency
Other DM supplies	Ketone strips Glucagon	Selection criteria provided for each

F.2.b. Basal insulin titration

The patient will receive instructions via the discharge order set and nurse to adjust the U300 basal insulin dose 2 unit Q4 days for glucose >130 mg/dl, provided no values <80 mg/dl.

F.2.c. Follow-up Encounters

The study nurse will contact the patient at 2 weeks and 6 weeks to confirm titration and hospital follow-up. Patients will be given an appointment day and time prior to discharge for the first phone contact at 2 week. Any specific medical concerns reported during any call will be forwarded to the primary provider. At 12 and 24 weeks, HbA1c is measured and the staff will assess outpatient follow-up, hospital readmission or emergency department visit, adherence to insulin and glucose monitoring, hyperglycemic and hypoglycemic events, and perform the DES-SF. Patients are instructed to maintain a glucose and insulin diary.

G. Procedures

Major study procedures and visits are summarized in Table 8.

H. Data Management and Analysis Plan

H.1. Data Management

The database used for this study is REDCap, which is a secure web-based application for building and managing data. It is designed specifically for clinical research and administered by the OSU Center for Clinical and Translational Research. Permission for data access or entry will be granted or revoked at a level that is appropriate for each individual involved in the study. Following verification, data will be locked. Data and data labels can be downloaded selectively (for interim progress reports) or in entirety (end of study) directly from REDCap in SAS or Excel format. The study team will record information from the 2, 6, 12, and 24 weeks visits (Table 9).

Table 9. Study Procedures and Visits

Visit number	0	1	2	3	4
Time of Visit	Screen/consent	2 week	6 week	12 week	24 week
Type of visit	In-person	Phone	Phone	In-person	In-person
Informed consent/contact team	x				
Randomization	x				
Load DOS into EMR and inform discharge team	x				
Provide study drug and glucose monitoring instructions	x				
Demographics/Socioeconomic status	x				
Diabetes history	x				
Hospitalization history	x				
PSS scale	x				
DES-SF	x			x	x
Newest Vital Sign	x				
Glucose/insulin diary	x				
Review DOS		x			
Ascertain health care utilization		x	x	x	x
Review glucose/insulin diary		x	x	x	x
Hypoglycemia/Hyperglycemia		x	x	x	x
Review insulin adherence, persistence		x	x	x	x
Nurse counsellor (DOS group only)		x	x	x	x
HbA1c	x			x	x
Fasting blood glucose	X			X	X

DOS=discharge order set, EMR=electronic medical record, PSS=Perceived Social Support scale, DES-SF=Diabetes empowerment scale-short form, In-Person clinic visits will be conducted at either CarPoint East or McCampbell Hall

H.1.a. Missing Data

All data analyses will be completed as intention to treat analyses (i.e., individuals analyzed by group according to original random assignment, without regard to adherence to the intervention). Longitudinal outcomes (e.g., HbA1c) will be analyzed using mixed models utilizing all available measurements from individuals randomized. Missing binary outcomes (e.g., accurate and complete discharge orders, adherence) and missing covariate data will be imputed, using multiple imputation in SAS v9.3 PROC MI.

H.2. Overview of Analytic Plan

Statistical analyses of these data must not only demonstrate the efficacy of *the discharge order set*, but also estimate effect sizes, examine intervention group differences and identify subgroup differences. Analysis will begin with characterization of the sample with descriptive statistics that identify differences between intervention and control groups (1) evident at baseline, despite randomization, and (2) between groups due to differential attrition. Data will be screened for normality, outliers, and homogeneity. Descriptive statistics will summarize the sample characteristics and distribution of each variable. We will test hypotheses for each aim.

H.2.a. Statistical Power and Sample Size

The sample size for our study was based on a comparison of change in HbA1c over three months adjusting for baseline covariates related to change in HbA1c: age, whether or not patient is new to insulin, and dose of insulin; the first two were selected based on our preliminary data and the latter was selected based on an expected relationship. The following expression, adapted from Oakes and Feldman,[65] was used to calculate the number of individuals per group:

$$n/group = \frac{4\sigma^2(1-\rho)(1-R^2)(Z_{1-\alpha/2}+Z_{1-\beta})^2}{\Delta^2}$$

where σ is the standard deviation of HbA1c, ρ is the correlation between baseline and 24 week HbA1c levels, R^2 is the proportion of variability in change in HbA1c explained by the baseline covariates, Δ is the difference in change in HbA1c between treatment groups, and $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ are standard normal quantiles calculated at the two-sided type-I error rate (α) and power ($1-\beta$). Using parameter values based on our preliminary data ($\sigma = 2.2\%$, $\rho = 0.25$, $R^2 = 0.5$) and based on the effect observed by Wexler[3] ($\Delta = 0.8\%$), we will need 89 individuals per treatment group with 24 week follow-up to achieve 80% power at $\alpha = 0.05$. Since we expect 20% attrition, we will recruit 111 individuals per group into our study. The study is powered to detect a difference in the primary endpoint only. However, additional secondary endpoints of strong interest are pre-specified and included in the analysis.

H.2.b. Endpoints

Primary: Difference in the change in HbA1c from baseline to 24 weeks (+/-2 weeks) post-discharge (%, mmol/l)

Secondary:

- Difference in the change in HbA1c from baseline to 12 weeks (+/-2 weeks) post-discharge (%, mmol/l)
- Difference in the change in HbA1c from baseline to 12 and 24 weeks (+/-2 weeks) post-discharge (%, mmol/l)
- Difference in the change in fasting plasma glucose (FPG) from baseline to 12 and 24 weeks in DOS vs ESC (mg/dl)
- Difference in the % of patients achieving HbA1C 7% in DOS vs ESC (12, 24 weeks)
- Difference in the % of patients achieving HbA1C 6.5% in DOS vs ESC (12, 24 weeks)
- Difference in the % of patients achieving individualized HbA1C target in DOS vs ESC (12, 24 weeks)
- Difference in the proportion of patients with accurate and complete discharge orders for basal insulin and related supplies. (%)
    - Assessed as complete dose, quantity dispensed, adequate refills (separate for basal and prandial insulin), and correct prescription for pen needles (presence, quantity, adequate refills), no jargon
- Difference in the proportion of patients with accurate and complete discharge orders for prandial insulin and related supplies. (%)
    - Assessed as complete dose, clear dosing instructions, quantity dispensed, adequate refills, and correct prescription for pen needles (presence, quantity, adequate refills), no jargon
- Difference in the proportion of patients with a discharge prescription for glucose monitoring supplies (%)
- Difference in adherence to glargine U300 (% taking >80% of doses) at 2, and 24 weeks
- Difference in the proportion of patients who remain on glargine U300 at 24 weeks (%)
- Difference in the mean dose of glargine U300 at 2 and 24 weeks (units)
- Difference in the frequency of glucose monitoring at 2 and 24 weeks (times per day)
- Difference in the proportion of patients who follow up with their primary care provider or endocrinologist within 2, 6 weeks of discharge (%)
- Difference in the incidence of documented symptomatic (BG <54 mg/dl) hypoglycemia (%)[66]

H.2.c Primary Aim: To determine whether a Discharge order set with nursing support (DOS) is associated with lower HbA1c at 24 weeks post-program than enhanced standard care (ESC) alone. We will test for a difference in 24 week change in HbA1c between the DOS and ESC groups using a linear mixed model for the longitudinal HbA1c measurements. Our model will contain a random subject-specific effect and fixed effects of time (baseline vs. 24 weeks), treatment, a treatment-by-time interaction, and baseline covariates related to change, which we expect to include age, whether or not patient is new to insulin, and dose of insulin based on our preliminary data. We will adjust for changes in prandial insulin dose by including dose as a time-varying covariate in our mixed models. The inclusion of covariates is not to account for differences in these factors across treatment groups (which we don't expect due to randomization) but to increase the precision of our treatment effect estimate. A Wald test of the treatment-by-time interaction will be used to test our primary hypothesis that DOS affects 24 weeks change in Hb1Ac.

H.2.d. Secondary Aims:

- Determine whether DOS is associated with lower HbA1c at 12 months compared to ESC.
- Determine whether the DOS in conjunction with nurse supported self-titration of basal insulin glargine U300 is associated with improved persistence with insulin therapy, adequate dose titration, and use of self-monitored blood glucose.
- Determine whether the DOS is associated with improved discharge instructions and processes of care for insulin-requiring patients. This will be measured in terms of clarity of instructions, adequacy and completeness of prescriptions for insulin and diabetes supplies, and follow-up plan.

Each of these secondary outcomes will be binary (e.g., adequate vs. inadequate dose titration). Missing values of the outcomes will be imputed using treatment group and baseline covariates. The difference in proportions between treatment groups will be computed for each data set and the results will be combined using Rubin's rules[67] to obtain a final two-sample test of proportions.

I. Potential Limitations & Proposed Solutions

Limitations of the study relate to the potential loss to follow-up. From our preliminary data, we have determined that even the addition of a single specially trained student improved successful telephone contacts substantially. Therefore, within the context of a specifically dedicated study staff and the other enhancements, it is anticipated that further improvement in successful telephone contacts can be achieved. Furthermore, a large percentage of individuals in the pilot studies are followed in the OSU health system, simplifying the access to follow-up data at 24 weeks. Finally, there may be some difficulty discerning whether the discharge instruction or the nursing support were the primary determinants of success. We already know that education alone is of limited value for in the management of chronic illness. The purpose of the study is really to serve as a model of a comprehensive discharge program with the intent to maximize potential benefits of its individual elements.

J. Work Plan and Timeline

The overall project is anticipated to last 3 years (Table 10). The first 3 months will involve project start-up activities, including development of the REDCap database, regulatory submission, and training study staff. Study recruitment and enrollment will commence during the second quarter of the first study year and is anticipated to last 18 months to achieve a final enrolled sample of 222 participants. The final visit is expected at 6 months post-enrollment. Data gathering activities are scheduled to take 3 additional months. Data processing activities will commence at the start of data gathering and continue through the 33 months. The last quarter of Study Year 3 will be spent preparing reports and manuscripts. It is anticipated that at least 2 posters and 2 manuscripts will be generated from this work, including the first manuscript demonstrating improved processes of care at discharge and the second manuscript demonstrating change in glycemic control, titration and persistence of insulin.

Table 10. Study Timeline

Activities	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Start-up procedures	X											
Recruit & enroll sample		X	X	X	X	X	X					
Follow-up visits			X	X	X	X	X	X	X			
Data analysis										X	X	
Prepare reports & manuscripts											X	X

Summary and Future Directions

For the hospitalized patient, multiple factors collude to impede successful transitions in care in the current fragmented health system. Diabetes provides a suitable framework for chronic disease management in general due to its complexity regarding therapies, self-care, and multiple comorbidities. This proposal seeks to redefine the role of diabetes management throughout the continuum of care. Future applications would include multi-center studies and studies to determine the efficacy of the individual components.

Appendix: Diabetes Discharge Orderset	➢ **Drop-down Choices**
Diet—*Note: Most patients will require consistent carbohydrate diet*	
➢ Consistent carbohydrate diet *Note: appropriate for most patients, including those discharging to skilled nursing*	☐ *45 grams per meal* ☐ *60 grams per meal*
☐ Flexible carbohydrate diet *Note: carbohydrate counting method, only if patient using prior to hospitalization or has demonstrated competency*	
Follow-up	
➢ Primary Care Provider	*[see below]*
➢ Endocrinologist *Note: If patient does not live near Columbus, please locate an Endocrinologist nearest to their home. The phone number for OSU Endocrinology is 614-685-3333*	☐ Call for an appointment. You should be seen within 2 weeks of discharge from the hospital, your diabetes medications may need adjustment ☐ Call for an appointment. You should be seen within *** weeks ☐ You have a follow-up appointment with *** on [date]
➢ Diabetes Education *Note: If patient does not live near Columbus, please locate a diabetes educator nearest to their home. The phone number for OSU Endocrinology is 614-685-3333*	☐ Survival skills ☐ General diabetes education
☐ Bring a blood sugar log (record of your glucose readings), medications and glucose meter with you.	
Notify Physician	
☐ Call your healthcare provider if you are having recurrent low sugars (less than 70 mg/dl) more than 2 days in a row or if you have any severe low sugars requiring the assistance of someone else to treat.	
☐ Call your healthcare provider if you have recurrent high (above 250 mg/dl) blood sugars for more than 3 days in a row, or if you have glucose readings over 250 mg/dl with new symptoms such as nausea, vomiting, or dizziness.	
Patient Instructions	
☐ Your target glucose is *** mg/dl fasting and under *** mg/dl nonfasting *<Note: Typical blood sugar goals for many people are 80-130 mg/dl in the mornings (fasting) and less than 180 mg/dl throughout the rest of the day>*	
☐ Instructions for Managing Your Diabetes at Home	*[Attachment]*
Diabetes Medication and Supply: *Note: U100 Insulin vials contain 1000 units, U100 pens contain 300 unit/pen, glargine U300 contains 450 unit/pen, degludec U200 contains 600 unit/pen, lispro U200 contains 600 unit/pen.* *[each prescription option is paired with U100 0.3 or 0.5 ML syringe or pen needles as appropriate]*	
➢ **Basal Insulin** ➢ Glargine U100 Solostar pen and pen needles ➢ Glargine U300 Solostar pen and pen needles ➢ Detemir U100 Flextouch pen and pen needles ➢ Degludec U100 Flextouch pen and pen needles ➢ Degludec U200 Flextouch pen and pen needles ➢ Glargine U100 vial and syringes	*[Example Drop-down Menu:]* ➢ ***Insulin Glargine 300 unit/ml pen*** *** units every day. ☐ *Increase *** unit every 4 days until AM (fasting) glucose is under *** mg/dl, provided that you have no glucoses under 80 mg/dl, do not go above *** unit per day.*

<table>
<tr>
<td>
➢ Detemir U100 vial and syringes
➢ NPH U100 vial and syringes
</td>
<td>
☐ [Cardiac surgery patients]: Reduce dose by 2 unit every day that you wake up with a glucose less than 100 mg/dl or if you have any glucose levels under 80 mg/dl.
☐ No titration
Dispense: 3 prefilled pens; Refills: 1
☐ Pen needle 31 G x 4 mm
For use with insulin once daily
Dispense: 50; Refills: 1
</td>
</tr>
<tr>
<td>
➢ Set Meal Insulin Dose: appropriate for most patients using prandial insulin in addition to consistent carbohydrate diet
➢ Aspart U100 Flextouch pen and pen needles
➢ Glulisine U100 Solostar pen and pen needles
➢ Lispro U100 Kwikpen and pen needles
➢ Lispro U200 Kwikpen and pen needles
➢ Aspart U100 vial and syringes
➢ Lispro U100 vial and syringes
</td>
<td>
[Example Drop-down Menu:]
➢ Insulin Glulisine 100 Unit/ML Pen-injector
*** units SQ QAC.
☐ High dose correction
➢ Standard correction
<table>
<tr><th>If your glucose is this</th><th>Add this much insulin to your mealtime dose</th></tr>
<tr><td>150-199</td><td>1</td></tr>
<tr><td>200-249</td><td>2</td></tr>
<tr><td>250-299</td><td>3</td></tr>
<tr><td>300-349</td><td>4</td></tr>
<tr><td>350-400</td><td>5</td></tr>
<tr><td>Over 400</td><td>6</td></tr>
</table>
☐ Low dose correction
Dispense: 3 prefilled pens; Refills: 1
☐ Pen needle 31 G x 4 mm
For use with insulin 4 times daily
Dispense: 150; Refills: 1
</td>
</tr>
<tr>
<td>
➢ Flexible Meal Insulin Dose: appropriate ONLY if patient using prior to hospitalization, discharging to Dodd Hall or demonstrates competency, in addition to flexible carb diet
➢ Aspart U100 Flextouch pen and pen needles
➢ Glulisine U100 Solostar pen and pen needles
➢ Lispro U100 Kwikpen and pen needles
➢ Lispro U200 Kwikpen and pen needles
➢ Aspart U100 vial and syringes
➢ Lispro U100 vial and syringes
</td>
<td>
[Example Drop-down Menu:]
➢ Insulin Glulisine 100 Unit/ML Pen-injector
1 unit for every *** grams of carbohydrate SQ QAC.
☐ High dose correction
➢ Standard correction
<table>
<tr><th>If your glucose is this</th><th>Add this much insulin to your mealtime dose</th></tr>
<tr><td>150-199</td><td>1</td></tr>
<tr><td>200-249</td><td>2</td></tr>
<tr><td>250-299</td><td>3</td></tr>
<tr><td>300-349</td><td>4</td></tr>
<tr><td>350-400</td><td>5</td></tr>
<tr><td>Over 400</td><td>6</td></tr>
</table>
☐ Low dose correction
Dispense: 3 prefilled pens; Refills: 1
☐ Pen needle 31 G x 4 mm
For use with insulin 4 times daily
Dispense: 150; Refills: 1
</td>
</tr>
<tr>
<td>
Glucose Monitoring
➢ Once per day (non-insulin requiring patients)
➢ 4 times per day before meals and at bedtime
➢ 6 times per day (before and 2 hours after meals)
</td>
<td>
[Example Drop-down Menu:]
☐ Glucose monitor (if patient does not have one at home)
Dispense: 1; Refills: 0
</td>
</tr>
</table>

	☐ **Glucose test strips** *Testing 4 times per day, ICD-10: **** *Dispense 150; Refills: 1* ☐ **Lancets** *Testing 4 times per day, ICD-10: **** *Dispense 150; Refills: 1* ☐ **Alcohol wipes** *Testing 4 times per day, ICD-10: **** *Dispense 150; Refills: 1*
☐ **Ketostix strips** (*for Type 1 DM or history of DKA*) *Test urine prn glucose >400 mg/dl or >250 mg/dl with nausea, vomiting or other symptoms of DKA* *Dispense 50; Refills: 0*	
☐ **Glucagon emergency kit** (*for Type 1 DM or history of severe hypoglycemia or hypoglycemia unawareness*) *1 mg SQ prn severe hypoglycemia* *Dispense 1; Refills: 0*	

HUMAN SUBJECTS

A. Protection of Human Subjects

A.1 Risk to human subjects

A.1.a Human Subjects involvement, characteristics, and design

This is a randomized controlled trial of the use of a discharge order set (DOS) with post-discharge nursing support in hospitalized patients with poorly controlled diabetes. The outcomes include glycemic control (HbA1c), persistence of insulin use and adequate dose titration, and discharge processes of care, measured in terms of clarity of instructions, adequacy and completeness of prescriptions for insulin and diabetes supplies, and follow-up plan. Patients in the standard group will receive basal insulin and otherwise enhanced standard care. Patients in the intervention group will undergo utilize a diabetes focused discharge order set and instructions for specific dose titration with nurse follow-up contacts at 2 and 6 weeks following discharge. Records will be obtained from primary physicians if needed. Specific medical concerns will be forwarded to the primary provider, who will receive a packet at discharge that will assist with transition of the patient's care to the community and updates at 3 months. HbA1c and diabetes empowerment, is checked at baseline and 12 and 24 weeks for both groups. Outcomes are assessed at 2, 6, 12 and 24 weeks.

The sample is obtained from two hospitals from a single academic medical center. The main campus hospital consists of University hospital, Ross Heart Hospital, James Cancer Hospital, and Brain and Spine hospitals and has a referral base from central and southern Ohio as well as a diverse array of medical and surgical patients. OSU East is a community hospital that serves a large percentage of local, often indigent patients. A total of 222 participants are planned, approximately 80% from the main hospital. Data will be entered into REDCap from both sites via an online secure database tool. Completed informed consent and questionnaires will be scanned into this system as well. The OSU electronic medical record has the capability of designating the patient is enrolled in a research study in order to improve communication between providers and patients.

Based upon preliminary data, we found that approximately 30% were of African American race. We are enrolling a wide age range, 25-75, in order to achieve optimal external validity, but have excluded the younger and older participants due to insufficient numbers in those ranges and possibly different educational needs, that may involve people (family) other than the patient. Participants are anticipated to be sick and have other comorbidities (in our pilot data, 70% were admitted for a problem that was not directly related to diabetes). However, all participants will be free-living in the community and have a phone. Due to bias introduced by additional support staff at institutions such as nursing homes and rehabilitation centers, these participants will be excluded. Participants who are unable to provide consent in English will be excluded as this number is very small and will hinder motivational interviewing (MI) process. Other vulnerable populations, such as prisoners will be excluded. Pregnant individuals will be excluded since the HbA1c is not as reliable and because such individuals have different motivations and follow-up already in place.

Permission will be obtained from the attending physician of the admitting inpatient service prior to approaching participants for enrollment. Randomization will be conducted using a computerized random number generator program that is weighted and will be stratified by race. The frequency of telephone follow-up is felt to be adequate to establish reasonable endpoints for reinforcement of behavior and capture a realistic window for readmission.

A.1.b. Sources of Materials

- Blood work will be collected for HbA1c at baseline and follow-up.

- Data that will be collected for both groups include:
  - Contact information, including email address and best times to reach the patient, contact information for two emergency contacts, and contact information of the patient's primary care provider
  - Type of diabetes, complications, duration
  - Education level, marital status, work status, home ownership, medical coverage, and demographics
  - Social support, measured using the Multidimensional Scale of Perceived Social Support.
  - Reason for hospital admission, medical history, concomitant medications, weight, height, BMI, standard of care lab results
  - Functional health literacy assessment.
  - Diabetes Empowerment Scale Short-Form (DES-SF): The DES-SF will be obtained at baseline and follow-up
  - Charlson comorbidity index
  - Blood Sugar Log
  - Outcomes including readmission or other acute care services, outpatient physician follow-up, medication adherence. Records will be requested from outpatient providers as needed.

A.1.c. Potential Risks

There are no physical risks that would not otherwise be anticipated, as the blood draw for HbA1c is considered standard of care. No specific prescriptive regimen for medications is planned and therefore this also represents standard of care. Furthermore, we already know that this is a high-risk population. Psychological harm may be a possibility if participants neglect other aspects of self-care in favor of diabetes. However, this seems unlikely and will be averted with frequent contact and anticipated increased outpatient follow-up. No financial or legal consequences are anticipated. Breach of confidentiality is a possibility but with standard procedures for immediate entry of paper data into the secure online database, use of a study identification code on all data gathering instruments, and the use of electronic health records, this should be limited.

Other forms of contact, such as internet, could be considered but this would not be a viable forum for all patients. Therefore, email (in secure mail format) will be reserved for follow-up of specific problems or in the event of failure to contact the patient.

A.2 Adequacy of Protection Against Risks

A.2.a Recruitment and Informed Consent

Potential participants will be identified during their hospitalization through screening inpatient medicine and surgery wards. A partial HIPAA waiver will be obtained for this purpose. Permission will be obtained from the admitting team's attending physician or appropriate designee. The patient will be approached in private. Personnel (coordinator) will describe the purpose of the study in the same words that are used on the consent form, which states lack of participation will not otherwise influence patient care. Participants are expected to read the consent form (or have it read to them) in full and be able to explain the study purpose, risks, and procedures to the investigator before consent will be considered complete and informed. Participants will be encouraged to ask questions and have any questions answered to their satisfaction. Participants that seem unsure or want to consider it further will be re-approached with their permission, after several hours or the following day or otherwise per the participant's request. The samples and study-related information will not be used if the participant subsequently declines enrollment.

A.2.b. Protections against risk

Participants will be assigned a study number that will be the primary means of identifying patient data. A key will be kept on the secure endocrine network drive but this will only be for internal investigator use. Any personal information acquired will be entered into the secure online database (REDCap), which is password protected, and allows limited access to varying degrees. Only immediate study staff (PI, nurse, research assistants) will have access to REDCap. Other personal information (such as signed consent forms) will be kept in the office of the PI or the study coordinator and locked when not in use. Personal data that is otherwise not recorded into the database will be destroyed immediately through appropriate confidential shredding bins. After the program is complete and the data has been analyzed, identifiable/coded(linked) data will be retained and stored confidentially for the minimum required amount of time. Personally identifiable past medical history and study data (glucose, laboratory assessments) will be obtained from EPIC/IHIS, REDCap and the chart reviews. No highly sensitive information (mental illness, HIV status, social security number) will be collected and vulnerable populations such as prisoners will not be enrolled.

During phone call follow-ups, diabetes-specific events will be referred to the participant's primary provider with use of the study nurse or PI as back-up for urgent matters only. Study-related adverse events will be recorded and severe adverse events will be reported to the study PI and the institutional review board. Any severe adverse events felt to be related to the study will be reported immediately to the PI and IRB. Participants may leave the study for any reason and are assured that this will not otherwise affect their care. Thus, informed consent is treated as a continual process.

A.3. Potential Benefits of the Proposed Research to Human Subjects and Others

Participants may benefit from more intensive interaction with study staff, through improved glycemic control as well as close follow-up and anticipatory guidance. Benefits to society include improved glycemic control and hospital readmission, which may result in reduced medical costs, particularly among uninsured individuals. The risks are primarily related to breach of confidentiality and are limited, though still possible. Given the safeguards that are put in place, the potential benefits should outweigh the risks.

A.4. Importance of the Knowledge to be Gained

The importance of the knowledge is in the understanding of the role of diabetes, in particular diabetes education and PN, on the discharge process. Currently, diabetes is overlooked in the hospital and at discharge, despite its importance for the overall well-being of the patient. The current protocol provides an easily adaptable hierarchical process for inpatient to outpatient transitions in care for a population of complicated medical patients. Currently, few randomized studies have examined whether telephone follow-up or post-discharge support is effective in this population. The rising epidemic of diabetes will continue to contribute significantly to the morbidity of these patients, frequently necessitating hospital care. Providing solutions to this problem is of considerable urgency. Therefore, the potential benefits outweigh the given the aforementioned risks.

A.5. Data and Safety Monitoring Plan

The Data and Safety Monitoring Plan is written to ensure the safety of the participants and to verify the validity and integrity of the data.

1. Study risk assessment:

☐ **Exempt** (protocols exempt from IRB review are *not* required to submit a DSMP)

☒ **Level I risk** (identify ***all*** applicable study procedures)

☐ **Anthropometric evaluations**	☐ **DEXA scans**
☐ **Electrocardiograms (ECG)**	☐ **Exercise testing**
☐ **Intravenous glucose tolerance tests (IVGTT)**	☐ **Intravenous catheter insertion**
☐ **Computerized Axial Tomography (CAT) or Magnetic Resonance Imaging (MRI)**	☐ **Observational/Behavioral studies**
☐ **Oral glucose tolerance tests (OGTT)**	☐ **Pathology slide review**
☐ **Special or prescribed diets/Nutritional studies**	☒ **Venipuncture**
☐ **Other low risk non-therapeutic tests or studies (list):**	

☐ **Level II risk** (identify ***all*** applicable study procedures)

☐ **Child population**	☐ **Normal volunteers using well-described research procedures**
☐ **Endoscopy**	☐ **Vulnerable population(s), e.g. minorities, indigent, MRDD, prisoners, military personnel, individuals with diminished capacity for decision-making and/or limited literacy skills (e.g. <8th grade reading level)**
☐ **Elderly population**	☐ **Pharmaceutical agent(s) under study/Phase IV (post-marketing) studies**
☐ **Insulin clamp**	☐ **Pregnant population**
☐ **Muscle biopsy**	☐ **Psych. or neuro. impaired population**
☐ **Research-associated procedures (please specify):**	
Other moderate risk non-therapeutic tests or studies (please specify):	

The risks for the actual study procedures are considered low as the intervention is limited to behavioral strategy with a blood draw that is otherwise considered to be standard of care. Study-related adverse events, enrollment compliance, proper informed consent, data analysis, confidentiality will be reviewed annually by the study PI and independent safety advocate (Carson Reider, PhD).

2. Plan for reporting adverse events and unanticipated problems:

Adverse event and unanticipated problem reporting will comply with University, as well as Federal guidelines, as appropriate. All adverse events and unanticipated problems will be reported to the IRB, and to the funding agency as well as other entities, as required. Such events or problems requiring reporting include those that may involve physical, psychological, social, legal and/or economic harms to the participants. Adverse events

will include severe hypoglycemia rates (defined as hypoglycemia associated with seizure or hemodynamic compromise in need of outside assistance), pregnancy, overdose, and breach of confidentiality. In addition the following definitions apply:

DEFINITIONS

Serious adverse event (SAE): any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening, (Note: the term "life-threatening" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or results in prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is a medically important event or reaction. Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Related Adverse Event, i.e. Adverse Drug Reaction (ADR): There is a reasonable possibility according to the investigator that the product may have caused the event.

Unexpected Adverse Event, i.e. Adverse Drug Reaction (ADR): An adverse reaction, the nature or severity of which is not consistent with the applicable product information (package insert/summary of product characteristics for an approved product). An expected ADR with a fatal outcome should be considered unexpected.

New safety finding: Any safety issue that may require expedited reporting because providing information that may lead to a change in the known risk-benefit balance for the product and as mentioned, but not limited to, in the following regulatory texts: US: FDA: 21 CFR Parts 312 Investigational New Drug Application - Section 312.32, (c) (1) IND safety reports.

REPORTING ADVERSE EVENTS

- The study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.
- The investigator shall be responsible for ensuring submission of required expedited and periodic reports to the appropriate Regulatory Authority (RA), the Ethics Committee and investigators.
- Periodic reports (e.g. Development Safety Update Report (DSUR)), submitted to Regulatory Authority will be first transmitted to Sanofi for review and comment.
- The study reports will contain a section describing safety review and conclusion and must be reviewed by Sanofi before finalization.
- *New Safety Findings in a study pertaining to safety of product must be transmitted within 1 business day. The investigator must provide to Sanofi upon request results of any relevant complementary exams performed to obtain the final diagnosis of any SAE (e.g., hospital discharge summary, autopsy, consultation).*
- The Institution must report the following information in English to the Sanofi group entity Pharmacovigilance contact:
  - Routine transmission of all Serious Adverse Events (SAEs) including pregnancy, overdose. These events must be transmitted within 1 business day of the Institution's awareness or identification of the event.
  - Routine transmission of SAEs related to the use of the Sanofi product must be transmitted within 1 business day of the Institution's awareness or identification of the event. The reference safety

information to be used by the Institution for evaluation of expectedness of adverse events shall be the current approved product label available in the country.
- Any Periodic reports (e.g. Development Safety Update Report (DSUR)), submitted to Regulatory Authority must be transmitted to Sanofi at the time of submission.
- *New Safety Findings* in a study pertaining to safety of product must be transmitted within 1 business day. (e.g., Data Safety Monitoring Board recommendations)

Defining and reporting of adverse events and/or unanticipated problems will otherwise follow the recommended guidelines and algorithm of the Office of Human Research Protection and comply with applicable University Human Research Protection Program Policies [http://orrp.osu.edu/irb/osupolicies/HRPPPolicies.cfm].

All serious adverse events and/or unanticipated problems (e.g. protocol deviations or violations), including any unexpected adverse event that occurs during the course of the investigation, will be promptly reported to the appropriate institutions and offices, e.g. OSU Institutional Review Board. The investigator will continue to follow or obtain documentation of the resolution course of such events.

These events and/or problems will be brought to the attention of the University's Institutional Review Board *as soon as possible* but at least within 10 days of the investigator or research team learning of the event. Any events that result in a temporary suspension or interruption of study activities in order to avoid potential harm to subjects should be reported within 48 hours, or as soon as feasibly possible. Where appropriate or as requested, a final report will be submitted.

Each submitted report will be in compliance with the appropriate HIPAA guidelines [i.e., not contain any personal identifiers of the study participant(s) for reports which will be disclosed, but will possess confidential patient identifiers (e.g., participant study identification number) that can be used by the investigator and study personnel to identify the patient(s)]. Expected adverse events, *excluding* those deemed to be serious, will only be summarily reported to the IRB at the designated intervals of continuing review.

Subjects who prematurely withdraw from the study due to an adverse event will be followed as is feasibly possible (e.g. telephone contact, and/or follow-up visits, etc.), until resolution of the event.

Data collection and safety monitoring activities for this study will continue until all subjects have completed their participation and all subjects are beyond the time point at which study-related adverse events and/or unanticipated problems would likely present.

3. Plan for assuring data accuracy and protocol compliance:

The clinical research coordinator and/or investigator will be responsible for collecting and recording all relevant data for the protocol. As these results are collected, all toxicities and adverse events will be identified, recorded, and reported to the principal investigator. Adverse events and unanticipated problems will be reported as described above. The principal investigator will determine the relationship of the adverse event(s) to the intervention(s), procedure(s), and/or agent(s) of the protocol and decide the appropriate course of action for the study participant(s).

Compliance will be achieved via IRB Continuing Review, and conscientious conduct by members of the study team, adhering to relevant regulations and the principles of the ethical conduct of human subject research.

4. Periodic Reports:

In accordance with Federal and institutional guidelines, an annual summary of all serious and unexpected adverse events, as well as of any unanticipated problems will be submitted to the OSU Biomedical IRB. The purpose is to review the entire study, determine that the risks and benefits are reflected in the actual experience of subjects and that the measures implemented to minimize risk continue and are deemed to be adequate. New data that would be expected to alter the risk/benefit profile will also be reviewed annually by the PI and IRB. The sponsor will be informed of any action taken by the OSU IRB or study monitor committee.

Note: *Nothing in the DSMP replaces a researcher's responsibility for prompt and appropriate reporting of serious adverse events, protocol amendments, data collection procedures, etc. to the OSU ORRP-IRB, sponsor(s), or other responsible parties. Any reporting required by the DSMP is in addition to these core compliance responsibilities.*

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