IDEAS FOR POTENTIAL DIABETES MANAGEMENT CLINICAL TRIALS
DMICC Meeting January 18-19, 2007

Category	Research Question	Study Population	Study Outcomes	Design Issues	Research Translation
#1 Glycemic control and intensive therapy in the elderly	Risk to benefit ratio of aggressive glycemic control is uncertain in elders **Hypothesis--Aggressive control is good** 1) What are the marginal benefits and risks of treating to LDL-c targets below 100 mg/dl among persons with Diabetes over the age of 65? 2) What are the marginal benefits and risks of treating to glycemic targets below an A1c of 8% among persons with Diabetes over the age of 65? 3) What are the relative benefits of treatment of hyperglycemia, HTN, or dyslipidemias among persons over 65 with multiple comorbidities where treatment of all intermediate risk factors simultaneously may not be feasible?	Persons with Type 2 DM 65 yrs of age or older with a predicted life expectancy of greater than 5 years Over-sample minorities with the highest prevalence of DM	DM related outcomes Cardiovascular outcomes Other potential outcomes: UTI, Pneumonia, Cellulitis, Falls, Fractures, Cognition, Function, Utilization, Costs	RCT, based in primary care Intervention--Usual care vs more intensive control by nurse practitioner "Real world" representative populations in this age group are likely to have higher rates of drop out secondary to illness and death. Research questions 1 and 2 could be addressed with RCT at the patient level Research question 3 would require a randomized block design and considerably larger sample size.	Almost 50% of persons with Type 2 DM are 65 years or older and have multiple comorbidities. With the exception of the HTN treatment trials, this group has been excluded from most of the diabetes and lipid RCTs. Knowledge about whether "treating to target" is beneficial in this group has huge implications for polypharmacy, costs, and quality of life for older persons with diabetes. An effectiveness trial that provides a clearer understanding of the relative benefits & harms of treating each of the intermediate risk factors could provide the critically needed information for priority setting with the complex older person with diabetes where equally aggressive treatment of all 3 risk factors is often times not feasible.
#2 Preventing beta-cell deterioration in T2DM and glycemic control	1) Can the deterioration of beta cell function be prevented in recent onset type 2 diabetic patients? 2) Will preservation of endogenous insulin secretion improve long term control?	Phase 1: Recent onset T2 DM – approx. 400 Phase 2: Recent onset T2 DM – characteristics, #: TBD	Phase 1: Assess endogenous insulin response after different Rx regimens Phase 2: Assess long term HbA1c, Rx needed and adverse events	Reasons 2 phase study needed: 1. Residual insulin secretion improves control 2. Preservation of insulin secretion possible 3.Best candidates recent onset T2D 4. Predictors of response /duration not well known (P1) 5. Long term benefit not well known (P2)	Possible effect on current Rx guidelines More aggressive early treatment of T2 DM Different optimal treatment regimens

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#3 Selecting optimum intervention strategies for type 2 diabetes	Which treatment strategies are most effective in achieving goal A1c in type 2 diabetes? RCT of ADA algorithm vs new medications vs "usual care"	Type 2 diabetes	1. A1c over time 2. Adverse effects 3. physiologicoutcomes, e.g., beta cell preservation 4. Other effects on CVD risk factors 5. Cost-effectiveness: $ per 1% decline in A1c	Using acceptable "surrogate" outcome of A1c makes the project practical.	Major economic implications. RCT comparisons of generic vs newer medications will not be done by pharmaceutical companies
#4 Glycemic control and CVD in adolescents and young adults with IGT	Will intensive treatment of impaired glucose tolerance aimed at truly normalizing fasting and 2 hour post-oral glucose load plasma glucose levels be of benefit with respect to preventing or delaying the development of CVD in this vulnerable population?	Obese adolescents and young adults (age range to be determined) with IGT	Ultimately (if study can be sustained long enough) clinical evidence of atherosclerosis Structural markers: Imaging studies assessing artery wall thickening, cardiac function, etc. Biomarkers Physiologic markers: FMD, etc	Long-term, large-scale RCT with 2 Rx groups: Conventional Rx: standard dietary counseling and appropriate treatment of co-morbidities (T2DM, hypertension, dyslipidemia) as they emerge Experimental (Intensive treatment) Group Phased-in aggressive management to normalize fasting (<100 mg/dl) and 2 hour pp glucose levels (<120 mg/dl). Life-style, exenetide, metformin, DPP-4 inhibitors, weight loss agents new agents can be used based on a predetermined plan and criteria. Treatment of co-morbidities identical with control group.	The study will establish that IGT is a real disease that needs to be treated in its own right—not just to prevent the development of T2DM. Just as the DCCT established A1c as a surrogate marker of microvascular disease in T1DM, results of this study will also help define useful surrogate markers of future macrovascular disease in obese young people.

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#5 Glycemic control and acute MI "DIGAMI 3"	Does normalization of blood glucose levels using an intensive insulin protocol in patients with acute myocardial infarction improve short or longer term prognosis, compared to a standard approach to glucose control?	Adults admitted to an acute care facility with the diagnosis of acute myocardial infarction AND: 1) previously diagnosed type 2 diabetes, OR 2) hyperglycemia at presentation ("stress hyperglycemia" or previously undetected DM)	1) in-hospital mortality and morbidity 2) mortality @ 12 months 3) re-current MI, chf, functional status at 12 month follow-up	1) acute treatment (24-48 hours peri-MI) vs. acute plus chronic (up to 12 months) 2) confounding effect of other MI therapies (thrombolysis, PTCA, etc.) 3) sample size (DIGAMI 2 may have been underpowered at ~1,200) 4) "standard care" comparison group – how to ensure adequate glycemic separation?	There are no evidence-based guidelines for glycemic management of patients with acute MI, yet many centers have instituted such programs, at substantial cost and some potential for patient harm (hypoglycemia). Coronary heart disease is the major cause of death for patients with diabetes. If proven effective, institution of intensive glucose management in acute MI has the potential to improve the poor prognosis of diabetic post-MI patients.
#6 **D**etermining **A**ppropriate **M**anagement **A**nd **G**oals for **E**veryday **Control** in non-ICU diabetic inpatients (DAMAGE CONTROL study)	Determine whether an inpatient regimen to titrate regimens during admission (including education) will improve long-term diabetes control, compared with usual care.	Adult diabetic inpatients on general (non-ICU, non-obstetric) medical and surgical services	1. HbA1c as outpatient 3-12 mo after admission 2. Frequency of hyper- and hypoglycemia during inpatient stay 3. Identify subsets that benefit from inpatient monitoring	RCT to different inpatient treatment regimens	~25-30% of all inpatients have diabetes and ~ 25% of diabetic patients are admitted annually-usually for reasons not related primarily to diabetes control. However, no evidence to support specific glycemic goals or management strategies. Despite the absence of data, intensive therapy regimens (expensive, resource requiring, and potentially dangerous) are being promulgated and adopted. Short-term glycemic control unlikely to improve acute outcomes in hospital, but may make inpatient period safer. Moreover, inpatient stay can be instructive/constructive with regard to diabetes management instead of destructive.

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# 7 Non-glycemic interventions and lower extremity problems in diabetes	Which therapeutic strategies will most effectively reduce lower extremity problems in diabetic patients?	Diabetic men and women with diabetes for 10 or more years but without LEA or history of foot ulcer	Composite outcome of foot ulcer, Charcot fracture or LEA	4 arm trial: 1. intensive behavioral intervention – podiatric offloading plus monitoring of plantar pressures and home based monitoring of foot temperatures 2. lower LDL to 70 and SBP to 115 + early revascularization 3. therapy with best new agent to ameliorate neuropathy 4. standard advice on foot care All 4 groups with same target for glycemic control; groups 1,3 and 4 have std LDL and SBP targets; groups 2 and 3 receive standard advice on foot care	Would provide needed information on best strategy for preventing foot problems, thus reducing morbidity and loss of productivity

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#8 Behavioral intervention in type 1 and 2 diabetes and effect on quality-of-life	Can a comprehensive self-management intervention (psychoeducation, cognitive-behavioral treatment, coping skills) have a clinically significant impact on improving quality of life and biobehavioral outcomes: a) among diverse groups of children and adolescents with Type 1 diabetes and their family members? b) older Americans with Type 2 diabetes?	a) Children and adolescents with T1DM, and their parents b) Adults age 45 and older, with T2DM. (Consider inclusion of family members where culturally appropriate.)	1.HRQOL scores BDI or CES-D 2.HbA1C 3.Blood lipids and other measures of CV health 4.Measures of age-appropriate self-management	Recruitment of diverse study populations • Comparison across diverse practice settings; e.g., private practice, academic clinics, community clinics. • For T1DM, consider summer camps, schools. For adults, consider worksites. • Tailoring intervene. to specific pops (e.g., age, culture, ed. level) • Comparison across diverse interventionists (advanced practice nurses, certified diabetes educators, psychologists, health educators, or those in entry level positions with special training in the intervention) • Cost-effectiveness of intervention. • Type 1 diabetes: Follow-up through childhood and adolescence into young adulthood • Type 2 diabetes: Consider follow-up into old age For Type 2 diabetes – issues of comorbidity; varied pharmacological interventions	Cost-Effective means to increase age-appropriate self-management in diabetes care Cost-Effective means to decrease depression & family conflict in families of children w/T1DM Cost-effective means to improve QOL among people of all ages with diabetes Sustained improvement in HgA1C as children and adolescents with T1DM mature Sustained improvement in HgA1C as adults age. Decreased complications and therefore decreased overall morbidity and cost associated with treatment.
# 9 Development if closed loop insulin pump for type 1 diabetes	Can a closed-loop insulin delivery system that uses an external sensor and external insulin pump that is used to regulate overnight insulin infusion rates prevent or markedly reduce the risk of nocturnal hypoglycemia in children and adolescents with T1DM?	Children and adolescents with T1DM who are well controlled with insulin pump therapy	Primary: Rates of severe hypoglycemic events during the overnight period Differences in the frequency of biochemical hypoglycemia; A1c; QOL and fear of hypoglycemia	RCT involving 2 groups of CSII treated youngster: Intensive open-loop treatment group Intensive open-loop during the day and closed-loop at night .	This study will be the first important step towards moving CL insulin delivery from the CRC into the real world

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#10 Polypill strategy to reduce vascular disease	For CVD Risk management, compared to "Community Usual Care", what will be the effectiveness of a strategy delivering "Combination Pharmacotherapy" to all high-risk people (i.e., diabetes), who do not have contraindications to aspirin, a statin, a ACE-I/ARB, or metformin?	Diabetes: FPG =>126 or 2HpG =>200	Primary: Diabetic Vascular diseases (composite of CVD mortality, clinical MI, stroke, CHF, renal and eye disease) Secondary: Quality of Life, Cost-effectiveness	Pre-stratify randomization by diabetes Exclude people with contraindications to combination therapy Providers in community be allowed to treat blood pressure, lipids, glucose as long as they don't use the drugs in combo therapy For study power within budget, generalizability & effectiveness, and translatability of results, consider: Large, simple, trial design using simple, low-cost, and clinically relevant measurements Collaborations with a few low-cost recruitment countries outside the US, especially, if non-Federal sources of funds can be tapped	A low-cost "Combo-Pill" (consisting of a aspirin, a statin, an ACE-I/ARB, and Metformin) given to all people with diabetes who don't have contraindications for any of these, can simplify treatment, lower cost, and be more effective than usual care at preventing the major vascular complications.

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#11 Pharmaceuticals vs. lifestyle changes	(1) Compared to standard recommendations, is initial normalization of the HbA1c with medications associated with: (a) A lower trajectory of progressive hyperglycemia? (b) Slower progression to complex therapy including insulin? (c) Reduced development of microangiopathy? (2) Is normalization of HbA1c using lifestyle and medicines that are thought to improve beta cell function associated with better outcomes than currently recommended first and second line oral agents?	Newly diagnosed type 2 diabetic subjects	(1) Achievement of HbA1c thresholds (e.g. 7%, 8%) (2) Requirement for insulin (HbA1c >7.0% and at least 3 oral agents) (3) Appearance of microangiopathy e.g. fundus photography, albuminuria, neuropathy measure.	(1) 3 groups of newly diagnosed diabetic subjects Group A: Treatment by ADA consensus recommendations (<7.0%) Group B: Treatment using metformin and sulfonylurea agents to achieve an HbA1c <6.1% Group C: Treatment using pioglitazone and a gliptin to achieve an HbA1c <6.1% (2) Titration to 3 drugs and then insulin in all groups at HbA1c >7.0% (3) Duration: 5 years + 5 years	(1) Screen rigorously for diabetes. If HbA1c > 6.1% (2) Normalize the HbA1c with lifestyle plus one or more drugs as rapidly as possible to produce long-term stabilization of glycemic control (3) Initiate therapy with drug A, then B, then C or If HbA1c is: 6.1-7% use max dose of any drug 7.1-7.5% begin with a 2-drug combination >7.5% begin with a 2-drug combination and titrate therapy without delay. However, the opportunity for stabilization may no longer be available.

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#12 Glycemic control and secondary intervention of ACS/MI/stroke	What are the benefits of treatment on CVD in acute coronary syndrome (ACS) for recent CHD patients with oral glucose tolerance tests at time of events? This proposal is based on Norhammer analysis in the Lancet 2002, which showed that among MI patients without known type 2 diabetes, 1/3 had newly diagnosed type 2 diabetes and 1/3 had impaired glucose tolerance. Among the IGT subjects, one could study prevention/delay of diabetes and among the new diabetic subjects, one could study progression to monotherapy failure.	Acute coronary syndrome and/or recent MI or stroke.	Incidence of CVD (estimated to be 10% in the first year and 6% in subsequent years) in ACS studies such as PROVE-IT or A-Z Incidence of DM among IGT subjects (4-6%/year)	This study must use interventions which don't increase CHD. Therefore, TZDs may not be useful. Possible three treatment groups: a) usual care, b) lifestyle, c) lifestyle + DPP IV inhibitors, d) DPP IV inhibitors. Metformin could be used as an add-on therapy for treatment failure. This sort of design may be the only way to find a study group in which the rate of incident CVD is as high or high than that of new diabetes. Among subjects who "want" a max stress test, subjects could be randomized to weight loss rather than weight loss + physical activity to make the study more generalizable (unlike Look Ahead). Other drugs to consider instead or in addition to DPP IV inhibitors might be rimonabant.	No previous studies have looked at preservation of beta cell function or prevention/delay of type 2 diabetes in people with recent MI. This might be a good population to show that diabetes prevention may also decrease CVD. Furthermore, the duration of the study could be 2-3 years.
#13 Weight control: lifestyle vs. bariatric surgery	Is bariatric surgery or an intensive lifestyle intervention more effective in improving outcomes in obese patients with recently diagnosed Type 2 diabetes?	Obese patients with recently diagnosed Type 2 diabetes	Weight loss Glycemic, blood pressure, lipid control Cardiovascular complications Quality of life	Obese patients with recently diagnosed Type 2 diabetes would be randomized to either bariatric surgery or an intensive lifestyle intervention (a la DPP or Look AHEAD) Outcomes (weight; blood glucose, blood pressure, lipid control; cardiovascular events, quality of life) would be assessed for 8-10 years	Bariatric surgery for obese patients with recently diagnosed Type 2 diabetes reduces long-term complications and associated human and economic costs compared with an intensive lifestyle intervention (or not)