

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

Category	Research Question	Study Population	Study Outcomes	Design Issues	Research Translation
<p>#1</p> <p>Combined drugs to prevent diabetes vs. lifestyle changes</p>	<p>Can sustained recovery from prediabetes be accomplished through early pharmacological intervention followed by maintenance lifestyle modification?</p>	<p>Subjects with prediabetes (i.e., impaired fasting glucose and/or impaired glucose tolerance)</p>	<p>Primary Outcome: Normalization of fasting plasma glucose and 2-hour post-load OGTT plasma glucose levels</p>	<p>Randomized, placebo controlled, parallel group, two-phase study, using 3 interventions:</p> <p>Phase 1 Group 1: Lifestyle modification (= DPP grade) Group 2: Glitazone + Metformin Group 3: Glitazone + DPP4 inhibitor</p>	<p>Initial aggressive pharmacotherapy to induce remission from prediabetes, which is then maintained by lifestyle modification, may be a strategy for stemming the tide of the diabetes epidemic in high-risk populations.</p> <p>A multi-modality approach as described may dramatically restore the vast majority of prediabetic subjects to normoglycemia. Such an effect, if sustained, could reduce the CVD burden associated with prediabetes, thus becoming a primary prevention intervention for CVD in high risk populations.</p>

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<p>#2</p> <p>Pharmaceuticals vs. lifestyle changes</p>	<p>For diabetes prevention, compared to a real-life translatable lifestyle intervention alone, what will be the effectiveness of:</p> <ol style="list-style-type: none"> 1. Adding a drug that lowers Insulin-resistance (e.g. Metformin)? 2. Adding a drug that improves beta-cell function (e.g., DPP-4-Inhibitors)? 3. Adding both metformin and a DPP-4-Inhibitor? 	<p>FPG =>100 and/or 2-h PG =>140</p>	<p>Primary: Diabetic Vascular diseases (composite of CVD mortality, Clinical MI, Stroke, CHF, Renal and Eye disease)</p> <p>Secondary: Diabetes Quality of Life, Cost-effectiveness</p>	<p>Four group versus Factorial design</p> <ol style="list-style-type: none"> (1) Lifestyle intervention should be based on what can be realistically delivered in real-life situations (e.g., group-based, using community delivery channels like YMCA) (2) For study power within budget, generalizability & effectiveness, and translatability of results, consider: (3) Large, simple, trial design using simple, low-cost, and clinically relevant measurements (4) Collaborations with a few low-cost recruitment countries outside the US, especially, if non-Federal sources of funds can be tapped 	<p>Combining drug therapy with lifestyle intervention (delivered in a low-cost, feasible manner) is more effective than lifestyle alone in preventing diabetes and its major vascular complications among people with prediabetes.</p>
<p>#3</p> <p>Community-based interventions to achieve behavioral changes likely to decrease weight and diabetes</p>	<p>What are the effects of community-based interventions on prevention or control of overweight/obesity and type 2 diabetes?</p>	<p>A set of small communities (towns or neighborhoods in cities of any size) suitable for clustered randomization of lifestyle interventions and longitudinal outcome measures in individuals</p>	<ol style="list-style-type: none"> 1. Structural changes in communities (ease of walking, physical recreation) and healthy food availability. 2. Changes in diet & exercise behavior, body size & shape, fitness, and glycemia in individuals. 	<ol style="list-style-type: none"> 1. Clustered randomization (large number of “communities”) 2. Interventions to facilitate physical activity and diet control 3. Structural outcomes measured in communities 4. Health outcomes measured in individuals 	<ol style="list-style-type: none"> 1. Behavior in “regular life” has important health effects relevant to obesity and type 2 diabetes. 2. Such behavior can be modified beneficially by community-based interventions. 3. Intervention in the community may help individuals overcome the difficulties of changing in isolation when their surroundings promote unhealthy behavior.

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<p>#4</p> <p>Weight control: lifestyle vs. bariatric surgery</p>	<p>Is bariatric surgery or an intensive lifestyle intervention more effective in improving outcomes in obese patients with recently diagnosed Type 2 diabetes?</p>	<p>Obese patients with recently diagnosed Type 2 diabetes</p>	<p>Weight loss</p> <p>Glycemic, blood pressure, lipid control</p> <p>Cardiovascular complications</p> <p>Quality of life</p>	<p>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)</p> <p>Outcomes (weight; blood glucose, blood pressure, lipid control; cardiovascular events, quality of life) would be assessed for 8-10 years</p> <p>Comment(DN): Randomization to surgery always problematic</p>	<p>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)</p>
<p>#5</p> <p>Weight control during pregnancy</p>	<p>Can lifestyle intervention delivered during pregnancy, and reinforced post-partum, reduce the risk of pregnancy-related residual weight gain?</p>	<p>Pregnant women recruited as early in pregnancy as feasible</p>	<p>Primary: Weight at 3 months post-partum</p> <p>Secondary:</p> <ul style="list-style-type: none"> - Glucose, CVD risk at 3 months post-partum; - Adiposity in offspring at 3 months 	<p>How to identify women early enough in pregnancy?</p> <p>Power and sample size issues</p> <p>Use large, simple trial design</p>	<p>If lifestyle intervention can be started early in pregnancy and reinforced immediately post-partum, there can be reductions in residual pregnancy-related weight gain, and improvements in the mother's and child's metabolic parameters</p>

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<p>#6</p> <p>Lifestyle in T2D</p> <p>Family-oriented intensive lifestyle intervention vs. standard lifestyle <u>intervention</u></p>	<p>Can the strong positive effect of the DPP intensive lifestyle intervention in the prevention of type 2 diabetes in individuals be strengthened with a family oriented intensive lifestyle intervention compared to standard lifestyle recommendations?</p>	<p>Multiethnic Family units of 2 or more persons which include at least one adult.</p>	<ul style="list-style-type: none"> • Type 2 diabetes in adults age 18 & older • Type 2 diabetes in children age 10 to 17yrs • Adult body mass & obesity • Childhood body mass & obesity • Physical Activity 	<ul style="list-style-type: none"> • Identifying time and space for a family unit intervention • Identification and training of appropriate interventionist, (i.e. Professional or Student) • Cost for space, interventionist, intervention materials. 	<p>Despite the initial success of individual lifestyle programs in the prevention of type 2 diabetes, weight regain is evident, with the possible conversion to type 2 diabetes after a few years. An intensive lifestyle intervention that addresses the family unit may produce the support needed by each family member to attain and maintain a healthier BMI and prevent the occurrence of type 2 diabetes in children and adults.</p> <p>According to the NIDDK Weight and Control Network about one-third of adults age 20 and older in the U.S. are overweight (BMI >25) and nearly one-third are obese (BMI >30). In Children age 6 to 19 up approximately 19% were considered overweight with up to about 37% at high risk for being overweight (BMI for age in the 85th percentile or higher) with obesity being a prominent risk factor for the development of type 2 diabetes.</p>

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<p>#7</p> <p>Polypill strategy to prevent vascular disease</p>	<p>For CVD prevention, compared to “Community Usual Care”, what will be the effectiveness of a strategy delivering “Combination Pharmacotherapy” to all high-risk people (i.e., prediabetes), who do not have contraindications to aspirin, a statin, a ACE-I/ARB, or metformin?</p>	<p>Prediabetes: FPG=>100 and/or 2-h PG =>140 or</p>	<p>Primary: Diabetic Vascular diseases (composite of CVD mortality, clinical MI, stroke, CHF, renal and eye disease) Secondary: Quality of Life, Cost-effectiveness</p>	<p>Pre-stratify randomization by prediabetes</p> <p>Exclude people with contraindications to combination therapy</p> <p>Providers in community be allowed to treat blood pressure, lipids, glucose as long as they don't use the drugs in combo therapy</p> <p>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</p>	<p>A low-cost “Combo-Pill” (consisting of a aspirin, a statin, an ACE-I/ARB, and Metformin) given to all people with prediabetes, 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.</p>