

St. Michael's Hospital Research Ethics Board Guidance Document for Reviewing Clinical Trials in Diabetes

1.0 Introduction

This document provides guidance for members of the Research Ethics Board (REB) at St. Michael's Hospital who are reviewing clinical trials in diabetes. This guidance is intended to ensure a consistent approach in the REB review of such trials, and should be used by investigators when they are preparing their REB submissions.

Each section is organized into three parts:

- 1) summary of the clinical trial evidence supporting the 2008 Canadian Diabetes Association (CDA) Clinical Practice Guideline statement
- 2) CDA guideline statement
- 3) guidance for the REB.

Trials that meet the guidelines will generally be considered acceptable by the REB. Trials that do not meet these guidelines will require convincing justification to gain REB approval.

2.0 Blood glucose levels above currently recommended targets during a clinical trial:

2.1 Background: The Diabetes Control and Complications Trial has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic microvascular complications, such as retinopathy, nephropathy and neuropathy.¹ Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.² There is strong data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control, although macrovascular risk reduction in this patient population is less conclusive.³

2.2 CDA Guidelines:

Glycemic targets must be individualized; however, therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve an A1C $\leq 7\%$ in order to reduce the risk of microvascular (Grade A, Level 1A) and, in individuals with type 1 diabetes, macrovascular complications (Grade C, Level 3).

In order to achieve an A1C of $\leq 7\%$, people with diabetes should aim for: a fasting plasma glucose or preprandial plasma glucose target of 4- 7 mmol/L (Grade B, level 2 for type 1 and Grade B, Level 2 for type 2 diabetes) and a 2 hour postprandial plasma

glucose target of 5-10mmol/L (Grade B, Level 2 for type 1 and Grade B, Level 2 for type 2).

Table 1. 2008 CDA Recommended Targets for Glycemic Control⁴

	A1C (%)	FPG or preprandial glucose (mmol/L)	2 hour post-prandial glucose (mmol/L)
Blood glucose targets for type 1 and type 2 diabetes	≤ 7	4-7	5-10 or 5-8 if A1C targets not being met

FPG= fasting plasma glucose

2.3 Guidance: Participants in a clinical trial not meeting the above targets should have clearly defined rescue criteria for hyperglycemia. Rescue therapy could be a range of options including assessment by the investigator or a protocol driven adjustment of therapy. Table 2 presents rescue criteria that the REB considers acceptable – the Table is based upon a combination of Health Canada and FDA guidance.^{5,6} It is recognized that these criteria are based on consensus, and some minor deviation from these criteria may be accepted for multicentre trials. For agents that lower postprandial rather than fasting glucose levels, the investigator is encouraged to enforce specific rescue criteria based on thresholds of unacceptable postprandial glucose encountered during the first 12 weeks of the study and unacceptable A1C levels encountered thereafter. It is expected that all participants in all clinical trials for Type 2 diabetes will receive dietary and lifestyle counseling consistent with Canadian Diabetes Association Clinical Practice Guidelines.

Table 2. Blood Glucose Levels Requiring Rescue Criteria

Stage of trial	Rescue criteria
Baseline to week 6	FPG > 15 mmol/L ⁵
Week 6 to week 12	FPG > 13.3 mmol/L ⁵
Week 12 to 24	FPG > 11.1 or A1c > 8 % ⁵
> 24 weeks	Dose escalation or the addition of other therapies should be instituted if the HbA1c >7% after 6 months of treatment. ⁶ Criteria for dose escalation, addition of other therapies or subject withdrawal should be defined for subjects with a HbA1c ≥ 8% at 52 weeks. ⁶

FPG= fasting plasma glucose

⁵ Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention- Draft Guidance by the U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, February 2008.

⁶ Health Canada Standards for Clinical Trials in Type 2 Diabetes in Canada Guidance Document, November 2007.

3.0 Participants not receiving metformin as first line therapy in the management of hyperglycemia in Type 2 Diabetes during a clinical trial:

3.1 Background: UKPDS 34 is a randomized controlled trial evaluating the effect of intensive blood glucose control with metformin in overweight individuals with type 2 diabetes.⁷ In the primary analysis (n=753) patients allocated metformin compared with the conventional group, had risk reductions of 32% (95% CI 13–47, p=0.002) for any diabetes-related endpoint, 42% for diabetes-related death (9–63, p=0.017), and 36% for all-cause mortality (9–55, p=0.011). In a secondary analysis (n=342) among patients allocated intensive blood glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032).

However, the data supporting the reduction in macrovascular complications with metformin is based on a relatively small number of participants (n=342).⁷ The Food and Drug Administration has concluded that no currently available oral hypoglycemic agent has been conclusively shown to reduce the risk of CAD.

3.2 CDA Guidelines: Metformin should be the initial drug used in both overweight patients [Grade A, Level 1A] and nonoverweight patients [Grade D, Consensus]. “The recommendation to use metformin as the initial agent in most patients is based on its effectiveness in lowering BG, its relatively mild side effect profile and its demonstrated benefit in overweight patients.” (2008 CDA CPG)

3.3 Guidance: Participants entering a trial where metformin is not used as initial therapy for the treatment of hyperglycemia should be informed of its recommended place in therapy and the reasons for this in the consent form. In addition, clinicians should be given the option of prescribing metformin to those participants they feel would benefit.

3.3.1. Example of consent form wording: “Current guidelines from the Canadian Diabetes Association recommend that metformin should generally be the initial medication used to lower blood sugar levels in most persons with Type 2 diabetes because of long experience with it and its excellent safety record with minimal risk for hypoglycemia (low blood sugar) or weight gain. If you are not already on metformin, you should feel free to ask your doctor about metformin (although there are appropriate reasons why some persons with diabetes are not on metformin).”

References

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-986.
2. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New Engl J Med.* 2005; 353(25):2643-2653.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352:837-853.
4. The Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008;32(suppl 1):S1-S201.
5. Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention- Draft Guidance by the U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, February 2008.
6. Health Canada Standards for Clinical Trials in Type 2 Diabetes in Canada Guidance Document, November 2007.
7. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet.*1998;352:854-865.