

Data and Safety Monitoring Board Guidelines (Revised Version) Program to Reduce Incontinence by Diet and Exercise

Summary of Revisions 11/2/04

- (Page 12) The estimated milestones and the DSMB meeting schedule have been changed to reflect changes to the recruitment schedule and the elimination of the month 3 visit. The milestones do not account for potential dropouts.
- Appendix II. Rules for Altering or Stopping PRIDE

Old Text: While statistical guidelines for stopping the study at one formal interim analysis (*approximately March 1, 2006*) are provided, multiple other considerations will guide the decisions of the DSMB.

New Text: While statistical guidelines for stopping the study at one formal interim analysis (*approximately June 1, 2006*) are provided, multiple other considerations will guide the decisions of the DSMB.

- Appendix II. A. 1.

Old Text: Recruitment goals will be established by the PRIDE Steering Committee and Coordinating Center based on the assumption that participants will be randomized in blocks of *approximately 84 every 5 months* over the 24-month enrollment period.

New Text: Recruitment goals will be established by the PRIDE Steering Committee and Coordinating Center based on the assumption that participants will be randomized in blocks of *approximately 60 every 4 months* over the 24-month enrollment period.

The Program to Reduce Incontinence by Diet and Exercise (PRIDE) was established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to determine if weight loss results in improvement in urinary incontinence among overweight and obese women with incontinence.

The progress of PRIDE and the study's potential to attain its goals will be regularly evaluated by an independent Data and Safety Monitoring Board (DSMB). This committee will periodically review the conduct and outcomes of the study and provide feedback to the NIDDK and PRIDE Investigators on the overall performance of the study with particular attention to protecting the safety of PRIDE participants.

The DSMB will consist of individuals who are independent of the institutions and investigators participating in the trial and who have no financial ties to the outcome of the trial.

A. Responsibilities of the DSMB

Prior to implementation of the trial, the DSMB will evaluate the study design, review informed consent documents and plans for recruitment, adherence, interventions, data quality and safety monitoring.

At periodic intervals during the course of the trial, the responsibilities of the DSMB are to:

- evaluate the progress of the study, including adequacy and timeliness of participant recruitment, adherence to the visit and interventions protocols, data quality and timeliness, efficacy of the intervention to produce and maintain weight loss, effects of weight loss on frequency of incontinence, participant safety, and other factors that can affect study outcome;
- consider factors external to the study when relevant information, such as scientific or therapeutic developments, may have an impact on the safety of the participants or the ethical conduct of the trial;
- ensure data integrity;
- conduct interim analyses in accordance with stopping rules that are clearly defined in advance of data analysis;
- ensure confidentiality of data and the results of monitoring;
- report to the NIDDK and PRIDE Investigators on the scientific progress of the trial and the safety of participants;
- make recommendations to the NIDDK, PRIDE Investigators and Institutional Review Boards on continuation, termination, or other modifications of the trial

B. Membership

The members of the DSMB are appointed by the NIDDK. The DSMB is comprised of individuals who are experts in urinary incontinence, weight loss, epidemiology and biostatistics. The NIDDK Project Scientist serves as Executive Secretary. No member of the DSMB should participate in the study as an investigator or be involved in any way in the conduct of the study, and no member may have any financial interest in the results of the study. Fiscal support for DSMB members from makers of weight loss products or treatments for urinary incontinence must be disclosed to the PRIDE Steering Committee, and the possibility of conflict of interest will be considered on a case-by-case basis. PRIDE DSMB members are listed in Appendix I.

C. DSMB Process

The DSMB will meet periodically by conference call and in person. Agendas for the meetings will be developed by the DSMB Chair and Executive Secretary with support from the Coordinating Center. An outline of proposed meetings is provided in Appendix III.

The first meeting should take place before initiation of the trial to discuss the protocol, interventions, and safety measures and to establish guidelines for monitoring.

Following the initial meeting, the DSMB should meet at least yearly to review accumulated data on adequacy and timeliness of participant recruitment, adherence to the visit and interventions protocols, data quality and timeliness, efficacy of the intervention to produce and maintain weight loss, effects of weight loss on frequency of incontinence, participant safety, and other factors that can affect study outcome. The initial meeting and meetings during which interim analyses are presented should be in person, but other meetings may be conducted by conference call (Appendix III). An emergency meeting of the DSMB may be called at any time by the Chair or NIDDK should questions of participant safety arise.

DSMB meetings will consist of an open and a closed session. The *open sessions* may be attended by investigators and NIDDK staff, and should always include the principal investigator and the study biostatistician. Issues discussed at open sessions will include conduct and progress of the study, recruitment, adherence with the visit and interventions protocols, data quality and timeliness, problems encountered and aggregate outcome data. Participant-specific data and treatment group data will not be presented in the open session.

The *closed session* will be attended only by voting DSMB members and appropriate NIDDK staff representative(s), but others may attend if requested by the DSMB. A representative from the UCSF Coordinating Center will attend all

closed sessions to present outcome data and answer questions about data format and derivation, but will not be a voting member. Between groups comparisons of all safety and efficacy variables will be presented at the closed session. All discussion at the closed session is completely confidential.

If requested by the DSMB, the closed meeting may be followed by an *executive session* which will include only voting DSMB members.

Should the DSMB decide to issue a recommendation to terminate or alter the study protocol, a full vote of the DSMB will be required. In the event of a split vote, a simple majority vote will rule and a minority report should be appended.

The DSMB will review the protocol of approved and funded studies ancillary to PRIDE, but will not review the conduct and outcomes of these studies.

D. Reports to the DSMB and Recommendations of the DSMB

1. Interim DSMB Reports - Interim reports are prepared by the PRIDE Coordinating Center and distributed to the DSMB members at least 5 days prior to a scheduled meeting. The interim reports will be numbered and provided in sealed envelopes within an express mailing package to maintain confidentiality. The contents and format of the report are determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB. Interim data reports generally consist of two parts:

Open Session Report - provides information on recruitment and projected completion dates, adherence to the visit and interventions protocol, quality and timeliness of data, baseline characteristics, and other general information on study status. The Open Report will also contain data on study drop-outs by group, including number, reason, and baseline characteristics. Open reports will include aggregate outcome data on changes in weight that occur during the weight loss intervention, but no data on changes in weight during the weight maintenance intervention or changes in frequency of incontinence.

Closed Session Report - contains data on study progress and outcomes between treatment groups, including changes in weight and frequency of incontinence, serious adverse events and safety. The Closed Session Report is confidential. Data files to be used for interim analyses will have undergone established editing procedures to the extent possible, but all data, both edited and unedited will be used to prepare interim reports. Interim analyses of outcome data will be performed only if they are specified and approved in advance and criteria for possible stopping are clearly defined (Appendix II).

Copies distributed prior to and during a meeting will be collected by the Coordinating Center following the meeting. One copy will be retained in a locked, confidential file at the Coordinating Center and all others will be shredded.

2. DSMB Recommendations. The DSMB Chair will prepare minutes of the open and closed sessions, including any recommendations for changes in the PRIDE protocol, that will be approved by the Board and sent to NIDDK. The NIDDK Project Scientist will distribute minutes of the open session to the PRIDE Principal Investigators within 4 weeks of each meeting.

The minutes of each DSMB closed session should conclude with a recommendation to continue, terminate or alter the study. A recommendation to terminate the study or alter the study protocol may be made by the DSMB at any time by majority vote. Such recommendations will be transmitted to the NIDDK and reviewed immediately. Recommendations of the DSMB that are accepted by the NIDDK will be transmitted by the Project Scientist to PRIDE Principal Investigators and business officials of the grantee institutions as rapidly as possible. In the event of a split vote in favor of continuation, a minority report should be included in the regular DSMB closed report. It is the responsibility of the Principal Investigators at each PRIDE site and the Coordinating Center to assure that DSMB recommendations are sent to co-investigators and to each IRB.

E. Access to Interim Data. Access to the accumulating endpoint data should be limited to as small a group as possible. The PRIDE Coordinating Center will prepare mock DSMB Closed Reports, tables and analyses using dummy treatment assignment variables. Before each DSMB meeting, one statistician/programmer at the Coordinating Center will complete the Closed Report using the real treatment assignment variables. No other personnel at the Coordinating Center, NIDDK or clinical sites will have access to treatment assignment codes.

F. Confidentiality

All closed materials, discussions, and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings are expected to maintain confidentiality.

Appendix I: PRIDE Data and Safety Monitoring Board Members**Independent Members**

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Appendix II. Rules for Altering or Stopping PRIDE

This section provides guidelines for altering the PRIDE protocol or stopping the study early. While statistical guidelines for stopping the study at one formal interim analysis (approximately June 1, 2006) are provided, multiple other considerations will guide the decisions of the DSMB.

A. Monitoring Recruitment, Retention and Data Quality

PRIDE must achieve planned power and data quality to provide a valid and accurate answer to study questions. The adequacy of recruitment, retention and data quality by clinical site will be assessed by the DSMB early in the study to ensure that the study is achieving planned power and data quality.

1. Recruitment goals will be established by the PRIDE Steering Committee and Coordinating Center based on the assumption that participants will be randomized in blocks of approximately 60 every 4 months over the 24-month enrollment period. Enrollment lagging more than 2 months behind these goals will be of concern, and may trigger added evaluation, effort and approaches to recruitment. Enrollment lagging more than 4 months behind these goals will be of major concern, and may trigger changes in enrollment criteria, interventions or other aspects of the trial protocol.
2. Goals for retention in PRIDE will require that no more than 15% of participants discontinue attending PRIDE assessment visits. Retention less than 85% will be of concern, and may trigger added evaluation, effort and approaches to improve retention. Retention of less than 75% will be of major concern, and may trigger changes in visit structure, interventions or other aspects of the trial protocol.
3. Data quality will be assessed using measures such as time from study visit to data entry, time to resolution of data queries, number of missing forms, and proportion of all study variables queried. Guidelines for concern regarding these measures are outlined below:

<u>Measure</u>	<u>Goal Value</u>	<u>Acceptable Value</u>
• time from visit to data entry	< 2 week	< 3 weeks
• time to resolution of queries	<2 week	< 3 weeks
• number of missing forms	0	< 5%
• proportion of variables queried	5%	<10%

B. Methods for Interim Monitoring of Weight Loss, Frequency of Urinary Incontinence and Safety

B.1. Stopping or Altering PRIDE for Safety

The primary aim of PRIDE is to determine if modest weight loss results in improvement in urinary incontinence among obese and overweight women with incontinence. The weight loss intervention includes standard approaches to diet and behavioral change that have been used successfully in many prior studies. An important secondary aim is to determine if a motivation-based weight maintenance program results in improved weight maintenance compared to a skills-based weight maintenance program. This intervention is innovative for weight maintenance, but the elements of this motivation-based program have been used in other successful behavioral interventions. PRIDE investigators believe that both the weight loss and weight maintenance interventions are safe. Investigators will carefully track potential serious adverse events that will be reviewed at each DSMB in-person meeting or conference call. If evidence of serious harm emerges, the PRIDE DSMB may decide to alter or stop the study at any time for safety concerns.

B.2. Stopping or Altering PRIDE for Efficacy

PRIDE investigators expect that, compared to usual care, the weight loss intervention will result in an average of 6% weight loss (about 6 kg) over 6 months and that this change in weight will result in a reduction of about 6 episodes of incontinence per week. There is no scientific or ethical reason to stop or alter the study if this intervention proves to be more effective than expected.

The expected efficacy of the innovative weight maintenance program is less clear, but PRIDE investigators believe that participants randomized to the skills-based program will regain about 1/3 of the weight lost, while those in the motivation-based program will regain no weight. There is no scientific or ethical reason to stop or alter the study if this intervention proves to be more effective than expected.

Thus, as long as no safety issues arise, PRIDE will not be stopped or altered if the interventions are unexpectedly effective.

B.3. Stopping or Altering PRIDE for Futility

Answering the main PRIDE research question requires that the weight loss intervention result in greater weight loss in the intervention compared to the usual care group. Based on effects in prior trials, participants in the weight loss group are expected to lose 6% of their body weight (6 kg), compared to no loss in the usual care group. However, the effect of this degree of weight loss on frequency of incontinence is not clear, and is the main question in PRIDE.

If the 6-month weight loss intervention does not result in substantial weight loss, we cannot address the main PRIDE research questions. If no weight loss occurs, we cannot determine if weight loss leads to improvement in urinary incontinence; similarly, if no weight loss occurs, we cannot determine if a motivation-based weight loss maintenance program is more effective than a skills-based program. Thus, if weight loss is less than expected in the weight loss group, the DSMB will give consideration to altering the intervention and to stopping the trial.

Stopping or altering PRIDE for futility will be based on estimates of the efficacy of the weight loss intervention at the point when approximately 75% of the participants have completed the program. Efficacy for weight loss will be assessed as the difference between the weight loss and usual care groups in change in weight from baseline to the end of the 6-month intervention period. Efficacy for improvement in incontinence will be assessed as the difference between the weight loss and usual care groups in change in number of incontinence episodes per week from baseline to the end of the 6-month intervention period. The analyses of these outcomes, as specified in the protocol, will use a random effects model for piece-wise linear mean trajectories for average weight and frequency of incontinence in the treatment and control groups. These analyses will not require alpha-spending.

At this interim analysis, consideration will be given to stopping the study for futility if the point estimate of the difference between the weight loss and standard care groups is not 4 kg or greater. The DSMB might consider continuing the study even if efficacy for weight loss is low *if* the intervention has resulted in an improvement in incontinence of at least 20% or greater. In this case, changes in dietary composition or exercise habits might be responsible for an improvement in incontinence.

C. Other Considerations

In addition to the statistical procedures described above, other important considerations will be weighed by the DSMB.

- Whether the results could be explained by possible differences between the groups in baseline variables;
- Whether the results could be explained by differences in retention or drop-outs between the groups;
- Whether the results are consistent among various subgroups of participants and across the centers involved in the study;
- Whether it is likely that the current trends in the data could be reversed if the trial were to be continued unmodified;
- The degree of additional precision or certainty in the results that could be obtained by continuing the trial; and,
- Whether there would be significant loss in external validity or credibility of the trial by change in protocol or discontinuation.

Appendix III: PRIDE DSMB Meeting Schedule, Milestones and Goals *

Type†	Date	Milestones	Goals and Analyses
IP-1	05/1/04	Prior to initiation of the trial	Review protocol, interventions, and safety measures and establish guidelines for monitoring and stopping the trial.
CC-1	12/04	Early in recruitment	Evaluate recruitment.
IP-2	06/05	120 participants randomized (36%) 60 participants completed 6-mo visit (18%)	Review and approve table formats for future conference calls and meetings. Evaluate recruitment, data quality, adherence to visit and intervention protocols.
CC-2	12/05	240 participants randomized (73%) 120 participants completed 6-mo visit (36%) 60 participants completed 12-mo visit (18%)	Evaluate recruitment, data quality, adherence to visit and intervention protocols, efficacy of weight loss intervention and safety.
IP-3	06/06	300 participants randomized (91%) 240 participants completed 6-mo visit (73%) 120 participants completed 12-mo visit (36%) 60 participants completed 18-mo visit (18%)	Evaluate recruitment, data quality, adherence to visit and intervention protocols, efficacy of weight loss intervention and safety. Interim analysis of efficacy of intervention on weight loss and incontinence.
CC-3	12/06	330* participants randomized (100%) 300 participants completed 6-mo visit (73%) 240 participants completed 12-mo visit (55%) 120 participants completed 18-mo visit (36%)	Evaluate recruitment, data quality, adherence to visit and intervention protocols, efficacy of weight loss intervention, and safety.

Milestones are based on the following assumptions: Randomization begins October 15, 2004. Participants are randomized in groups of 60 (providing 10 for each of 3 groups at the 2 clinical sites) every 4 months. The milestones do not account for potential dropouts. *The last group randomized will consist of 30 participants
† IP = DSMB in person meetings, CC = conference call with DSMB.

Additional meetings, conference calls or meetings may be held if deemed necessary by the DSMB

