Cover Page for Protocol

Sponsor name:	Novo Nordisk A/S
NCT number	NCT03799198
Sponsor trial ID:	NN8022-4432
Official title of study:	Real world effectiveness of combining an employer-based weight management program with medication for chronic weight management in employees with obesity – a pragmatic randomized trial
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16.1.1 Protocol and protocol amendments

Real world effectiveness of combining an employer-based weight management program with medication for chronic weight management in employees with obesity – a pragmatic randomized trial

Protocol No. NN8022-4432

Novo Nordisk

Novo Nordisk

October 10, 2018

Version 1.0

Trial Phase: 4

STUDY APPROVALS

Protocol No: NN8022-4432
October 10, 2018

Sponsor Approval:

Name: [redacted]
Title: [redacted], Clinical Development & Outcomes Research

Signature: _____

Date: _____

Name: [redacted]
Title: [redacted], Biostatistics

Signature: _____

Date: _____

Study Physician Agreement:

I have read the protocol "Real world effectiveness of combining an employer-based weight management program with medication for chronic weight management in employees with obesity – a pragmatic randomized trial" and agree to ensure that all staff members involved in the conduct of this study are informed of their obligations and that they meet the commitments of the protocol in accordance with Good Clinical Practice (GCP) requirements. I have familiarized myself with the prescribing information corresponding with the study drugs associated with this study. I agree to provide information regarding the risks associated with study drugs to subjects who are prescribed study drugs in a manner consistent with standard care.

I acknowledge that I am responsible for overall study conduct. I understand GCP requirements and agree to personally conduct or supervise the described pragmatic study in accordance with GCP.

Signature: _____

Print Name: _____

Date: _____

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SYNOPSIS

Title: Real world effectiveness of combining an employer-based weight management program with medication for chronic weight management in employees with obesity – a pragmatic randomized trial

Sponsor: Novo Nordisk

Study Treatment: Cleveland Clinic's Integrated Medical Weight Management Program (WMP) with medication approved for chronic weight management in the US, i.e., "WMP + Rx"

Active Ingredient: One of following approved medications: orlistat (per os (p.o.)), lorcaserin or lorcaserin extended-release (p.o.), phentermine/topiramate extended-release (p.o.), naltrexone/bupropion extended-release (p.o.), liraglutide 3.0 mg (subcutaneous (s.c.))

Comparator Treatment: Cleveland Clinic's Integrated Medical WMP with no medication for weight management, i.e., "WMP"

Protocol No.: NN8022-4432

Study Site: This is a single-center study conducted at the Cleveland Clinic's Endocrinology and Metabolism Institute, Cleveland, Ohio.

Country: United States

Subjects: Eligible subjects include adults with obesity (body mass index (BMI) $\geq$ 30 kg/m^2) enrolled in the Cleveland Clinic Employee Health Plan for whom treatment with medication for chronic weight management may be indicated.

Planned enrollment in this study is 200. Subjects will be randomized 1:1 to receive either WMP + Rx or WMP alone.

Study Objectives: The objectives of this study are as follows:

- The primary objective is to demonstrate superior effect of treatment with an employer-based weight management program in combination with medication for chronic weight management compared to an employer-based weight management program alone in subjects with obesity on weight loss.
- The secondary objectives are to compare the effects of treatment with an employer-based weight management program in combination with medication for chronic weight management to an employer-based weight management program alone in subjects with obesity with regards to:
    - Categorical weight loss
    - Adherence to the weight management program
    - Patient-reported outcomes (PROs) on work productivity and work limitations
- Furthermore, the secondary objectives will assess adherence to medication for chronic weight management (only in the treatment arm randomized to an employer-based chronic weight management program with medication for chronic weight management).

Study Design: This is a one-year, single-center, randomized, open-label, parallel-group pragmatic clinical trial (PCT) comparing Cleveland Clinic's existing Integrated Medical WMP combined with

medication for chronic weight management versus Cleveland Clinic's existing Integrated Medical WMP with no medication for weight management in subjects with obesity. Subjects will be randomized 1:1 to receive either Cleveland Clinic's Integrated Medical WMP with medication for chronic weight management ("WMP + Rx") or Cleveland Clinic's Integrated Medical WMP alone ("WMP").

To preserve the real-world nature of the study, the subject experience will be as close to routine clinical care as possible. The weight management program provided to all study subjects will be similar to the Integrated Medical WMP that is currently offered by the Cleveland Clinic. Consistent with standard practice of the Integrated Medical WMP, subjects in both treatment groups will attend monthly shared medical appointments (SMAs) and will be responsible for a co-payment. In the WMP + Rx arm, obesity medications approved by the Food and Drug Administration (FDA) for chronic weight management are allowed and selection of specific medication is at the discretion of the study clinician. To simulate the co-payment that would be applied if a health plan covered treatment with medications for chronic weight management, subjects will pay a set fee for the obesity medication.

Study visits include an individual screening and randomization visit (visit 1; informed consent must be obtained at visit 1 before screening), followed by twelve once-monthly visits set up in the context of SMAs (visit 2 to visit 13). All subjects will be referred to a nutritionist appointment between visit 1 and visit 2. End of Study (EOS) is visit 13 (month 12 (-14 days, +28 days)). Effort will be made to obtain a month 12 (visit 13) weight measurement from all randomized subjects, unless they have withdrawn consent. There will not be a follow-up period.

Subject Selection:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for the study:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine eligibility for the study.
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Body mass index (BMI) ≥ 30 kg/m^2
4. Enrolled in Cleveland Clinic Employee Health Plan, and expecting to be covered by the Cleveland Clinic Employee Health Plan for the duration of the study

Exclusion Criteria:

Subjects presenting with any of the following exclusion criteria will not be eligible for the study:

1. Contraindications to all of the medications approved by the FDA for chronic weight management according to the label.
2. Previous participation in this study. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
4. Participation in another clinical trial within 30 days before screening.
5. Treatment with any medication with the intention of weight loss within 90 days before screening.

6. Previous or current participation in Cleveland Clinic's Integrated Medical Weight Management Program.
7. History of (or plans during the study period for) bariatric surgery, or use of minimally-invasive weight loss devices (i.e., intragastric balloons, lap bands) not removed within 1 year prior to screening.
8. History of type 1 or type 2 diabetes mellitus.
9. HbA1c ≥ 6.5% at screening or within 90 days prior to randomization.
10. Any condition, unwillingness or inability, not covered by any of the other exclusion criteria, which, in the study clinician's opinion, might jeopardize the subject's safety or compliance with the protocol.

Study Procedures:

- Potentially eligible subjects will be identified during the course of routine implementation of Cleveland Clinic's Employee Wellness Program, "Healthy Choice," or referred to the study via the study advertisement or another health care provider.
- Study clinicians will obtain informed written consent from subjects and if eligible, subjects will be randomized to either WMP + Rx or WMP.
- Study data will be collected on electronic Case Report Forms (eCRFs) via an electronic data capture (EDC) system.
- Assessments at the screening and randomization visit (visit 1/baseline (month 0)) include: eligibility (including urine pregnancy test (if applicable) and point of care (POC) hemoglobin A1c (HbA1c) measurement if an HbA1c measurement is not available within 90 days prior to randomization), demographic data, relevant medical history, concomitant medications, height, and body weight.
- All subjects will enroll in the Integrated Medical WMP at the Cleveland Clinic's Endocrinology and Metabolism Institute. In this program, as part of usual care, subjects will:
    - discuss and choose one of three diet options: protein-sparing modified fast, Mediterranean, or meal replacement.
    - be referred to a nutritionist appointment.
    - initiate a series of twelve monthly study visits (visits 2-13) in the context of SMAs covering nutrition, physical activity, appetite control, sleep issues, and anxiety/depression/stress.
    - be referred to an exercise physiologist for a personalized physical activity program.
    - if assessed relevant by the study clinician, be referred to a mental health specialist and/or sleep clinic.
- Subjects enrolled in the WMP + Rx arm will be provided a prescription for medication indicated for chronic weight management (obesity medication) at the time of randomization (visit 1).
- Disallowed medications:

- Other than the medication prescribed by the study clinician for chronic weight management in the WMP + Rx arm, use of any medication, on- or off-label, for weight loss purposes is not allowed in either arm during the study.
- The use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors for diabetes diagnosed during the study is not allowed.

- Assessments during monthly study (i.e., SMA) visits include: weight, pregnancy and serious adverse events (SAEs), attendance at SMAs, and use of disallowed medications.
- Prescription fill data for obesity medication (WMP + Rx arm) will be collected from randomization through EOS.
- **Questionnaires:** PROs on work productivity and work limitations will be assessed by the Work Productivity and Activity Impairment Questionnaire Specific Health Problem v2.0 (WPAI:SHP) and the Work Limitations Questionnaire 8-Item (WLQ-8) Self-administered Short Form at visit 1, visit 7, and visit 13.

Study Duration: Total study duration for the individual subjects will be approximately one year. Subjects will be followed and data collection will continue for the full duration of the study, unless the subject withdraws informed consent. The full duration of the study is defined as up to and including visit 13. Effort will be made to obtain a month 12 (visit 13) weight measurement from all randomized subjects.

Analysis: Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of an employer-based WMP combined with obesity medication compared to an employer-based WMP alone.

The primary estimand for all endpoints is an "intention-to-treat" estimand. This estimand will quantify the average treatment effect of an employer-based WMP combined with medication for chronic weight management compared to the employer-based WMP alone after 12 months, in all randomized subjects and regardless of adherence to randomized treatment.

The secondary estimand for body weight loss, categorical weight loss, and PROs is an "if all subjects had adhered" estimand. This estimand will quantify the average treatment effect of an employer-based WMP combined with medication for chronic weight management compared to the employer-based WMP alone after 12 months, in all randomized subjects had they adhered to their randomized treatment for the entire planned study duration.

The primary endpoint is percent change in body weight from baseline (month 0) to month 12 (visit 13). The study is designed to have 80% power to confirm superiority of WMP + Rx versus WMP alone on % weight change from baseline (month 0) to month 12 (visit 13).

The full analysis set (FAS) comprising all randomized subjects analyzed according to the treatment group to which they were assigned at randomization will be the analysis population for the evaluation of both the primary and secondary estimands. The primary estimand will be estimated based on the FAS and % weight change will be modeled using linear regression (Analysis of Covariance (ANCOVA)) with randomized treatment as a factor and baseline body weight (kg) as a covariate. Prior to analysis, missing month 12 weight data will be imputed by multiple imputations. For the secondary estimand, the primary endpoint will be analyzed using a mixed model for repeated measurements (MMRM) including all subjects, but for subjects considered non-adherent to randomized treatment, only data prior to non-adherence will be used.

The significance level used in all statistical analyses will be 5% (two-sided).
Supplementary Analyses: A supplementary analysis will be conducted on the subset of subjects with month 12 (visit 13) body weight data who adhered to randomized treatment up to and including visit 13.
Secondary Analyses: Secondary analyses will compare WMP + Rx versus WMP in terms of categorical weight loss, adherence to the WMP, and PRO measures. Additionally, adherence to obesity medication will be descriptively summarized for the WMP + Rx arm. The primary estimand will be assessed for all secondary endpoints. Additionally, the secondary estimand will be assessed for categorical weight loss and PRO measures.
Safety: For the purposes of this study, adverse events (AEs) will only be required to be collected if they meet the definition of an SAE. Study clinicians are responsible for reporting all SAEs and following the subject until the outcome of the event is closed out. All SAEs will be reported from randomization until EOS at month 12, or until the subject withdraws from the study. Study clinicians are also responsible for recording all pregnancies in female subjects from randomization until EOS at month 12 or subject study withdrawal. The subject will be followed for the duration of the pregnancy until one month post-delivery to report the pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age. Safety will be summarized descriptively.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
BMI	Body Mass Index
eCCG	Electronic Case Report Form Completion Guidelines
CFR	Code of Federal Regulations
CI	Confidence Interval
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMR	Electronic Medical Record
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act
GCP	Good Clinical Practice
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonists
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors

Abbreviation	Definition
IRB	Institutional Review Board
LSFV	Last Subject First Visit
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurements
OR	Odds Ratio
PCD	Primary Completion Date
PCT	Pragmatic Clinical Trial
PDC	Proportion of Days Covered
PO	Per Os
POC	Point of Care
PRO	Patient Reported Outcome
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SGLT-2	Sodium-Glucose Co-transporter 2
SMA	Shared Medical Appointment
SOC	System Organ Class
US	United States
WLQ-8	Work Limitations Questionnaire 8-Item

Abbreviation	Definition
WMP	Weight Management Program
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire Specific Health Problem

1 INTRODUCTION

The prevalence of obesity has been increasing globally based on pooled data from the years 1975 to 2016. [1] In the United States (US), nearly 40% of adults have obesity, with prevalence ranging from 22% to 38% among the different states. [2] Obesity raises the risk of morbidity from a multitude of diseases, including hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, fatty liver disease, and some cancers. [3] [4] Obesity is also associated with increased risk of all-cause and cardiovascular diseases mortality. [5] In recognition of the biological basis and seriousness of obesity, several professional associations and health organizations worldwide [4] [6] [7] [8] now recognize obesity as a disease.

Lifestyle intervention in the form of improving diet and increasing physical activity is foundational treatment for obesity and overweight [9], but the majority of people with obesity and overweight struggle to achieve and maintain their weight loss. [10] Medications approved for chronic weight management can be useful adjuncts to lifestyle change for patients who have been unsuccessful with diet and exercise alone. [11] Five medications have been approved by the US Food and Drug Administration (FDA) for chronic weight management: orlistat (per os (p.o.), lorcaserin or lorcaserin extended-release (p.o.), phentermine/topiramate extended-release (p.o.), naltrexone/bupropion extended-release (p.o.), liraglutide 3.0 mg (subcutaneous (s.c.)).

In the US, employers are the ultimate purchasers of health care for the majority (56%) of Americans. [12] Recommendations support addressing obesity in the workplace; however, real-world evidence of best practices for chronic weight management, including impact of longer-term pharmacological treatment, in the employer context is lacking. [13] Currently, in order for medications for chronic weight management to be included in the health care offered to employees, employers have to “opt-in” or deliberately decide to pay for these medications for employees, even when payers have added them to their formulary. The Cleveland Clinic provides a unique environment to investigate the impact of including approved medications for chronic weight management in the context of an employer-based weight management program. The Cleveland Clinic is one of the largest hospital systems in the US. The Cleveland Clinic’s Employee Health Plan provides health coverage for approximately 66,000 adults, including employees and spouses. Among this population, approximately 18,000 are known to have obesity defined by body mass index (BMI) $\geq$ 30 kg/m^2, making the prevalence of obesity within the Cleveland Clinic Employee Health Plan consistent with that observed in the general US adult population. [2] Cleveland Clinic’s Employee Health Plan provides employees diagnosed with obesity support for participating in a weight management program of their choice, but does not currently offer coverage for medications for chronic weight management. One of the weight management programs offered to employees is the Cleveland Clinic’s Integrated Medical Weight Management Program (WMP). This program is administered through shared medical appointments (SMAs) which is a concept based on the chronic care model [14] that combines group appointments for patients with clinical intervention, consisting of encounters with a

nutritionist, exercise physiologist, and endocrinologist/obesity medicine specialist. [15] [16] [17] As part of the comprehensive evaluation of a patient with obesity in which mood disorders and obstructive sleep apnea are common, at risk patients are also referred to a mental health provider and/or sleep clinic.

The use of a pragmatic clinical trial (PCT) design aims to study the effects of a weight management program that includes treatment with medication for chronic weight management in an employer-based real-world setting while employing a prospective comparison between two randomly assigned interventions in employees with obesity. The two interventions included in this study are a weight management program combined with FDA approved medication for chronic weight management versus a weight management program without medication for weight management.

The key objective of the study is to demonstrate the impact of including medication for chronic weight management in a real-world employer setting of an integrated medical weight management program.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate superior effect of treatment with an employer-based weight management program in combination with medication for chronic weight management compared to an employer-based weight management program alone in subjects with obesity on weight loss.

2.2 Secondary Objectives

The secondary objectives are to compare the effects of treatment with an employer-based weight management program in combination with medication for chronic weight management to an employer-based weight management program alone in subjects with obesity with regards to:

- Categorical weight loss
- Adherence to the weight management program
- Patient-reported outcomes (PROs) on work productivity and work limitations

Furthermore, the secondary objectives will assess adherence to medication for chronic weight management (only in the treatment arm randomized to an employer-based chronic weight management program with medication for chronic weight management).

3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this study is:

- Change from baseline (month 0) to month 12 (visit 13) in body weight (%)

3.2 Secondary Endpoints

Supportive secondary endpoints of this study include:

- Subjects who after 12 months achieve (yes/no):
  - ≥5% reduction in body weight from baseline
  - ≥10% reduction in body weight from baseline
- Adherence to Cleveland Clinic's Integrated Medical WMP from baseline (month 0) to month 12 (visit 13), as:
  - Number of SMAs attended
  - Subjects attending ≥9 SMAs (yes/no)
- Adherence to medication for chronic weight management from baseline (month 0) to month 12 (visit 13) in the treatment arm randomized to the WMP in combination with medication for chronic weight management, as:
  - Proportion of days covered (PDC) by prescription claims for medication for chronic weight management
  - Subjects covered by prescription claims for medication for chronic weight management for at least 80% of days (yes/no)
- Change in PROs from baseline (month 0) to month 12 (visit 13) in
  - Work limitation as measured by Work Limitations Questionnaire Self-administered Short-Form (WLQ-8)
    - At-Work Productivity Loss Index (point)
    - Time Management (point)
    - Physical Tasks (point)
    - Mental/Interpersonal Tasks (point)
    - Output Tasks (point)

- Work productivity as measured by Work Productivity and Activity Impairment Questionnaire Specific Health Problem V2.0 (WPAI:SHP)
  - Work time missed due to excess weight (%)
  - Impairment while working due to excess weight (%)
  - Overall work impairment due to excess weight (%)
  - Activity impairment due to excess weight (%)

4 STUDY DESIGN

4.1 Overview

This is a one-year, single-center, randomized, open-label, parallel-group PCT comparing Cleveland Clinic's existing Integrated Medical WMP combined with medication for chronic weight management versus Cleveland Clinic's existing Integrated Medical WMP with no medication for weight management in subjects with obesity. Subjects will be randomized 1:1 to receive either Cleveland Clinic's Integrated Medical WMP with medication for chronic weight management ("WMP + Rx") or Cleveland Clinic's Integrated Medical WMP alone ("WMP").

To ensure that the study setting is as close to real-world as possible, the weight management program provided to all study subjects will be similar to the Integrated Medical WMP that is currently offered by the Cleveland Clinic. In this program, SMAs are covered by the Cleveland Clinic Employee Health Plan and employees are responsible for a co-payment.

In the WMP + Rx arm, obesity medications approved by the FDA for chronic weight management listed in Table 5-1 are allowed. Selection of specific medication is at the discretion of the study clinician. Subjects randomized to the WMP + Rx arm will pay a fee for the medication, simulating the co-payment that would be applied if the Health Plan covered treatment with medications for chronic weight management.

Total study duration for the individual subjects will be approximately one year. Subjects will be followed and data collection will continue for the full duration of the study, unless the subject withdraws informed consent. The full duration of the study is defined as up to and including visit 13.

Study visits include an individual screening and randomization visit (visit 1; informed consent must be obtained at visit 1 before screening), followed by twelve once-monthly visits set up in the context of SMAs (visit 2 to visit 13; further described in Section 5.2.2.1). All subjects will be referred to a nutritionist appointment between visit 1 and visit 2. End of Study (EOS) is visit 13 (month 12 (-14 days, +28 days)) (section 5.5). Effort will be made to obtain a month 12 (visit 13) weight measurement from all randomized subjects. Subjects who potentially have stopped attending the SMAs prior to EOS will be encouraged to attend visit 13 for a weight measurement

and completion of questionnaires within the visit window, unless they have withdrawn consent. There will not be a follow-up period.

4.2 Study Site and Subject Selection

4.2.1 Study Site

This is a single-center study conducted at the Cleveland Clinic's Endocrinology and Metabolism Institute, Cleveland, Ohio.

4.2.2 Subject Recruitment and Eligibility

Eligible subjects include adults with obesity (BMI $\geq$ 30 kg/m^2) enrolled in the Cleveland Clinic Employee Health Plan for whom treatment with medication for chronic weight management may be indicated. Subjects must also meet all of the inclusion criteria (section 4.2.3) and none of the exclusion criteria (section 4.2.4). Inclusion and exclusion criteria are minimally restrictive to ensure that a broad population of employees (and health plan member spouses) with obesity is captured, in order to generate data on a heterogeneous population that reflects a real-world population in scope for employer-based weight management programs, and support the study objectives of evaluating the impact of including medication for chronic weight management in a real-world employer-based integrated chronic weight management program.

To preserve the real-world nature of the study, potential subjects will be approached for enrollment into the study in a manner consistent with how health plan members are approached for participation in the Integrated Medical WMP as part of Healthy Choice, the wellness program benefit for Cleveland Clinic Employee Health Plan subscribers and their spouses. Members of Cleveland Clinic Employee Health Plan receive an annual end-of-year communication via e-mail/US mail with notification of the Healthy Choice status of both the employee and spouse (if applicable) and enrollment instructions. If an employee or spouse has one of qualifying chronic diseases (asthma, diabetes, hyperlipidemia, hypertension, tobacco use, or overweight), he/she is eligible for the Healthy Choice program only if he/she joins the disease management program for that diagnosis.

The Integrated Medical WMP employed in this study is one of the weight management programs offered to health plan members with obesity via the Healthy Choice program. Health plan members identified as eligible for one of Cleveland Clinic's employer-based weight management programs will be invited to attend an informational session and will be approached for potential enrollment into the study. If he/she decides to participate in the Integrated Medical WMP and is interested in the study, the prospective subject will be scheduled for a screening and randomization visit (i.e., study visit 1) with a study clinician. If he/she chooses not to participate in the study, it will not have any implications for the employee, and he/she may join the Integrated Medical WMP or other weight management programs offered to health plan members with obesity via the Healthy Choice program.

Additionally, potential study participants will be recruited through an advertisement outlining the details of this study posted on the Cleveland Clinic intranet, or through referral by another health care provider. Potential study participants identified in this manner will also be informed of the Integrated Medical WMP and requirements of this study prior to screening and randomization.

4.2.3 Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for the study:

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine eligibility for the study.
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Body mass index (BMI) ≥ 30 kg/m^2
4. Enrolled in Cleveland Clinic Employee Health Plan, and expecting to be covered by the Cleveland Clinic Employee Health Plan for the duration of the study

4.2.4 Subject Exclusion Criteria

Subjects presenting with any of the following exclusion criteria will not be eligible for the study:

1. Contraindications to all of the medications approved by the FDA for chronic weight management according to the label.
2. Previous participation in this study. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
4. Participation in another clinical trial within 30 days before screening.
5. Treatment with any medication with the intention of weight loss within 90 days before screening.
6. Previous or current participation in Cleveland Clinic's Integrated Medical Weight Management Program.
7. History of (or plans during the study period for) bariatric surgery, or use of minimally-invasive weight loss devices (i.e., intragastric balloons, lap bands) not removed within 1 year prior to screening.
8. History of type 1 or type 2 diabetes mellitus.
9. HbA1c ≥ 6.5% at screening or within 90 days prior to randomization.

10. Any condition, unwillingness or inability, not covered by any of the other exclusion criteria, which, in the study clinician's opinion, might jeopardize the subject's safety or compliance with the protocol.

4.2.5 Subject Enrollment

Planned number of subjects to be screened: 240

Planned number of subjects to be randomized: 200

Expected number of subjects to complete (defined as end of trial on-site weight measurement) the trial: 150

4.2.6 Randomization

Subjects will be randomized to either WMP + Rx or WMP in a 1:1 ratio via centralized allocation. The study design and subject randomization is depicted in Figure 1.

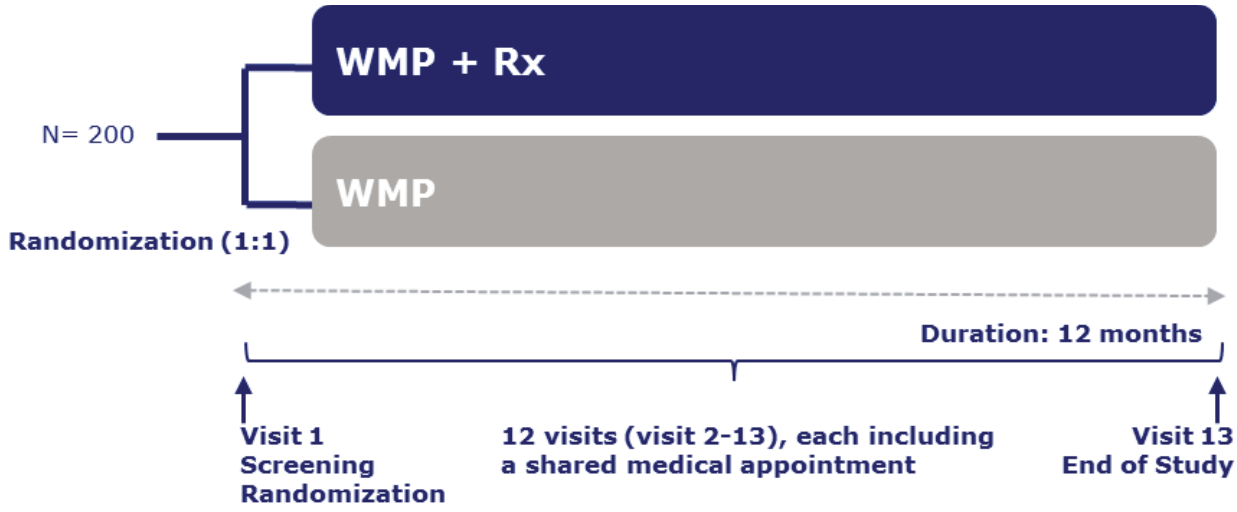

Figure 1. Study design diagram. Subjects will be randomized in a 1:1 manner using centralized allocation to receive WMP + Rx or WMP.
WMP + Rx: Cleveland Clinic's Integrated Medical Weight Management Program with medication for chronic weight management; WMP: Cleveland Clinic's Integrated Medical Weight Management Program alone

5 STUDY PROCEDURES

The study visit schedule and data collection are summarized in Appendices 1-1 and 1-2. Study clinicians or site personnel will collect subject characteristics and study data at each study visit as outlined in the Time and Events Schedule (Appendix 1-1), either directly from the subject or extracted from the subject's medical records, and enter them into the electronic Case Report Form (eCRF).

5.1 Enrollment Procedures

Potentially eligible subjects will be identified during the course of routine implementation of Cleveland Clinic's wellness program, Healthy Choice, through an advertisement outlining the details of this study posted on the Cleveland Clinic intranet, or through referral by another health care provider (section 4.2.2). Eligibility for the study will be assessed by the study clinician using the inclusion and exclusion criteria. Informed consent will be obtained prior to any study-related activities.

5.2 Screening and Randomization Visit

Following informed consent and confirmation of eligibility, subjects will be randomized to either WMP + Rx or WMP. Data collection at the screening and randomization visit will include data on inclusion/exclusion criteria as well as the data outlined in the sections below. All subject information collected prior to randomization is considered medical history and will be collected per routine medical practice. Subjects will also complete PRO questionnaires (section 5.3.1). Additionally, a nutritionist appointment will be scheduled for the subject.

5.2.1 Subject Characteristics

Baseline assessments at the screening and randomization visit will include: eligibility (including urine pregnancy test (if applicable) and point of care (POC) hemoglobin A1c (HbA1c) measurement if an HbA1c measurement is not available within 90 days prior to randomization), demographic data, relevant medical history, concomitant medications, height, and body weight (as measured on a designated calibrated scale). Height and body weight will be recorded to one decimal place.

5.2.2 Treatments

To preserve the real-world nature of the study, the subject experience will be as close to routine clinical care as possible.

5.2.2.1 Weight management program

All subjects will enroll in the Integrated Medical WMP at the Cleveland Clinic's Endocrinology and Metabolism Institute. After randomization, subjects will discuss and choose one of three diet options: protein-sparing modified fast, Mediterranean, or meal replacement. Subjects will then be referred to a nutritionist appointment. Consistent with real-world implementation of the WMP, the subject's diet choice will be at the discretion of the subject and subjects will be free to change their diet choice throughout participation in the WMP.

Subjects will then initiate a series of twelve monthly study visits in the context of SMAs with up to approximately 10 subjects each. The SMAs will be run by a health care provider and a nutritionist and will be approximately 90 minutes in length. The 5 components of the WMP will be reviewed at every SMA and include: nutrition, physical activity, appetite control, sleep issues, and anxiety/depression/stress. SMA content will focus on accomplishing a healthier lifestyle,

including rotating topics related to nutrition (meal plan education, self-monitoring/record-keeping, emotions related to eating such as comfort foods, “fear” foods, etc., stimulus control, problem-solving, eating competence skills, mindful eating, internal regulation skills relating to hunger/fullness/satisfaction, how to choose and prepare healthy food, trying new foods, social eating and eating outside of the home); information and advice regarding different exercise programs and compliance with exercise physiologist referral; issues related to healthy sleep habits; and specific topics regarding behavior modification and stress management (goal setting, accountability, relapse prevention).

As part of the WMP, subjects will be referred to an exercise physiologist for a personalized physical activity program. Additionally, if assessed relevant by the study clinician, subjects may also be referred to a mental health specialist and/or sleep clinic.

Subjects in the two treatment arms will be allocated to separate SMA groups according to their randomized intervention (WMP + Rx versus WMP). In addition, effort will be made to keep the initial assigned SMA groups intact for the duration of the study for continuity of SMA participants (subjects and providers) month to month. All subjects will be responsible for paying the SMA monthly co-payment, as currently required by the Cleveland Clinic Employee Health Plan. Consistent with usual practice, subjects will be eligible for reimbursement of their SMA co-payments if they are compliant with their treatment plan according to the pre-defined Cleveland Clinic Health Plan criteria for weight management SMAs (attend SMAs, have a realistic personalized (based on BMI) weight loss goal set, demonstrate actual weight loss during each quarter, adhere to any medications etc.).

5.2.2.2 Obesity medication (WMP + Rx arm only)

After randomization, subjects randomized to the WMP + Rx arm will initiate treatment with prescription medication indicated for chronic weight management (obesity medication). The prescription will be provided at the time of randomization (visit 1) as agreed between the study clinician and the subject, and this and any monitoring, counseling or follow-up will be consistent with usual clinical practice and standard of care. Medication choice, dose, and dose escalation will be at the discretion of the study clinician among those medications indicated for chronic weight management (Table 5-1). Only medications approved by the FDA for chronic weight management are allowed; all other medications for the purpose of weight management, on- or off-label, are not allowed.

Subjects in the WMP + Rx arm may switch to another obesity medication (switch), temporarily discontinue (suspend), or permanently discontinue (discontinue) obesity medication throughout the study according to standard clinical practice at the discretion of the study clinician. If a subject chooses to suspend or discontinue his/her obesity medication, he/she will be asked to notify the study clinician of his/her decision to ensure a safe withdrawal. In case of an obesity medication discontinuation, subjects will be encouraged to initiate treatment with another obesity medication (i.e., to switch) at the discretion of the study clinician according to routine practice.

Subjects who discontinue obesity medication will be encouraged to continue attending the study visits and assessments in their originally allocated treatment arm.

In order for the study to remain as close as possible to real-world conditions, subjects randomized to WMP + Rx arm will pay a nominal fee for the prescribed obesity medication simulating the co-payment patients would pay at a retail pharmacy if the medication was covered by their employer. The fee will be the same for all obesity medications utilized in the study regardless of market price. All prescription medications approved in the US for chronic weight management will be available for study subjects randomized to WMP + Rx (Table 5-1).

Table 5-1. Approved medications for chronic weight management in the US available in the study.

API (route of administration)	Brand name	Year of FDA approval
Orlistat (p.o.)	Xenical®	1999
Lorcaserin/Lorcaserin extended-release (p.o.)	Belviq®/Belviq XR®	2012
Phentermine/Topiramate extended-release (p.o.)	Qsymia®	2012
Naltrexone/Bupropion extended-release (p.o.)	Contrave®	2014
Liraglutide 3.0 mg (s.c.)	Saxenda®	2014

FDA: Food and Drug Administration; API: active pharmaceutical ingredient; s.c.: subcutaneous; p.o.: per os (by mouth)

5.2.2.3 Concomitant medications

Concomitant medications for medical conditions other than obesity are allowed in both treatment arms at the discretion of the study clinician, except for the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors for diabetes diagnosed during the study. Other than the medication prescribed by the study clinician for chronic weight management in the WMP + Rx arm (section 5.2.2.2), use of any medication, on- or off-label, for weight loss purposes is not allowed in either arm during the study. Through routine medication review during SMA study visits, use of medications that are not allowed per protocol (i.e., “disallowed”) will be identified and will be indicated in the eCRF. The subject will remain in the study.

5.3 Questionnaires

5.3.1 Patient Reported Outcomes (PROs)

Work productivity and work limitations will be assessed by the following instruments at visit 1, visit 7, and visit 13. Subjects will self-administer these instruments on paper. Site study personnel will review for completeness and enter responses into the eCRF.

5.3.1.1 Work Productivity and Activity Impairment Questionnaire Specific Health Problem v2.0 (WPAI:SHP)

The WPAI:SHP questionnaire (Appendix 2-1) assesses both work productivity through absenteeism (i.e., work time missed), presenteeism (i.e., impairment at work or reduced on-the-job effectiveness), and work productivity loss, as well as daily activity impairment (e.g., work around the house, shopping, exercising, childcare, studying) attributable to excess weight. WPAI:SHP outcomes are expressed as impairment percentages, with higher scores indicating greater impairment and less productivity, i.e., worse outcomes.

5.3.1.2 Work Limitations Questionnaire 8-Item (WLQ-8) Self-administered Short Form

The WLQ-8 questionnaire (Appendix 2-2) assesses the degree to which subjects have difficulty related to time management, physical tasks, mental/interpersonal tasks, and output tasks due to their physical and/or emotional health. The WLQ-8 produces subscale scores as well as an index of overall at-work productivity loss. WLQ-8 outcomes are expressed as proportion time with difficulty, with higher scores indicating greater limitations, i.e., worse outcomes.

5.4 Study Period

Subjects will be followed from baseline (month 0) to EOS at month 12 (visit 13), during which study clinicians or trained site personnel will collect study data and record them in the eCRF during monthly SMA study visits, including: weight as measured on a designated calibrated scale, pregnancy and serious adverse events (SAEs) (section 7), attendance at SMAs, and use of disallowed medications (section 5.2.2.3). PRO questionnaires will be completed as described in section 5.3. (Appendix 1-1)

Other than withdrawal of consent, subjects will remain in the study, and effort will be made to obtain a month 12 (visit 13) weight measurement from all randomized subjects regardless of SMA attendance or obesity treatment discontinuation during the study period. If a subject stops attending SMAs prior to EOS, he/she will be encouraged to attend visit 13 for a weight measurement within the visit window. Subjects who come back for a visit 13 weight measurement will also be asked to complete the PRO questionnaires during the visit and to report SAEs or disallowed medication use.

5.5 End of Study (EOS)

EOS is defined as 12 months (-14 days, +28 days) after baseline.

If a subject does not attend visit 13, a stepwise approach to obtaining weight will be implemented according to the following hierarchy:

1. Subject called into office for month 12 weight measurement (-14 days, +28 days from scheduled month 12/visit 13).
2. Recent (-14 days, +28 days from scheduled month 12/visit 13) weight extracted from the electronic medical record (EMR).

3. Recent (-14 days, +28 days from scheduled month 12/visit 13) subject-reported weight used.

5.6 Pharmacy Data

In addition to prospectively collected clinical data and PROs, this study will also collect prescription fill data for obesity medication from randomization through EOS.

5.7 Withdrawals

5.7.1 Study Site

The Sponsor and/or the Institutional Review Board (IRB) reserves the right to terminate participation of the study site at any time. The study site may also be terminated for cause per contractual agreement. In such cases, all data collection will end. After the collected data are received, the study clinicians will be compensated as contractually agreed.

5.7.2 Subjects

Participation in the study is voluntary, and all subjects are free to withdraw his/her consent at any time. A subject will only be withdrawn from the study if he/she withdraws consent. In the event of study withdrawal, the study clinician will record the reason for study withdrawal and continue to follow-up with the subject as medically indicated for any unresolved SAEs or pregnancies, if subject agrees. Upon subject consent withdrawal from the study, all data collection will end, but all study data collected up to withdrawal will be included in the study database.

6 STATISTICAL METHODS

6.1 Analysis Overview

Subjects will be randomized 1:1 to WMP + Rx or WMP alone. The data analyses for this study will be outlined in further detail in a Statistical Analysis Plan (SAP).

The significance level used in all statistical analyses will be 5% (two-sided).

6.1.1 Estimands

Two estimands, each targeting a unique research question, have been defined to adequately describe the effect of an employer-based WMP combined with obesity medication compared to an employer-based WMP alone.

Primary estimand

The primary estimand for all endpoints is an “intention-to-treat” estimand (also known as an “effectiveness” or a “treatment policy” estimand). This estimand will quantify the average treatment effect of an employer-based WMP combined with medication for chronic weight

management compared to the employer-based WMP alone after 12 months, in all randomized subjects and regardless of adherence to randomized treatment.

Secondary estimand

The secondary estimand for body weight loss, categorical weight loss, and PROs is an "if all subjects had adhered" estimand (also known as an "efficacy" estimand). This estimand will quantify the average treatment effect of an employer-based WMP combined with medication for chronic weight management compared to the employer-based WMP alone after 12 months, in all randomized subjects had they adhered to their randomized treatment for the entire planned study duration as defined in Section 6.4.3.

6.1.2 Primary Endpoint and Confirming Hypothesis

The primary endpoint is percent change in body weight from baseline (month 0) to month 12 (visit 13), as defined:

$$\% \text{ weight change} = \frac{\text{body weight at visit 13} - \text{body weight at baseline}}{\text{body weight at baseline}} \times 100\%$$

where a negative value indicates a body weight loss from baseline (month 0) to month 12 (visit 13).

One confirmatory hypothesis will be tested:

- Superiority of WMP + Rx versus WMP alone on % weight change from baseline (month 0) to month 12 (visit 13).

The test will be evaluated as a two-sided test of the null hypothesis that the mean weight change (%) in the two treatment arms is the same (H_0: % weight change [WMP + Rx] = % weight change [WMP]). Superiority will be claimed if the two-sided p-value is less than 5% and the estimated difference in mean weight change favors WMP + Rx (H_a: % weight change [WMP + Rx] < % weight change [WMP]).

6.2 Study Populations

The following analysis sets will be defined:

Full analysis set (FAS): Includes all randomized subjects analyzed according to the treatment group to which they were assigned at randomization.

6.3 Sample Size Determination

6.3.1 Power and Sample Size for Primary Objective

Assumptions for sample size calculations included:

- Two sample two sided t-test with equal variances
- 5% significance level, but superiority is only claimed if estimated difference in mean weight loss favors WMP + Rx (this corresponds to a one-sided test on a 2.5% significance level).
- 1:1 randomization
- 50% of subjects in both arms are expected to drop out (based on input from the Cleveland Clinic)
    - Among subjects who drop out, 50% are expected to return for a month 12 (visit 13) assessment (retrieved drop outs).
    - Retrieved and non-retrieved drop outs in the WMP arm are assumed to have the same effect as subjects who complete the WMP arm.
    - Non-retrieved drop outs in the WMP + Rx arm are assumed to have an effect corresponding to subjects in the WMP arm.
    - Retrieved drop outs in the WMP + Rx arm are assumed to have an effect corresponding to half the weight loss difference (compared to WMP) of subjects who complete the study in the WMP + Rx arm.
- The following expected distribution of prescriptions in the WMP + Rx arm (based on input from the Cleveland Clinic):
    - 0% Orlistat (Xenical®)
    - 10% Lorcaserin/Lorcaserin extended-release (Belviq®/BelviqXR)
    - 30% Phentermine/Topiramate extended-release (Qsymia®)
    - 30% Naltrexone/Bupropion extended-release (Contrave®)
    - 30% Liraglutide 3.0 mg (Saxenda®)

Table 6-1 presents several sample size scenarios and power calculations based on the above assumptions, varying expected mean differences in weight loss between treatment arms (treatment effect) over 1 year and standard deviations (SD) as the variation of weight loss between subjects within the same treatment arm. Treatment effect scenarios of 3, 3.5, 4, and 5% were chosen based on product labels. SD of 8, 9, 10, and 11 % were chosen based on the NN8022 (SCALE) program [18] [19] [20] and the TRAMOMTANA [21] study.

Table 6-1. Power calculations for selected total N, treatment effects, and standard deviations

	Treatment effect (%)															
	3				3.5				4				5			
	SD (%)				SD (%)				SD (%)				SD (%)			
Total N	**8**	**9**	**10**	**11**	**8**	**9**	**10**	**11**	**8**	**9**	**10**	**11**	**8**	**9**	**10**	**11**
160	0.65	0.55	0.47	0.40	0.79	0.69	0.59	0.52	0.88	0.80	0.71	0.63	0.98	0.94	0.88	0.82
180	0.71	0.60	0.52	0.44	0.83	0.74	0.65	0.56	0.92	0.84	0.76	0.68	0.99	0.96	0.92	0.86
200	0.75	0.65	0.56	0.48	0.87	0.78	0.69	0.61	0.94	0.88	**0.80**	0.73	0.99	0.97	0.94	0.89
240	0.82	0.73	0.64	0.56	0.92	0.85	0.77	0.69	0.97	0.93	0.87	0.80	1.00	0.99	0.97	0.94
300	0.90	0.82	0.74	0.65	0.97	0.92	0.86	0.78	0.99	0.97	0.93	0.88	1.00	1.00	0.99	0.98

Total N = sum of subjects in both treatment arms; treatment effect = difference in one-year weight loss of WMP + Rx compared to WMP alone; standard deviation (SD) =variation in weight loss between subjects within the same treatment arm.

Based on the above mentioned assumptions and results from the referenced studies, a 4% treatment effect and 10% SD is a conservative, yet realistic scenario. Therefore, a total sample size of 200 subjects (100 subjects per treatment arm) with 80% power for the confirmatory hypothesis assuming a 25% attrition rate over 12 months was chosen.

6.3.2 Interim Analysis

There is no interim analysis planned for this study.

6.4 Primary Estimand for the Primary Endpoint

The primary estimand will be estimated based on the FAS and % weight change will be modeled using linear regression (Analysis of Covariance (ANCOVA)) with randomized treatment as a factor and baseline body weight (kg) as a covariate. The treatment difference between WMP + Rx and WMP alone will be estimated and reported together with the associated 95% confidence interval (CI) and corresponding p-value.

6.4.1 Primary Estimand Missing Data Imputation

Prior to analysis, missing month 12 weight data will be imputed by multiple imputations. For the primary analysis, missing month 12 weight data will be imputed by sampling among all available assessments at visit 13 in the WMP arm (including values from retrieved drop outs). This approach is also known as “jump to reference” and makes the assumption that subjects instantly lose any effect of randomized treatment beyond what can be expected from the WMP after

discontinuation. Body weight measurements at visits between baseline (month 0) and month 12 (visit 13) are not used for this imputation approach. Imputation details will be further described in the SAP.

6.4.2 Sensitivity Analysis of the Primary Estimand for the Primary Endpoint

A multiple imputation approach as described by McEvoy [22] will be used as sensitivity analysis. In this approach, month 12 measurements at visit 13 for non-retrieved drop outs will be imputed by sampling from values obtained from retrieved drop outs in the corresponding treatment arm and according to the timing of last available body weight. If this approach is not feasible, no sensitivity analysis will be done.

6.4.3 Secondary Estimand for the Primary Endpoint

The secondary estimand of the primary endpoint will address the efficacy of medication for chronic weight management if all subjects adhere to their randomized treatment (WMP + Rx or WMP). For the secondary estimand, the primary endpoint will be analyzed using a mixed model for repeated measurements (MMRM) including all subjects, but for subjects considered non-adherent to randomized treatment, only data prior to non-adherence will be used. Month 12 (visit 13) assessments for retrieved drop outs will not be used in this analysis. The MMRM for efficacy will only use assessments from subjects who are adherent to the randomized treatment until end of treatment, or up until the subject is considered non-adherent to the randomized treatment. Subjects in the WMP arm will be considered non-adherent if/when criterion 1 below is met. Subjects in the WMP + Rx arm will be considered non-adherent if/when criterion 1 or 2 is met:

1. Missing 4 SMA visits. In this case, the last assessment made prior to the 4th missed SMA visit will be used as the last assessment. This is also the case if, e.g., 4 SMA visits in a row are missed.
2. Period with no coverage of prescription claims according to PDC exceeds 20% of planned medication duration, or number of days from visit 1 to visit 13. For subjects that drop out early, the expected visit 13 date (derived from the subjects' planned SMA group visit) will be used to calculate planned study duration. The last assessment made prior to exceeding 20% of planned study duration with no prescription claims will be used as last assessment.

The MMRM for efficacy will be fitted using % weight change with randomized treatment as factor and baseline body weight (kg) as covariate, all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

6.4.4 Supplementary Analyses

The analyses of % weight change will be supplemented with a completer analysis based on the subset of subjects with month 12 (visit 13) body weight data who were adherent to the randomized treatment.

Completer analysis

In the context of this supplementary analysis, completers will be defined as subjects with month 12 (visit 13) body weight data who adhered to randomized treatment up to and including visit 13. Adherence is defined as for the secondary estimand for the primary endpoint in section 6.4.3, i.e., subjects in the WMP arm will be considered non-adherent if/when criterion 1 above is met and subjects in the WMP + Rx arm will be considered non-adherent if/when either criterion 1 or 2 above is met. As an example, a subject in the WMP + Rx arm that misses visit 10, 11, and 12, but attends all other visits and is covered by prescription claims for at least 80% of the planned study duration, is considered a completer in this context if month 12 (visit 13) weight data are available.

This analysis will use the same ANCOVA model described for the primary estimand analysis of the primary endpoint (section 6.4).

6.5 Primary Estimand for the Secondary Endpoints

The following analyses are planned to further support the primary objective to compare weight loss of WMP + Rx versus WMP. They will also address the secondary objectives of this study to compare WMP + Rx versus WMP with respect to categorical weight loss, WMP adherence, and PROs, as well as adherence to obesity medication within the WMP + Rx cohort.

All secondary analyses described in this section will be the primary estimand based on the FAS. No sensitivity analyses are planned for the secondary endpoints.

6.5.1 Categorical Weight Loss

For the categorical weight loss endpoints (≥5% weight reduction from baseline, ≥10% weight reduction from baseline), the proportion of subjects achieving each endpoint will be analyzed using a logistic regression model with treatment as categorical effect and baseline weight (kg) as covariate. From the model, the estimated odds ratio (OR) (WMP + Rx / WMP) will be presented with the 95% CI and p-value. An OR above 1 favors WMP + Rx. Missing weight data will be imputed as described for the primary estimand for the primary endpoint (section 6.4.1).

6.5.2 Adherence to Weight Management Program (WMP)

WMP adherence will be assessed through SMA attendance endpoints. SMA attendance will be reported as the percentage planned SMAs attended, i.e., number of SMAs attended/12 planned SMAs. SMA attendance and the proportion of subjects achieving ≥9 SMAs will be descriptively summarized by treatment arm. No formal statistical testing will be conducted.

6.5.3 Adherence to Obesity Medication

Adherence to obesity medication will be assessed through PDC (to be defined in the SAP) for the WMP + Rx treatment arm only. The PDC and the proportion of subjects with at least 80% PDC will be descriptively summarized for the WMP + Rx treatment arm. No formal statistical testing will be conducted.

6.5.4 Patient Reported Outcome (PRO) Analysis

Work productivity and work limitations will be assessed by the WPAI:SHP and WLQ-8 instruments (section 5.3.1). Analysis of change from baseline (month 0) to month 12 (visit 13) in work productivity and work limitation endpoints defined in section 3.2 will follow the method described for the primary estimand for the primary endpoint: ANCOVA model with randomized treatment as a factor and baseline value of the endpoint variable as covariate. Estimated difference (WMP + Rx minus WMP) in change from baseline (month 0) to month 12 (visit 13) will be presented with 95% CI and corresponding p-value. If examination of the data indicate that it is not justifiable to model data based on assumptions of normality, e.g., many responses of 0% or close to 0%, alternative statistical modeling will be used (e.g. logistic regression after definition of a responder limit).

6.5.5 Supplementary Patient Reported Outcome (PRO) Analysis

As a supplementary PRO analysis, the PRO analysis described in section 6.5.4 will be repeated for change from baseline (month 0) to month 6 (visit 7) in work productivity and work limitation endpoints.

6.6 Secondary Estimand for the Secondary Endpoints

Categorical Weight

The secondary estimand for the categorical weight endpoint of ≥ 5% reduction in body weight from baseline (5% responder) will be assessed using the MMRM for efficacy as described for the secondary estimand for the primary endpoint in section 6.4.3. Analysis will only use assessments from subjects who are adherent to the randomized treatment until end of treatment, or up until the subject is considered non-adherent to the randomized treatment. From the MMRM, individually predicted values for % weight change at month 12 will be used to classify each subject as 5% responder or not. This classification will then be analyzed using a logistic regression model with treatment as the only factor. From the model, the estimated OR (WMP + Rx / WMP) will be presented with the 95% CI and p-value.

PROs

The secondary estimand for change from baseline (month 0) to month 12 (visit 13) in work productivity and work limitation endpoints (section 3.2) will be assessed using the MMRM for efficacy as described for the secondary estimand for the primary endpoint in section 6.4.3. The MMRM for efficacy will only use PRO assessments from subjects who are adherent to the randomized treatment until end of treatment, or up until the subject is considered non-adherent to the randomized treatment. The MMRM for efficacy will be fitted using change in PRO endpoint with randomized treatment as factor and baseline value of the endpoint variable as covariate, all nested within visit. An unstructured covariance matrix for measurements within the same subject will be employed, assuming that measurements for different subjects are independent.

Supplementary PRO Analysis

As a supplementary PRO analysis, the above described PRO analysis will be repeated for change from baseline (month 0) to month 6 (visit 7) in work productivity and work limitation endpoints.

6.7 Safety Analysis

SAEs will be collected as described in section 7. No formal safety analyses are planned for this study. SAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and descriptively summarized by System Organ Class (SOC) and Preferred Term (PT).

7 ADVERSE EVENT (AE) REPORTING

7.1 Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product or medical device, which does not necessarily have to have a causal relationship to the product or device. Worsening of existing medical conditions, if considered serious and related by the investigator, should be reported as AEs.

For the purposes of this study, AEs will only be required to be collected if they meet the definition of an SAE (section 7.2).

7.2 Serious Adverse Events (SAEs)

All AEs meeting the definition of SAE will be collected. An SAE is defined as any AE which results in at least one of the following outcomes:

- Initial inpatient hospitalization or prolongation of existing inpatient hospitalization
- A life-threatening event, i.e., an event in which the subject was at immediate risk of dying at the time of the event; not an event that hypothetically could have caused death had it been more severe
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect in offspring
- Death
- Is deemed serious for any other reason, i.e., if it is an important medical event based on appropriate medical judgement which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other listed outcomes.

7.2.1 Reporting Period of Serious Adverse Events (SAEs)

SAEs will be reported from randomization until EOS at month 12, or until the subject withdraws from the study. Study clinicians will follow SAEs that occur in any subject during this study in a manner consistent with routine clinical practice.

The study clinician is responsible for alerting Novo Nordisk or its designee to any SAE within 24 hours of becoming aware of it via electronic data capture (EDC) entry. The subject should be followed until the outcome of the event is closed out. Follow-up information should be reported within 24 hours of it becoming available. Requests for follow-up information should be resolved within 14 calendar days.

The study clinician is responsible for assessment of causality and outcome of SAEs, as defined in Appendix 3. Causality and outcome should be provided at the time of reporting an SAE.

If an investigator becomes aware of SAEs after EOS at end of month 12, that are possibly related to the study product, these should be reported as spontaneous events.

7.3 Pregnancy

Any abnormal pregnancy outcome (e.g., spontaneous miscarriage, fetal death, congenital anomaly/birth defect, etc.) is considered an SAE. For the purposes of this study, any pregnancies in participating female subjects will be reported, along with pregnancy outcome and any AEs or SAEs observed in the fetus or newborn until 1 month of age.

7.3.1 Reporting Period of Pregnancy

Pregnancies will be reported from the time a subject is randomized until EOS at month 12 or until the subject withdraws from the study. Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The study physician will collect follow-up information on subject and neonate, which will be forwarded to Novo Nordisk. Any termination of pregnancy should be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure. A spontaneous abortion is always considered to be an SAE and should be reported as such.

7.4 Technical Complaints

Technical complaints may be reported as per usual practice and local regulations. However, any SAEs resulting from a technical complaint must be reported via the EDC.

8 DATA COLLECTION

8.1 Data Sources

Data sources include primary data collected prospectively by study site at study visits (demographic and clinical data, subject-completed PRO data) and entered into the eCRF, as well as secondary data collection utilizing pharmacy dispensing data. In order to maintain subject confidentiality, each subject will be assigned a unique subject study ID number upon signing informed consent to use in place of subject name or any other identifying information (e.g., medical record number). Primary eCRF data and pharmacy derived variables will be integrated into one analysis dataset.

8.2 Electronic Case Report Forms (eCRFs)

Study data prospectively collected at the study site will be entered into eCRF by trained site study personnel through a fully validated, 21 CFR 11 and HIPAA compliant EDC system. Subjects will complete PRO questionnaires on paper and the site study personnel will enter the completed forms into the EDC system. Site users will be provided eCRF Completion Guidelines (eCCGs) to assist with study data collection and entry. Study personnel will access the EDC system through a secure study website.

The study clinician has the ultimate responsibility for the collection and reporting of all study data through the eCRFs, as well as ensuring that they are accurate and complete to the extent possible.

8.3 Database Lock

Database lock will occur once data collection of the last subject follow up visit and data management activities are complete.

9 STUDY MANAGEMENT

9.1 Regulatory and Ethical Consideration

All study activities will be conducted in accordance with Good Clinical Practice (GCP) guidelines. Study personnel at clinician sites will be provided training on the study protocol, the Informed Consent Form (ICF), data collection, and data entry to ensure both the protection of potential study subjects as well as the scientific integrity of the study. Site monitoring will be conducted by HealthCore staff.

9.1.1 Institutional Review Board (IRB)

The study clinician will have prospective IRB approval of the study protocol, ICF, and any subject information or recruiting materials prior to commencement of any study activities at his/her site. In the case of a protocol amendment, the study clinician must sign the revised protocol and submit the amendment to the IRB for review and approval prior to implementation of any changes specified in the protocol amendment. All changes in research activity and all unanticipated problems involving risk to human subjects or others must be reported to the IRB as required.

The study clinician will obtain continued review of the IRB study approval at intervals not to exceed one year or otherwise specified by the IRB.

9.1.2 Informed Consent

An ICF describing the purpose, procedures, and potential risks and benefits of the study will be developed and approved by the IRB prior to study initiation. Written informed consent will be obtained prior to initiation of any study-related procedures. Each subject will receive a copy of

the signed ICF. The study clinician will retain the original signed ICF for each subject. The IRB must prospectively approve any changes to the ICF during the course of the study before use.

If a protocol amendment increases the potential risk to the subject, the ICF must be revised and submitted to the IRB for review and approval prior to implementation. The revised ICF must then be used to obtain consent from new subjects entering the study as well as from currently enrolled subjects if they are affected by the amendment, per IRB guidance.

9.2 Record Retention and Access

This study may be subject to audits or inspections by regulatory authorities or Novo Nordisk (or its designee). To enable such inspections and/or audits, the study clinician must agree to maintain and allow access to required subject and study records. The study clinician agrees to keep the identity of all participating subjects (sufficient information to link records, e.g., hospital records), all original signed ICFs, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, reports) as specified in the Clinical Study Agreement.

10 PUBLICATION OF STUDY RESULTS

All information collected for this study is considered confidential information belonging to Novo Nordisk. Information regarding the study will be disclosed at clinicaltrials.gov and novonordisk-trials.com. It will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors (ICMJE) [23], the Food and Drug Administration Amendment Act (FDAAA) [24], European Commission Requirements [25] [26] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

The Primary Completion Date (PCD) is the last assessment of the primary endpoint, and is for this trial Last Subject First Visit (LSFV) + 12 months (-14 days +28) corresponding to visit 13. If the last subject is withdrawn early, the PCD is considered the date when the last subject would have completed visit 13. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

A final study report will be generated following completion of data collection and analysis. Results and findings will be submitted to conferences and for publication in peer-reviewed scientific journals. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of studies regardless of outcome. Public disclosure includes publication of a paper in a

scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this study will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.

11 INDEMNIFICATION

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the trial or by persons for whom the said site or investigator are responsible.

12 REFERENCES

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Appendix 1-1: Time and Events Schedule

Study NN8022-4432	**Screening and Randomization**	**Weight Management Program**											
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Timing of visit (months)	0	1	2	3	4	5	6	7	8	9	10	11	12
Visit window (days)	0	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	-14, +28
SUBJECT-RELATED INFORMATION AND ASSESSMENTS													
Informed consent	X												
Demography[a]	X												
Inclusion criteria	X												
Exclusion criteria	X												
Randomization	X												
Medical history/concomitant illness	X												
Concomitant medication	X												
Disallowed medication[b]		X	X	X	X	X	X	X	X	X	X	X	X

Study NN8022-4432	**Screening and Randomization**	**Weight Management Program**											
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Timing of visit (months)	0	1	2	3	4	5	6	7	8	9	10	11	12
Visit window (days)	0	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	-14, +28
EFFICACY													
Height	X												
Body weight	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
WPAI-SHP	X						X						X
WLQ-8	X						X						X
SMA attendance		X	X	X	X	X	X	X	X	X	X	X	X
SAFETY													
Adverse event	X[d]	X	X	X	X	X	X	X	X	X	X	X	X
REMINDERS													
HbA1c	X[e]												
Urine pregnancy test	X[f]												
Schedule nutritionist appointment	X												
Refer to exercise physiologist	X												

[a] *Demography consists of date of birth, sex, ethnicity, and race.*

[b] *Disallowed medications include GLP-1 RAs or SGLT-2 inhibitors for diabetes and any medication on- or off-label prescribed for weight loss other than the medication prescribed by the study clinician for chronic weight management (section 5.2.2.3). Use of these medications will be assessed during routine medication review at SMAs and entered into the eCRF.*

[c] *If a subject does not attend the SMA at visit 13, a stepwise approach to obtaining weight data will be applied to obtain a month 12 weight measurement (-14 days, +28 days from scheduled month 12/visit 13): calling subject in for a month 12/visit 13 weight measurement, extract recent weight data from the electronic medical record, or use recent subject-reported weight.*

[d] *Screening and randomization are one visit. Serious adverse event and pregnancy collection will begin after informed consent and randomization.*

[e] *A POC HbA1c measurement will be performed at screening if an HbA1c measurement is not available within 90 days prior to randomization.*

[f] *A urine pregnancy test will be performed prior to randomization in women of child bearing potential who are not using adequate contraception at the discretion of the study physician.*

WPAI:SHP: Work Productivity and Activity Impairment Questionnaire Specific Health Problem; WLQ-8: Work Limitations Questionnaire Self-administered Short-Form; SMA: Shared Medical Appointment

Appendix 1-2: Data collected from pharmacy card

Study NN8022-4432	**Visit 1 to visit 13**
Pharmacy card dispensing data for medication for chronic weight management (mediation, fill date, days supply, quantity dispensed)	X

Appendix 2-1: PRO Instruments – Work Productivity and Activity Impairment Questionnaire Specific Health Problem v2.0 (WPAI:SHP)

**Work Productivity and Activity Impairment Questionnaire:
Specific Health Problem V2.0 (WPAI:SHP)**

The following questions ask about the effect of your PROBLEM on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your PROBLEM? *Include hours you missed on sick days, times you went in late, left early, etc., because of your PROBLEM. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your PROBLEM affect your productivity <u>while you were working</u>?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If PROBLEM affected your work only a little, choose a low number. Choose a high number if PROBLEM affected your work a great deal.

   Consider only how much <u>PROBLEM</u> affected productivity <u>while you were working</u>.

PROBLEM had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	PROBLEM completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your PROBLEM affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If PROBLEM affected your activities only a little, choose a low number. Choose a high number if PROBLEM affected your activities a great deal.

   Consider only how much <u>PROBLEM</u> affected your ability to do your regular daily activities, other than work at a job.

PROBLEM had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	PROBLEM completely prevented me from doing my daily activities

   CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Reilly MC, Zbrozek AS, Dukes E: The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993; 4(5):353-365.

Appendix 2-2: PRO Instruments – Work Limitations Questionnaire 8-Item Self-administered Short Form (WLQ-8)

CONFIDENTIAL

Work Limitations Questionnaire©

Self-Administered Online Short-Form

Instructions

Health problems can make it difficult for working people to perform certain parts of their jobs. We are interested in learning about how your health may have affected you at work during the past 2 weeks.

(1) The questions will ask you to think about your physical health or emotional problems. These refer to any ongoing or permanent medical conditions you may have and the effects of any treatments you are taking for these. Emotional problems may include feeling depressed or anxious.

(2) The questions are multiple choice. They ask you to answer by placing a mark in a box.

For example:

a. How satisfied are you with your local schools?

(*Mark one box.*)

Not At All Satisfied	☐
Moderately Satisfied	☐
Very Satisfied	■

b. How satisfied are you with your local police department?

(*Mark one box.*)

Not At All Satisfied	☐
Moderately Satisfied	■
Very Satisfied	☐

These marks tell us you are very satisfied with your local schools and moderately satisfied with your local police department.

v05_20_2010

OPTIONAL PAGE

(3) Before you begin answering any questions, we would like you to write some information on the calendar.

- Find today's date. Mark that box.
- Count back 2 weeks and mark that box too.

This 2-week period is the subject of most of the questions. Feel free to mark other important dates such as birthdays, family events, or work deadlines. Please use the calendars to help you answer correctly.

Insert calendar here.

v05_20_2010

Questions 1 through 5 ask about how your health has affected you at work during the past 2 weeks. Please answer these questions even if you missed some workdays.

- *Mark the "Does not apply to my job" box only if the question describes something that is not part of your job.*
- *If you have more than one job, report on your **main** job only.*

1a. In the past 2 weeks, how much of the time did your physical health or emotional problems make it **difficult** for you to get going easily at the beginning of the workday?

(*Mark one box.*)

Difficult all of the time (100%)	☐
Difficult most of the time	☐
Difficult some of the time (about 50%)	☐
Difficult a slight bit of the time	☐
Difficult none of the time (0%)	☐
Does not apply to my job	☐

1b. In the past 2 weeks, how much of the time did your physical health or emotional problems make it **difficult** for you to start on your job as soon as you arrived at work?

(*Mark one box.*)

Difficult all of the time (100%)	☐
Difficult most of the time	☐
Difficult some of the time (about 50%)	☐
Difficult a slight bit of the time	☐
Difficult none of the time (0%)	☐
Does not apply to my job	☐

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These questions ask you to rate the amount of time you were able to handle certain parts of your job without difficulty.

2a. In the past 2 weeks, how much of the time were you **able** to sit, stand, or stay in one position for longer than 15 minutes while working, without difficulty caused by physical health or emotional problems?

(*Mark one box.*)

Able all of the time (100%)	☐
Able most of the time	☐
Able some of the time (about 50%)	☐
Able a slight bit of the time	☐
Able none of the time (0%)	☐
Does not apply to my job	☐

2b. In the past 2 weeks, how much of the time were you **able** to repeat the same motions over and over again while working, without difficulty caused by physical health or emotional problems?

(*Mark one box.*)

Able all of the time (100%)	☐
Able most of the time	☐
Able some of the time (about 50%)	☐
Able a slight bit of the time	☐
Able none of the time (0%)	☐
Does not apply to my job	☐

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This question asks about difficulties you may have had at work.

3. In the past 2 weeks, how much of the time did your physical health or emotional problems make it **difficult** for you to concentrate on your work?

(*Mark one box.*)

Difficult all of the time (100%)	☐
Difficult most of the time	☐
Difficult some of the time (about 50%)	☐
Difficult a slight bit of the time	☐
Difficult none of the time (0%)	☐
Does not apply to my job	☐

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The next question asks about difficulties in relation to the people you came in contact with while working. These may include employers, supervisors, coworkers, clients, customers, or the public.

4. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to speak with people in-person, in meetings or on the phone?

(*Mark one box.*)

Difficult all of the time (100%)	☐
Difficult most of the time	☐
Difficult some of the time (about 50%)	☐
Difficult a slight bit of the time	☐
Difficult none of the time (0%)	☐
Does not apply to my job	☐

v05_20_2010

These questions ask about how things went at work overall.

5a. In the past 2 weeks, how much of the time did your physical health or emotional problems make it **difficult** for you to handle the workload?

(*Mark one box.*)

Difficult all of the time (100%)	☐
Difficult most of the time	☐
Difficult some of the time (about 50%)	☐
Difficult a slight bit of the time	☐
Difficult none of the time (0%)	☐
Does not apply to my job	☐

5b. In the past 2 weeks, how much of the time did your physical health or emotional problems make it **difficult** for you to finish work on time?

(*Mark one box.*)

Difficult all of the time (100%)	☐
Difficult most of the time	☐
Difficult some of the time (about 50%)	☐
Difficult a slight bit of the time	☐
Difficult none of the time (0%)	☐
Does not apply to my job	☐

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Appendix 3: Causality and Outcome Definitions for Serious Adverse Event (SAE) Reporting

Assessment of Causality

The investigator is obligated to assess the relationship between trial product and the occurrence of each AE/SAE.

Relationship between an AE/SAE and the relevant trial product(s) should be assessed as:

- **Probable:** Good reason and sufficient documentation to assume a causal relationship.
- **Possible:** A causal relationship is conceivable and cannot be dismissed.
- **Unlikely:** The event is most likely related to etiology other than the trial product.

Alternative etiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to trial product administration will be considered and investigated.

The investigator should use the individual product information for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**

The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Final Outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved:** The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- **Recovering/resolving:** The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.

- **Recovered/resolved with sequelae:** The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequelae meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved:** The condition of the subject has not improved and the symptoms are unchanged or the outcome is not known.
- **Fatal:** This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with a fatal outcome must be reported as an SAE.
- **Unknown:** This term is only applicable if the subject is lost to follow-up.