

# OBEDIS Core Variables Project: European Expert Guidelines on a Minimal Core Set of Variables to Include in Randomized, Controlled Clinical Trials of Obesity Interventions

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**Guidelines**

# OBEDIS Core Variables Project: European Expert Guidelines on a Minimal Core Set of Variables to Include in Randomized, Controlled Clinical Trials of Obesity Interventions

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**Keywords**
Obesity · Interventions · Variables · Precision medicine · Stratification

**Abstract**
Heterogeneity of interindividual and intraindividual responses to interventions is often observed in randomized, controlled trials for obesity. To address the global epidemic of obesity and move toward more personalized treatment regimens, the global research community must come together to identify factors that may drive these heterogeneous responses to interventions. This project, called OBEDIS (OBEsity Diverse Interventions Sharing – focusing on dietary and other interventions), provides a set of European guidelines for a minimal set of variables to include in future clinical trials on obesity, regardless of the specific endpoints. Broad adoption of these guidelines will enable researchers to harmonize and merge data from multiple intervention studies, allowing stratification of patients according to precise phenotyping criteria which are measured using standardized methods. In this way, studies across Europe may be pooled for better prediction of individuals' responses to an intervention for obesity – ultimately leading to better patient care and improved obesity outcomes.

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## Introduction

Obesity is a problem that represents a significant health and economic burden in Europe and throughout the world. The prevalence of obesity across European countries has tripled in the last several decades [1], making it one of the leading public health challenges.

A critical part of addressing this global epidemic is to improve the evidence base for more effective treatments for obesity; however, a challenge revealed in the randomized, controlled trials (RCTs) of obesity interventions is the remarkable heterogeneity of interindividual and intraindividual responses among adult patients – whether the intervention pertains to lifestyle (dietary, physical activity [PA]), or is a pharmacological or surgical intervention aiming at weight loss. Most obesity RCTs include a heterogeneous mixture of patients that, despite meeting the inclusion criteria for the study, vary remarkably when it comes to the medical

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history of their disease, associated complications, and many other factors (including genetics, lifestyle, environmental, and psychosocial factors) that may drive the varying responses to the same intervention. Also, different trials take different approaches to measuring the same variable. This emphasizes the need to appropriately stratify patients according to precise phenotyping criteria, as measured using standardized methods, that might predict an individual's response to an intervention: enabling a paradigm shift in individually tailored obesity treatment, going from "one-size-fits-all" to precision medicine.

One important clinically relevant question is whether, among the patients who respond poorly to a given therapy, a better response might be achieved by applying a different therapy or by administering the current therapy differently. Specific patient characteristics could theoretically provide justification for choosing an alternative treatment either as a first choice or, dependent on poor response, as a second choice, but an increased burden is thus placed on researchers to provide evidence for the benefit of choosing or switching between alternative therapies.

Even for the largest and most comprehensive published clinical studies on obesity, stratification leads to subgroup analyses with reduced statistical power. Moreover, some trials do not report methods for measuring relevant obesity phenotypes in sufficient detail. Thus, it is necessary to harmonize and merge the data from multiple intervention studies – but data pooling is only possible with trials that include a common set of variables measured in the same way, including samples that are collected using consistent methods or procedures, described in enough detail.

Funded by a European grant, a group of European obesity researchers convened in 2018 to create a plan for helping shape future RCTs in the field of obesity by identifying the minimal set of variables that should be included in trials of different kinds of obesity interventions, whatever the type and the endpoints of the intervention. The experts intend for this minimal core set to be adopted in future studies while acknowledging that in addition, RCTs or other trials will collect data on extra variables, depending on the specific area of focus. As such, the current initiative, called OBEDIS (OBEsity Diverse Interventions Sharing – focusing on dietary and other interventions) and funded by the Joint Programming Initiative – A Healthy Diet for a Healthy Life (JPI HDHL), was created to provide the research community with a blueprint for designing future RCTs in order to allow the sharing and merging of datasets, and to enable meaningful subgroup analyses. To achieve this, the OBEDIS experts surveyed the scientific literature, especially the published work on stratifying populations of individuals with obesity. They shared their expert opinions on a recommended minimal core set of variables to be included in all future trials of adult obesity interventions and sought to reach consensus on both these variables and the related assessment methods.

## Methods

*Expert Involvement and Working Methods*

The OBEDIS project coordinators, supported by the European Association for the Study of Obesity (EASO), invited leading experts to contribute to this consensus on a minimal core set of variables for RCTs of obesity interventions. These European researchers represented 13 countries and were chosen for their research record and expertise related to obesity and intervention studies in the field. The total group was comprised of 30 experts (including the 4-person coordination/management team); three scientific advisory board (SAB) members; one project manager; one funding agency (JPI HDHL) representative; and one medical writer. The OBEDIS experts were purposely selected from countries with different healthcare models and demographics. These multiple perspectives were considered necessary in the discus-

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sions, in order to serve the field best by choosing a minimal core set of variables that are applicable across different geographies and cultures.

The experts were divided into small working groups according to their expertise. They completed reviews of published RCTs in their respective domains and held initial discussions. After this foundational preparatory group work, these experts and SAB members met for a 2-day workshop in Paris, France, in October 2018, to discuss the recommendations and come to a consensus on a core set of variables to recommend in each domain.

*Criteria for Minimal Core Set*

A variable is defined as "a property with respect to which individuals in a sample differ in some ascertainable way" [2]. The minimal core set is a set of variables recommended to be measured in all trials for obesity, regardless of the type of intervention. It is understood that over time this core set will be updated according to the scientific advances in each of the identified domains.

For a variable to be included in the minimal core set, it was required to fulfill the following criteria:

- It provided information that made it likely to impact treatment response, according to the relevant literature (especially studies that aimed to stratify patients)
- It was feasible: Given that each clinical trial has limits on budget and time as well as research team expertise, the OBEDIS group aimed to minimize the burden of including each variable in future trials. The scientists paid considerable attention to factors that would encourage widespread adoption of these measures by the European obesity research community, especially the overall number of variables that should be systematically collected. The group preferred measures that were:
  - Low-cost or free to utilize/able to be collected with minimal equipment or human resources
  - Less invasive/quick to implement
  - For questionnaires: Available and/or validated in multiple languages or across cultures

The group provided an estimate of the average cost of including these measures in a European trial (Table 1). While inclusion of these variables will in some cases introduce additional cost to individual clinical trials, they will also extend the insights made possible by each trial – making the overall research agenda proceed more purposefully and at a lower cost.

While the primary purpose of the initiative was to identify a minimal core set, additional relevant variables and/or measures were identified in some cases, and these were included in what was called the "expanded set."

*Selection of Minimal Core Set*

Each group presented the variables frequently used in the studies to date, and selected them based on their experience, the scientific literature, and their projections about the future direction of the field in each domain. The group then voted on each item in the minimal core set (with the outcome determined by a simple majority). The approach to this OBEDIS project was pragmatic and guided at every turn by the existing body of evidence on interventions for obesity while taking into account the constraints of the minimal core set.

The experts understand that few trials will restrict themselves to only this core set and will collect additional variables depending on their specific aims and outcomes. Trial investigators may opt to carry out more detailed measurements for a certain variable when it corresponds to the main objective of the study – and in this case, regardless, the OBEDIS group recommends collecting the overlapping measures in the minimal core set to facilitate data integration on a larger scale.

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**Table 1.** Summary table

| Category | Variables | Methods | Cost | Time |
|---|---|---|---|---|
| **Environment and context** | | | | |
| Medical history of obesity | Age at onset of obesity<br>Maximal and minimal body weight after 18 years of age<br>Variation of body weight during the past 3 months<br>Previous attempts to lose weight and weight maintained after weight loss<br>Etiology<br>Parental history, including maternal bariatric surgery | Custom questionnaire | | |
| Basic background information | Number of years of education and country | Custom questionnaire | | |
| Quality of life and handicap | QoL health profile score, overall self-rated health status, and index value | EQ-5D-5L, https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/ | | 2 min |
| **Lifestyle and behavior** | | | | |
| Dietary intake | Dietary intake<br>Dietary quality<br>Emotional eating | EPIC-Norfolk FFQ or a region-specific validated FFQ<br>Dutch Healthy Diet index or region-specific validated index<br>Dutch eating behavior questionnaire, Emotional subscale | | Up to 60 min |
| Physical activity and sedentary behavior | Physical activity level<br>Sedentary behavior: week day time and weekend day time<br><br>Cardiorespiratory fitness<br>Muscle strength | Accelerometer<br>Accelerometer and Paffenbarger Physical Activity Questionnaire<br>6-min walk test<br>Southampton grip-strength measurement | Equipment costs EUR ±300 each, reusable | Accelerometry: one week measurement, 15 min analysis<br>Questionnaire: 10 min<br>Walk test: 15 min<br>Grip strength: 5 min |
| Sleep | Sleep duration and timing<br>Presence of sleep apnea | Custom questionnaire<br>STOP-BANG, http://stopbang.ca/osa/screening.php | | 5 min |
| Stress and other psychological variables | Perceived stress | Perceived stress scale | | 5 min |
| **Subject characteristics** | | | | |
| Anthropometry, body composition, and energy expenditure | Weight and BMI<br>Waist, hip, and neck circumference<br>Fat mass and fat-free mass | Scale<br>Measuring tape<br>DXA | <br><br>DXA: variable cost | 5 min<br>5–15 min (depends on type of machine) |
| Hormonal status | Thyroid stimulating hormone<br>Menopausal status, current medication | Third generation TSH assay<br>Custom questionnaire | EUR 4 | 1 min<br>1 min |
| **Comorbidities** | | | | |
| Type 2 diabetes | Fasting glycemia (2 measurements)<br>Hemoglobin A1c<br>Fasting insulin and insulin-derived sensitivity indices<br>Family history of diabetes | Standard assays<br><br><br>Custom questionnaire | EUR 0.3<br>EUR 7<br>EUR 9 | 1 min<br>1 min<br>5 min<br>1 min |
| Cardiovascular risk | Smoking habits<br>Blood pressure and heart rate<br>Total cholesterol, HDL cholesterol, triglyceride<br>hs-CRP<br><br>Heart electrical activity<br>Cardiorespiratory fitness | Custom questionnaire<br>Automatic BP device<br>Any robust assay<br>Automated immunonephelometric or immunoturbidimetric or immunoluminometric assay<br>1- to 5-min ECG<br>6-min walk test | <br><br>EUR 25<br>EUR 10 | 1 min<br>3 min<br>1 min<br><br>10 min<br>15 min |
| Liver disease | NFS and FIB-4: ALT, AST, GGT, platelet count and albumin<br>Alcohol intake | Standard assays<br>WHO AUDIT questionnaire | | |
| Osteoarthritis | Quality of life | EQ-5D-5L (see above) | | |

https://docs.google.com/presentation/d/1yA-Azdn_RypwhoZfAncVTZXGOGduNN-UVWE4k-DBumY/edit?usp=sharing

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*Parallel Efforts*

The OBEDIS work with European experts occurred in parallel with a similar United States initiative funded by the National Institutes of Health: the ADOPT (Accumulating Data to Optimally Predict obesity Treatment) core measures project [3]. In the OBEDIS workshop, the experts noted that the existence of this parallel work highlights the need for such efforts in the field. OBEDIS scientists wish to connect ideas across these two projects and build joint efforts in the same direction, for the overall benefit of the field globally.

## Results

The expert guidelines detailed herein represent a practical advancement in the field of research on obesity interventions. Below, the results are described in four categories – environment and context, lifestyle, subject characteristics, and complications – with a final section looking ahead to implications for future medical practice. Table 1 summarizes the variables and methods. Issues pertaining to obesity interventions are covered in a separate paper.

The OBEDIS experts unanimously agreed that standard operating procedures (SOPs) are of critical importance, because only with consistent harmonized procedures can data be pooled across studies. The recommended detailed assessment methods for these measurements are detailed in the supplementary materials (for all online suppl. materials, see www.karger.com/doi/10.1159/000505342).

*Environment and Context: Medical History of Obesity, Basic Background Information, Quality of Life/Handicap*

No living entity exists in isolation: across the biological sciences, researchers consider environmental influences as major drivers of behavioral change. Various environmental factors are considered relevant in obesity, since they may contribute to the emergence and maintenance of the condition and relevant behaviors. The context where patients live and work may also impact response to interventions, making contextual factors potentially useful for patient stratification at baseline.

Medical History of Obesity

Minimal core set recommended variables:

- Age at onset of obesity
- Maximal and minimal body weight after 18 years of age
- Variation of body weight during the past 3 months
- Previous attempts to lose weight and weight maintained after weight loss
- Etiology: categories from Hebebrand et al. [4]
- Parental history, including history of bariatric surgery

Expanded set recommended variables:

- Body weight self-monitoring

The medical history of obesity is a recall of weight-related events and problems experienced by the patient. In adult obesity, the medical history of the disease is important because factors in the history of a patient can not only affect the course of weight gain and loss through the lifespan but may modulate the response to a specific type of intervention. Medical history variables in three main categories are relevant to intervention responses: the development of the current obesity state and previous attempts to treat it; the disease etiology; and variables related to conception and perinatal history. Comorbid medical conditions that may influence intervention outcome, or disorders for which the treatment influences outcome, are discussed elsewhere in this paper.

In considering the development of the patient's current obesity state, the OBEDIS group recommends documenting both the age of the onset of obesity, and the maximal and minimal body weight during adulthood. The age at obesity onset is important because occurrence prior to age 18 can influence the development of complications later on [5]. Meanwhile, minimal and maximal body weight in adulthood are also relevant; in particular, using maximum body mass index (BMI; rather than using BMI at the time of study) to assess mortality risks leads to stronger associations between excess weight and mortality [6]. Another potentially important factor is recent body weight fluctuations [7]; the group recommended assessing weight changes over the past 3 months. Assessing body weight self-monitoring behaviors is not recommended for the minimal core set of variables but may be included in the expanded set.

Previous attempts to treat obesity are also relevant: for instance, in some studies a greater number of previous weight loss attempts predicted greater weight loss [8] and some evidence suggests weight cycling may increase the likelihood of future weight gain [9]. Data for the minimal core set should include: the number of attempts, whether the patient has undertaken individual/group behavioral interventions (pertaining to nutrition/PA/psychology), whether treatment included obesity drugs or bariatric surgery, and the maximal weight loss and weight regain as a result of these attempts.

The etiology of the patient's obesity may affect response to intervention. In most individuals with obesity, the disease is multifactorial – that is, resulting from the complex interaction of many genetic/epigenetic and environmental factors. However, in cases where a defined etiological factor can be identified (a genetic mutation, for example), the OBEDIS group recommends using the categories outlined in Hebebrand et al. [4]. Trained medical staff should be able to identify syndromic obesity to either avoid the inclusion of these patients if the trial is not specific to genetic obesity or include these patients as a separate subgroup.

Factors related to periconceptional and perinatal history of the patient may also affect response to obesity interventions [10]: family disease history, maternal obesity before conception, complications and health conditions during pregnancy (including maternal gestational diabetes), magnitude of gestational weight gain, preterm or term birth, and birth weight (macrosomia). Typically, not all of this information is known to the patient, but in the minimal core set the OBEDIS group recommends assessing two particularly important factors prior to conception: parental obesity [11] and maternal history of bariatric surgery.

No standardized medical history questionnaire for obesity is in use throughout Europe. Various standardized questionnaires exist to assess some of the above items, but many are not available in different European languages. Thus, the OBEDIS group recommends assessing the above medical history variables via custom questionnaire (self-report), specified in the supplementary materials. Where available, medical records (registers or electronic medical charts) may be used to corroborate the information.

The group agrees that, in the future, researchers should set about developing a standardized clinical questionnaire related to the medical history of obesity, which would be translated into different languages for use by researchers and healthcare professionals across Europe. A further endeavor – which would prove extremely valuable for research purposes – is to develop a European register of health information that included data on medical history, health status, and treatment of individuals over time.

Basic Background Information

Minimal core set recommended variables:

- Number of years of education and country

Both education and other measures of socioeconomic status, such as income, may modify intervention outcomes for certain kinds of obesity interventions. Variations across education

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level were observed for the outcome suicide and self-harm when comparing a dietary/lifestyle modification program and bariatric surgery [12]; a similar pattern was found for the outcome of sleep medication use [13]. In higher-income countries, an inverse association tends to exist between educational attainment and obesity [14].

Number of years of education is widely used for assessing patient educational attainment [15] and is recommended in this context. While this measure does not allow complete comparability of data between countries, the minimal core dataset would ideally specify the country along with the number of years of education.

Quality of Life/Handicap

Minimal core set recommended variables:

- Quality of life (QoL): EQ-5D-5L health profile scores, overall self-rated health status, and index value

QoL is a subjective factor that is defined by the World Health Organization (WHO) as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [16]. Health-related QoL is a broad-ranging, multidimensional assessment of one's own health; it is an outcome measure that is frequently assessed along with handicap: "a disadvantage for a given individual that limits or prevents the fulfillment of a role that is normal for that individual" [17]. Given that health is "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [18], a complete assessment of health status – especially in chronic diseases – should include both objective measures (using a biomedical framework) and subjective measures (using a psychosocial framework; e.g., QoL) [19, 20].

In the field of obesity research, health-related QoL can be an independent outcome variable for assessing the effectiveness of therapeutic strategies for obesity, complementary to the degree of weight loss and to the improvement in complications [21, 22]. In addition to its outcome value, QoL can also have predictive value (i.e., prediction of biopsychosocial outcomes) and discriminative value (e.g., differentiating between patients with or without other medical conditions) [23]. QoL is an important variable in economic evaluation of healthcare interventions, as it is used to calculate quality-adjusted life years, the most commonly used effect measure in cost-effectiveness analyses.

QoL, as a patient-reported outcome, is assessed using self-administered questionnaires. Many questionnaires have been validated in the field of obesity [for reviews see 24, 25]. The OBEDIS group used several criteria (consistent with the general criteria above) to choose the most suitable QoL questionnaire: type of concept assessed (i.e., assessment of QoL, but not symptoms/functional status or handicap), brevity, convergent validity, cross-cultural validation (particularly important in this European work), and copyright (including no or limited fees for use). The European group agrees that the EQ-5D-5L satisfies the greatest number of criteria for suitability of widespread use – especially cross-cultural validation, minimal number of items, and free copyright. This tool, designed in 1990 by The EuroQol Group (comprised of international multidisciplinary researchers devoted to measuring health status), was revised in 2005 and validated in 2011 [26, 27]. The questionnaire includes five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and an overall visual analog scale. Importantly, it has been validated in patients with obesity and who have undergone obesity surgery, and is sensitive to change [28, 29]. In cases where the main goal of the study is related to QoL, however, an additional obesity-specific measure may be useful to assess this parameter in more depth.

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*Lifestyle and Behavior: Dietary Intake, PA and Sedentary Behavior, Sleep, Stress and Other Psychological Variables*

While human behaviors vary substantially and occur in a complex interplay with an individual's social and physical environments, characterization of specific behavior patterns is useful for predicting clinical outcomes. Discussed in this section are behaviors and lifestyle factors that affect energy balance, weight loss, and/or weight maintenance.

Dietary Intake

Minimal core set recommended variables:

- Dietary intake: EPIC-Norfolk FFQ or a region-specific validated FFQ (Food Frequency Questionnaire)
- Dietary quality: Dutch Healthy Diet index or region-specific validated index
- Emotional eating: DEBQ (Dutch Eating Behavior Questionnaire)

Expanded set recommended variables:

- Dietary intake: 3-day weighed food record

Eating behavior, defined as an individual's food and beverage consumption and habitual eating patterns [30], is a complex and important modifiable behavior that directly affects weight and nutritional status through the lifespan. In obesity, assessment of eating behavior is necessary given the dual burden of disease and potential undernutrition. Obesity interventions that target eating behavior mostly aim to decrease energy intake to induce negative energy balance – a necessary condition for weight loss. Modification of dietary intake is a well-known requirement for successful treatment of adult obesity [31]. The benefits of dietary interventions for obesity go beyond weight loss, since a body of evidence shows that changes in dietary quality per se may decrease the risk of various comorbid health conditions and even reduce all-cause mortality [32, 33]. Dietary intake constitutes a critical factor that interfaces with genetic heterogeneity and metabolic phenotypes, resulting in different health outcomes; for example, dietary fat intake can interact with genotype and/or phenotype to affect the risk of obesity [34, 35]. In addition, dietary fatty acid exposure can also interact with sex and genes together to predict the development of the metabolic syndrome [36, 37].

Many dietitians and nutrition scientists recognize the need to move from population-based nutrition to personalized subgroup-based nutrition [38]. Obesity is highly heterogeneous, so personalized or targeted interventions are warranted [39] but a major challenge is to determine which diet-related variables stratify individuals into groups that will respond to a given intervention.

For all adult trials on obesity interventions, regardless of whether they focus on diet, the OBEDIS group recommends assessing both dietary intake and overall diet quality. The OBEDIS group acknowledges, however, the particular difficulty of identifying dietary assessment tools applicable to the broad range of cultural and geographic groups across Europe. While obtaining data on energy, and macronutrient and micronutrient intake is a major objective, the various assessment tools that exist are each appropriate for a specific country or region.

Dietary intake is a detailed account of which foods and beverages are consumed, and in what quantities, during a set period of time. Initiatives exist (beyond the scope of these guidelines) that propose the most appropriate dietary assessment method in order to collect good quality dietary data, depending on the study objectives. The group recommends assessing this parameter in the minimal core set using a food frequency questionnaire (FFQ); the experts put forth the EPIC-Norfolk FFQ for consideration [40], while noting that the FFQ used in each trial should be validated according to the country in which it is being used. A 3-day weighed food record is appropriate for detailed studies where greater insights and links to biological readouts are required; such an assessment may capture short-term changes as a result of intervention. In the expanded set of variables (or depending on the study question)

the experts recommend the use of a 3-day weighed food record, which is more suitable for detecting the effects of an intervention. Reviews like Dao et al. [41] can help researchers select and implement the most appropriate dietary assessment method(s) to collect high-quality dietary data.

The group also recommends in the minimal core set an assessment of dietary quality, while acknowledging that the healthy eating indices applicable in Europe are linked with country-specific dietary guidelines and guidelines for PA. The Dutch Healthy Diet index [42, 43] was cited as a useful tool; however, the experts emphasize that the index used in a given trial must be adapted according to local guidelines and habits. The group also notes that in some contexts, it is important to use additional measures for tracking specific components of diet: for example, fiber intake or sugar-sweetened beverage consumption or the consumption of processed food.

The group agrees the nutrition community should invest in the design and validation of assessment tools for dietary intake (included validated smartphone apps) that improve upon the ones currently available. Dietary intake assessment is highly challenged by the lack of accurate biomarkers, particularly in relation to energy intake and macronutrient intake, whilst micronutrient status may be more feasible.

Biomarkers of dietary compliance were discussed by the OBEDIS experts. Such biomarkers are required to provide subjective insight in relation to habitual diet, as well as compliance to dietary interventions. However, those currently available have inherent limitations; for example, serum fatty acids only provide a short-term and limited assessment/reflection of dietary fatty acid intake. These biomarkers are not recommended for the minimal core set, but the experts note the critical importance for trials with free-living interventions of having an objective measure of compliance to identify nonresponse due to either noncompliance or lack of biological response.

When faced with stress, individuals exhibit differences in eating patterns: approximately 40% increase and 40% decrease their energy intake, while around 20% do not change [44]. Regardless of whether overall energy intake is increased, however, stress begets a shift toward choosing foods higher in sugar and fat. Hyper-palatable foods may act as a distress coping mechanism, particularly in those who have previously associated intake with relief [45]. Dieting constitutes a risk factor for emotional eating, since stress and negative affect can be consequences of energy restriction, and paradoxically, may lead to food-related coping strategies [46]. There may also be a biological basis for emotional eating, as individuals who exhibit this pattern demonstrate a blunted hypothalamic-pituitary-adrenal axis response to cortisol that leads to increased food intake [47].

Emotional eating is associated with current and prospective weight, and interacts with perceived stress, negative life events, and short sleep duration [47]. Greater weight loss success has been associated with decreased emotional eating score during a behavioral weight loss program [48]. Eating in response to distress may also influence the timing of meal consumption – and because recent studies have indicated that meal timing in relation to sleep phase is an important factor for weight regulation, clinical trials should capture individuals' tendency toward emotional eating. The recommended tool for assessing these behaviors in the OBEDIS minimal core set is the Emotional Eating Subscale of the Dutch Eating Behavior Questionnaire (DEBQ) – a clinically relevant questionnaire with good validation [49].

PA and Sedentary Behavior

Minimal core set recommended variables:

- PA: PA levels via accelerometry
- Sedentary behavior (SB): week day time and weekend day time via accelerometry; Paffenbarger Physical Activity Questionnaire

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- Physical fitness: cardiorespiratory fitness (CRF) via 6-min walk test and muscle strength via Southampton grip-strength measurement

Expanded set recommended variables:

- CRF: Chester step test

PA is any bodily movement produced by the contraction of skeletal muscles that results in energy expenditure (EE) above resting levels [50], while exercise is a subtype of PA: one that is planned, structured, repetitive, and designed to improve or maintain physical fitness, physical performance, or health [50].

PA helps adjust energy balance in those with obesity. Yet when diet is held constant, individuals in different BMI categories may experience different effects of PA on weight [51]. Overall, studies report inconsistent results on how increased PA (including exercise training) affects weight loss; however, an inverse association has been shown between PA and long-term weight gain [52], although it is recognized that relatively high levels of PA might be required. There is general agreement that a major benefit of PA in subjects with obesity is prevention of weight regain after weight loss [53].

Studies show PA attenuates many health risks that are associated with overweight or obesity, and importantly, numerous health benefits result from increased PA even with no weight loss or only modest weight loss [54]. Current evidence indicates that PA, at levels that are feasible to perform in subjects with overweight or obesity, only results in modest weight loss [52].

SB is defined as any waking behavior characterized by an EE equal to or lower than 1.5 metabolic equivalent tasks (or MET, with 1 MET representing EE by a subject at rest, sitting); this includes behaviors carried out while sitting, reclining, or lying [55]. Independent of PA levels, SB is associated with a higher risk of cardiometabolic disease and other complications. Decreasing SB is promoted in parallel with interventions that aim to increase habitual PA [55].

The OBEDIS group agrees on the importance of including both objective and subjective measures of PA and SB in each clinical trial. Objective data on both of these can be gathered most commonly using an accelerometer – a type of movement sensor that is feasibly used in large-scale studies to quantify PA intensity and duration as well as SB duration, including breaks in sedentary time, with minimal inconvenience to the participant. The group recommends this method while noting several limitations: when worn on the hip, accelerometers typically miss upper body movement; neither do they provide data on body posture nor data in cycling or aquatic activities [56]. The required accelerometer data comprises PA level as well as week day time in SB and weekend day time in SB. A subjective measure of PA and SB is also needed to add important information, such as the specific types of activities performed, the perceived level of exertion during exercise, and additional information about the context (place, time) of the PA. For these purposes, the group put forward a short questionnaire called the Paffenbarger Physical Activity Questionnaire. This widely used instrument is available in multiple languages and has ten questions that focus on moderate-to-vigorous PA, ranging from common activities such as stair climbing and walking to specific leisure activities [57].

In addition to PA and SB, physical fitness is an important patient characteristic that may also relate to outcomes of the intervention(s). Physical fitness is a physiological attribute determining a person's ability to perform muscle-powered work, and it has been defined as "the ability to carry out daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and respond to emergencies" [52]. One major component of physical fitness is CRF. High CRF is associated with greater longevity and reduced cardiovascular risk in all BMI categories [58, 59].

While the usual measure of CRF is maximal oxygen uptake ($VO_2$ max, or maximal aerobic power) during an exercise test [60], requirements for specialized equipment and expertise

render it impractical for the minimal core set. The OBEDIS experts instead recommend the use of the 6-min walk test [61], a field submaximal exercise test for assessment of physical function that requires a 30-m hallway and no specialized training or equipment. The test measures the distance an individual can quickly walk on a flat, hard surface over a period of 6 min, and it can be used to predict $VO_2$ max [62, 63]. The expanded set, however, may include the Chester step test as a measure of CRF: in this validated assessment of aerobic capacity, the participant is asked to step on and off an elevated platform in time with an audible metronome beat [64].

Another important component of physical fitness is muscular fitness. A measure of muscle strength, as an important component of muscular fitness, is therefore also recommended for the minimal core set, since the evidence in aggregate shows that muscle strength is associated with reduced mortality in all BMI categories and that resistance training (designed to increase muscle strength), even without weight loss, improves health risk [53]. More importantly, weight loss treatments may be associated with decreases in muscle strength, especially if the treatment does not include exercise. The Southampton grip-strength measurement is chosen for this purpose [65].

Given these recommendations, the group notes an added value of the assessment methods in the minimal core set: some of the chosen methods are useful for assessing several variables. This is the case for the use of accelerometers to assess both PA and sleep behaviors; grip strength to measure both muscular fitness and (in the expanded set) sarcopenia; and the 6-min walk test to predict CRF.

Habitual PA, SB, and physical fitness all must be measured at baseline (before any exercise training or intervention occurs) and at the end of an intervention; in trials longer than 6 months, these variables should be measured every 6 months.

Sleep

Minimal core set recommended variables:

- Sleep duration and timing
- Presence of sleep apnea: STOP-BANG

Expanded set recommended variables:

- Sleep duration and timing: accelerometry

Sleep is influenced by the circadian clock – a self-sustained molecular oscillator, which aligns endogenous rhythms with daily exogenous signals to coordinate metabolism and behavior [66]. Ample data show mistimed sleep contributes to "chronodisruption" [67] or "circadian-phase misalignment" [68] and promotes weight-related pathologies [69, 70].

Commonly, sleep disruption occurs because of atypical work schedules: night shift work patterns are associated with the risk of overweight/obesity – especially abdominal obesity – and permanent night shifts appear to confer a higher risk than rotating night shifts [71]. A lesser degree of chronodisruption called "social jetlag," however, can result from social activities and has been associated with an increased BMI [72]. Given these data, the OBEDIS group recommends systematically recording whether individuals work on atypical schedules (specifically: the presence of night shift work and permanent night work), and whether they experience social jetlag. Although the Munich Chronotype Questionnaire (MCTQ) is sometimes used for these purposes, the OBEDIS group recommends a shorter custom assessment (see supplementary material) for patients to self-administer. Quantitative sleep data acquired from an accelerometer may be used (as part of the expanded set) in trials where resources allow.

Prolonged wakefulness and sleep deprivation are hallmarks of modern lifestyles. Across cross-sectional and longitudinal studies, individuals' sleep duration shows a somewhat inconsistent pattern of association with obesity [73]. Experimental data suggest that sleep

restriction increases food intake and alters EE [74]. The OBEDIS group advocates for a basic assessment of sleep duration in the minimal core set. Specific questionnaires exist that capture various dimensions of sleep, including sleep duration, but many are subject to copyright restrictions and/or lack validated translations into different languages. For assessing sleep duration, the OBEDIS group recommends a custom, self-administered questionnaire (shown below).

In individuals with obesity, disordered breathing during sleep is prevalent. Well-documented is the idea that obstructive sleep apnea (OSA) overlaps with obesity-related risks [75] and impacts metabolic risk [76]. Use of the OSA therapy continuous positive airway pressure (CPAP) may also change energy balance or metabolism [77], with potentially positive effects on glycemic control [78]. The presence of OSA and the use of CPAP should therefore be assessed. While the gold-standard objective measure of OSA is the apnea-hypopnea index with nocturnal polysomnography, the OBEDIS group recommends subjective assessment using a brief questionnaire called the STOP-BANG [79]. This questionnaire, which is freely available, was created to screen for symptoms of OSA in surgical patients and in all individuals. It can be completed in approximatively 1 min and has good predictive ability for mild, moderate, and severe OSA [80]. CPAP use may be assessed using a custom questionnaire item.

Stress and Other Psychological Variables

Minimal core set recommended variables:

- Perceived stress: Perceived Stress Scale (PSS)

Previous research has indicated the necessity for simultaneous assessment of sleep and stress in trials on obesity [81]. Poor sleep and emotional stress are predictors of incident obesity and may have an additive role [82]. Not only does perceived stress associate with BMI, waist circumference, and serum triglyceride level [83], but also, those with poor sleep and incident obesity appear to have the greatest emotional stress and the shortest subjective sleep duration [84].

Perceived stress is the degree to which situations in life are appraised as stressful by the individual. The expert group recommends subjective assessment of individuals' stress levels via the PSS [85]. As the most widely used psychological instrument for measuring the perception of stress, the scale includes direct queries about a patient's current levels of experienced stress. The items on the questionnaire are general, easy to grasp, and require a total of 2 min for completion. An additional advantage of the tool is the availability of validated versions in many languages.

*Subject Characteristics: Anthropometry, Body Composition, EE, and Hormonal Status*

All trials involving individuals with obesity include measures of participants' characteristics, including anthropometric measures, body composition, and/or EE. Aspects of hormonal status are also important characteristics to consider in trials, as detailed below.

Anthropometry, Body Composition, and EE

Minimal core set recommended variables:

- Weight and BMI
- Anthropometry (waist, hip, neck circumference)
- Fat mass and fat-free mass: dual energy X-ray absorptiometry (DXA)

Expanded set recommended variables:

- EE: open-circuit indirect calorimetry

The WHO defines obesity as "a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired" [86]. In clinical trials on obesity, researchers must quantify this increased adiposity in a way that allows comparisons between

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subjects, and over time in the same subject. Patient-reported data are not adequate for these purposes. The OBEDIS experts acknowledge that the study of body composition assessment methods is rapidly moving forward, far beyond basic calculations of BMI, and this may present an important opportunity for identifying precise body composition subgroups that may respond predictably to an intervention.

BMI – calculated from measures of a subject's height and weight – is the simplest and most frequent way of classifying an individual as underweight, normal weight, overweight, or obese, and is therefore recommended for inclusion in the minimal core set. Although the relationship between BMI and all-cause mortality has been confirmed [87], BMI as a "surrogate measure" of obesity does not directly capture large interindividual variation in excess adipose tissue. This makes BMI misleading for individuals who exhibit differences in proportions of lean body mass and fat mass (for instance, elite athletes and those with sarcopenia) [88]. Indeed, going beyond a patient's BMI adds valuable additional information about health [89–91]. Recent work shows it is the excess fat that constitutes a risk factor for a range of comorbid diseases: type 2 diabetes (T2D), ischemic heart disease, hyperlipidemia, sleep apnea, certain forms of cancer, and others [92].

Further anthropometric measures – waist, hip, and neck circumferences – are recommended in all clinical trials focusing on obesity, as ways to assess subjects' fat distribution. Ample evidence shows increased central or android fat distribution (assessed via waist-to-height ratio) is associated with greater risk to health [93, 94] compared to more peripheral or gynoid fat distribution. Adding waist circumference to other anthropometric measures is valuable for predicting metabolic phenotypes [95] and a rationale even exists for how variables that include waist circumference directly affect intervention response [96]. Waist-to-hip ratio predicts cardiovascular morbidity and mortality in those with obesity and T2D [97–99]. In addition, neck circumference has been shown valuable for identifying excess body weight [100, 101] and associates with the presence or severity of different comorbidities [102–104].

Many options exist for more precise measurements of body composition. Available methods, each with their pros and cons, include bioelectrical impedance analysis (BIA), magnetic resonance imaging, computerized tomography scan, air displacement plethysmography (BOD POD), underwater weighing, and DXA. Body weight, BMI, or variables derived from weight alone are unable to distinguish between fat-free mass and fat mass, yet these components have specific medical relevance: increased fat-free mass may be found in athletes, who are not obese despite a high body weight/BMI; decreased fat-free mass is characteristic of a pathological condition called sarcopenia (or sarcopenic obesity), which needs to be detected; and fat-free mass is a determinant of EE (see below). Meanwhile, the visceral component of total body fat has unique physiological characteristics, which influence disease-related processes in the body [105]. Increased visceral adipose tissue in those with obesity is associated with an increased risk of metabolic (glucose intolerance, T2D) and cardiovascular disease (CVD).

The OBEDIS group agrees that precisely capturing the amount and distribution of body fat is required for the minimal core set of variables. At present, however, no easy methods exist for assessment. BOD POD and BIA are two-compartment models (capturing fat mass and fat-free mass), while DXA is a three-compartment method (dividing the body into fat mass, lean body mass, and bone mineral content). This relatively accurate, noninvasive method enables rapid measurement of percent body fat, although it remains dependent on several assumptions (namely, the constancy of fat-free mass composition) and exposes participants to a small dose of ionizing radiation. But because DXA is validated for those with obesity, it is the OBEDIS group's recommendation.

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The use of DXA, a method that requires specialized equipment, is an exception to the general principle of simplicity in the OBEDIS minimal core set, but the group agrees that the potential predictive value of DXA-generated data is sufficiently great to enable rapid progress in the field. In cases where trial limitations in budget, equipment, or expertise render it impossible to incorporate DXA, the group recommends BIA or plethysmography as an alternative to measuring fat mass and fat-free mass. Overall, the expert group concurs that the field needs more research and development on easy and inexpensive tools for precise measurements of body composition.

Energy balance in obesity may be important for prediction of intervention outcomes [106]. EE is one component of energy balance, and hence, highly relevant for evaluating body weight changes. A subject's EE is likely to change in the course of an intervention, as it can vary with changes in body weight [107] or fat-free mass; changes in the composition of body weight gained or lost; adaptive thermogenesis (thyroid hormones, sympathetic nervous system, brown adipose tissue); and pharmacologic agents [108].

Twenty-four-hour EE is the sum of basal metabolic rate (BMR), adaptive thermogenesis (food, thermoregulation, etc.), and PA/exercise thermogenesis; it can be measured in free-living individuals with doubly labelled water, but this method is expensive and restricted to a few specialized centers. Resting EE can be measured by indirect calorimetry – but again, this method is not feasible in all centers, and accurate measurements require very strict conditions (overnight fast; no PA prior to measurement, requiring that measurement is done on inpatients; thermoneutrality, etc.). BMR varies according to body composition (mainly fat-free mass), and hormonal status (thyroid hormones, sympathetic nervous system/catecholamines, brown adipose tissue). BMR can be predicted with equations based on body weight or body composition:

BMR = a • body weight + b (where a and b are different for males and females); or
BMR = a • fat-free mass + b (where a and b are identical for both males and females).

Expressing results as kcal expended per kg body weight or per kg fat-free mass invariably underestimates values in overweight/obese individuals and should not be used. Results should instead be expressed as percentages of predicted value based on validated equations (Mifflin Jeor or others; see supplementary materials).

EE is an essential feature for metabolic phenotyping, but direct measurement of EE should be included in the OBEDIS expanded set rather than in the minimal core set. The energy requirements of individuals included in a study can instead be predicted based on the BMR prediction equations above, multiplied by a PA level of 1.1–1.9 for PA level [109]. Measurement of EE may nonetheless be highly relevant in some mechanistic studies, since variations in BMR may occur during interventions due to changes in body weight/fat-free mass (body composition-dependent changes) and changes in tissue (fat-free mass) metabolic activity. Such measurements are best done by open-circuit indirect calorimetry using standardized procedures. Simultaneous measurement of body composition is strongly recommended for data interpretation.

Hormonal Status

Minimal core set recommended variables:

- Thyroid-stimulating hormone (TSH): third generation TSH assay
- Menopausal status (in females), current medications

Expanded set recommended variables:

- Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (in women)
- Androgens: mass spectrometry-based assays

Endocrine and gynecological system alterations can occur in obese individuals, and many different measurements give insights into these complications; these include markers of thyroid status, that can be related to regulation of energy balance, and markers of gonadal axis in both sexes [110, 111]. Among these hormones, the group recommends the measurement of TSH to assess thyroid function; FSH and LH may be used in the expanded set to confirm, when necessary, menopausal status in women. In both males and females, androgens might provide valuable additional information; however, should their measurement be included, it should be mandatorily accomplished by mass spectrometry-based assays [112].

A panel of peptides and cytokines is usually characterized in studies focusing on obesity, including leptin, as a marker of body fat; adiponectin, as a predictor of metabolic dysregulation; tumor necrosis factor alpha and interleukin-6, as markers of inflammation; ghrelin, as a hunger signal; glucagon-like peptide-1 and peptide YY as a measure of satiation signal function. Consequently, measurement of each of these hormones may be included in clinical trials for obesity, according to the specific research question. However, preanalytical and analytical issues related to the measurement of most of these substances dramatically affect the consistency of the results. Assay standardization and harmonization among labs are urgently needed to generate normative values. In addition, mass spectrometry-based assays for the quantitative and qualitative (isoforms, posttranslational modifications, etc.) assessment of peptide hormones are regarded as promising for their thorough characterization; however, the introduction of such techniques into routine clinical labs does not appear feasible in the near future.

*Complications: T2D, Cardiovascular Risk, Liver Disease, and Other Long-Term Obesity Complications*

The many complications of obesity are of interest because of their associations with poorer overall health and with more complex clinical management. These comorbid conditions, and the medications taken to ameliorate them, may affect response to intervention. The major comorbid conditions in obesity are addressed in this section.

Type 2 Diabetes

Minimal core set recommended variables:

- Fasting glycemia (two measurements)
- Hemoglobin A1c: HPLC-CE or HPLC-MS
- Fasting insulin and insulin-derived insulin sensitivity indices
- Family history of diabetes

Expanded set recommended variables:

- Hyperinsulinemic-euglycemic clamp

Obesity is associated with alterations in normal endocrine and metabolic functions, leading to a number of pathological conditions: among these, T2D – affecting around 30–40% of obese individuals [113]. Although metabolically healthy obese individuals exist, epidemiological evidence shows a high incidence of metabolic syndrome in those with obesity [114]. In patients with both obesity and T2D, interventions that lead to successful weight management substantially improve outcomes related to metabolic control [115]. Response to interventions may also be modified by the use of various antidiabetic medications, which might affect weight either positively or negatively [113].

The OBEDIS group recommends including several T2D-related variables in all clinical trials on obesity interventions: two measurements of fasting plasma glucose for assessing T2D, hemoglobin A1c (HbA1c) for screening and monitoring of glycemic control, and fasting insulin as a surrogate marker for insulin resistance as well as indicating the secretory capacity of the beta cells. HbA1c measurement is recommended both for assessing blood glucose

control in people with diagnosed T2D, and for diagnosing the disease or its early stages ("prediabetes"). The group agrees that C-peptide could take the place of fasting insulin as a marker of remaining insulin secretion. Further, insulin-derived insulin sensitivity indices should be calculated [116]: Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) represents the presence and extent of insulin resistance; whereas HOMA-beta reflects beta cell function. Both calculations are mainly used in clinical studies. Several additional factors related to T2D are important to know – the individual's family history of T2D (to indicate possible genetic risk), as well as current medication and dosages. Recommendations on specific methods for each of these parameters are detailed in Table 1. There are more invasive measures of insulin secretion and sensitivity (hyperinsulinemic-euglycemic clamp, intravenous glucose tolerance test, etc.) and more comprehensive measures of key aspects of metabolic flexibility, but these tests are not feasible for all large-scale clinical interventions.

Cardiovascular Risk

Minimal core set recommended variables:

- Smoking habits
- Blood pressure and heart rate: automatic blood pressure device
- Total cholesterol, high-density lipoprotein cholesterol, triglyceride
- Inflammation: C-reactive protein (CRP)
- Heart electrical activity: 1- to 5-min electrocardiography (ECG)
- CRF: 6-min walk test

Individuals with obesity often exhibit disordered vascular and heart function, and an elevated risk of CVD. Intervention strategies may be modified by the presence of CVD or its various risk factors [117].

Most CVD risk is driven by age plus three other major CVD risk factors in addition to diabetes; namely, high cholesterol, high blood pressure, and smoking, together accounting for about 80% of population-attributable risk [118]. Cardiovascular risk algorithms exist [119–122], but due to the imprecise estimates they provide and the factors that are included in these algorithms, they may not prove useful in the context of short-term interventions for obesity. While risk scores were not included in the minimal core set, the OBEDIS group proposes measuring smoking status as well as several parameters related to vascular and cardiac function, which may help, now and in the future, to stratify individuals in order to optimize intervention outcomes.

Assessment of current smoking habits in the minimal core set is achieved using two custom questions: number of cigarettes per day and duration of smoking.

Related to vasculature (atherosclerosis), the group recommended obtaining data on selected serum biomarkers: total cholesterol, high-density lipoprotein cholesterol, triglycerides, and high-sensitivity CRP (hsCRP). Fasting hsCRP is included as a surrogate marker of inflammation, and CRP appears to be one of the best-established CVD risk markers [123–127] while having the advantage of being analyzed in a standardized and relatively inexpensive way. Additional measures relevant to CVD, including blood glucose and insulin concentrations, which capture insulin resistance and beta-cell function [128], are covered in the T2D section. The adipokine interleukin-6 also seems promising [129], and is recommended for the expanded set, with the recommendations about its measurement proposed in the supplementary materials.

Among the variables related to cardiac function that could potentially modulate response to interventions for obesity, the following are recommended by the OBEDIS group for assessment: blood pressure, cardiopulmonary function, and electrical activity of the heart as measured by ECG. It is well-established that blood pressure may be modified by certain interventions, with weight loss causing important decreases in blood pressure [130]. Despite

somewhat limited reproducibility for automatic blood pressure devices, the group recommends using these in order to reduce human error. As an indirect but validated way to assess CRF, the group identifies the 6-min walk test [131–134] rather than the determination of maximal aerobic capacity ($VO_2$ max), which is expensive and has a poor association with fat mass and the loss thereof [135–137]. Finally, the group recommends performing a 1- to 5-min ECG as detailed in Table 1. Although not fully validated for hard endpoints, 1- to 5-min ECG is often used in small intervention clinical trials [138] and predicts cardiovascular death; thus, it may be used as a noninvasive means of risk stratification [139].

Assessing the presence of OSA is also essential, since OSA is associated with hypertension and an increased risk for CVD and T2D [140]. These measures are detailed in the section on sleep behaviors.

Liver Disease

Minimal core set recommended variables:

- Nonalcoholic fatty liver disease (NAFLD) fibrosis score (NFS) and fibrosis-4 index (FIB-4): ALT, AST, GGT, platelet count, and albumin from blood
- Alcohol intake: WHO AUDIT questionnaire

Obesity comes with an increased risk of different forms of NAFLD: steatohepatitis (increased liver triglycerides), possibly progressing to fibrosis (irreversible scarring of the liver) [141]. Tracking the occurrence of these liver conditions is deemed important for the minimal core set, as these conditions may affect a subject's response to intervention. To detect fibrosis noninvasively, most guidelines [142, 143] recommend using the FIB-4 or the NFS, both of which are low cost and straightforward.

Given the relationship of alcohol intake to liver disease, the OBEDIS group also recommends a brief assessment of alcohol intake using the WHO's AUDIT questionnaire [144].

Other Long-Term Obesity Complications: Osteoarthritis and Cancer

Minimal core set recommended variables:

- QoL: EQ-5D-5L

Expanded set recommended variables:

- Pain-related physical functioning: WOMAC VA 3.0

Over the long term, besides the significantly increased risk of CVD and T2D, obesity confers an increased risk for several other conditions: major medical complications (cancer), and functional complications (arthrosis). Data on these conditions are part of a comprehensive assessment of the obesity phenotype.

Obesity increases the risk for osteoarthritis, a degenerative condition of joint pain and dysfunction [145]. The presence of this condition is normally assessed through specific self-administered validated osteoarthritis questionnaires. But (pain-related) physical functioning is the most important factor related to osteoarthritis that may change with an intervention [146], and the OBEDIS group decided this factor is adequately assessed by an overall QoL questionnaire. The addition of a specific osteoarthritis questionnaire to the QoL questionnaire recommended above would provide marginal improvement in predictive ability. In the expanded set of variables, however, investigators may want to include the Western Ontario and McMaster Universities (WOMAC VA 3.0) osteoarthritis index, a self-report questionnaire covering hip and knee osteoarthritis [147].

Those with obesity experience cancer at a higher rate than the general population [148] and a patient's history of cancer may be relevant to the exclusion criteria in a clinical trial. Once a patient is enrolled in a trial, however, investigators may want to track cancer occurrence. The OBEDIS group decided that including cancer data in the minimal core set was not necessary; because of the long delay before cancer occurrence, the following data need only

be collected in cohorts with more than 5 or 10 years of follow-up: date of diagnosis and cancer type (according to the International Classification of Diseases). The data should be obtained from medical records where possible and validated by independent medical experts.

*Future Medical Practice*

Several areas of analysis have the potential to advance precision medicine within the field of obesity: tissue phenotyping, as well as genetics, and omics.

It is already known that researchers may gain insights into the molecular underpinnings of variability in weight loss by precisely analyzing different body tissues in individuals with obesity [149]: apart from components of blood, urine, and stool, this may include biopsies and/or assessments of white adipose tissue, skeletal muscle, and the liver. Precise phenotyping of patients by tissue analysis is a promising area within the field of obesity; some studies have successfully used this approach to identify subgroups of participants that have increased susceptibility to obesity or that will predictably respond to a treatment [150, 151]. However, the complexity of these methods rules them out for the minimal core set at present.

In the future, patients may be stratified based on the presence of specific genetic markers. Data from family, twin, and adoption studies show that both body weight (40–70%) and body fat distribution are highly heritable [152]. Heritability also seems to play a role in the nature, magnitude, and/or timing of response to obesity interventions [153]: studies have shown genetic influences on dietary interventions [154, 155] and heritability of response to bariatric surgery (Roux-en-Y) [156]. Obesity-related gene expression may be attenuated by PA. This field is expected to advance rapidly over the next few years and zero in on very specific genetic markers for patient stratification.

Beyond human genes, advances in high-throughput technologies for analysis of biologic molecules have created the potential for defining the biological characteristics of those with obesity with great precision. New omics technologies enable examination, not only of a patient's genome, but also of complete sets of transcripts, proteins, and metabolites. Analyses that fall under the category of omics are those that provide "a comprehensive, or global, assessment of a set of molecules" [157]: genomics, epigenomics (reversible modifications of DNA or DNA-associated proteins across the genome), proteomics, metabolomics (small molecule types), microbiomics, lipidomics, transcriptomics, and others. Already, findings from omics studies have identified important avenues of research in obesity: for instance, epigenomic studies have mechanistically linked aspects of the environment before conception with the probability of becoming obese later in life [158, 159], while weight loss induced by gastric bypass surgery affects a patient's DNA methylation and gene expression profile [160].

The analyses mentioned above are key components of certain obesity intervention studies, depending on their aims. The OBEDIS group considered the pros and cons of including genetic and omics data, as well as tissue analyses, in the minimal core set for all obesity-focused clinical trials; the group concludes that at present, the ability of these tests to explain variability in weight loss is not great enough to justify the added costs. The group strongly suspects, however, that as costs fall and evidence increases, researchers will soon have adequate justification for including such analyses in all trials.

In anticipation of the probability that certain blood measurements may yield new insights in the near-term future, biobanking is highly recommended by the group – whole blood where possible, but at a minimum, samples of whole blood dried on paper. Dried blood spots are suitable for many potential future measurements, and also have the advantages of easy and low-cost collection and storage.

The OBEDIS group agrees that consent is another important issue to address for this field: a challenge is to develop SOPs around consent, which will allow sharing and reuse of

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omics and other data over the long term and as new discoveries are made. The group envisions a set of consent-related SOPs implemented across Europe, adapted to local circumstances.

## Conclusion

The expert consensus detailed herein represents a practical advancement in the field of obesity research – with the group members supporting the adoption of these variables in future clinical trials, collected systematically either before or both before and after intervention. The group fully expects to add further variables to this minimal core set as more data become available in each of the identified domains or remove variables if they do not impact differential treatment response. Basic and preclinical research should, of course, continue in tandem, building a larger context for informing better intervention strategies and identifying the appropriate adult patient groups for each specific intervention.

The translational potential of the work begun here is therefore of high value: over time, this project should enable more efficient convergence of evidence to support better care for those with obesity. The OBEDIS group sees the ability to pool datasets and compare very large numbers of trial participants as key to the advancement of "precision" or "personalized" medicine. In the future, when a clinician encounters a newly referred adult patient with obesity, he or she will be able to group the patient according to baseline characteristics and suggest a tailored intervention plan, backed by robust data.

The OBEDIS workshop and the resulting guidelines, achieved only through the support of EASO, represent an historic collaboration in the field of obesity in Europe. The experts welcome feedback that will help these measures to be widely adopted throughout the field.

## Disclosure Statement

K. Clément is a consultant for Danone Research and LNC therapeutics for work unassociated with the present study. M. Neovius has received advisory board fees from Itrim and Ethicon Johnson & Johnson. L. Tappy received a research grant from Soremartec Italy srl and speaker's fees from Soremartec Italy srl and Nestlé AG, Switzerland. No other authors have conflicts of interest to declare.

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## Author Contributions

All authors contributed to the guidelines described in this paper. M. Alligier and M. Laville led the initiative with J. Bouwman, K. Clément, and D. Langin. K. Campbell prepared the manuscript.

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