EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2026
EMA/126591/2026

Guideline on the clinical evaluation of medicinal products for weight management - Addendum on weight control in children

Draft

Draft agreed by the CVS Working Party	28 May 2026
Adopted by CHMP for release for consultation	15 June 2026
Start of public consultation	24 June 2026
End of consultation (deadline for comments)	31 October 2026

This guideline replaces Guideline on clinical evaluation of medicinal products used in weight control - Addendum on weight control in children (EMEA/CHMP/EWP/517497/2007).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	***Obesity, children, adolescents, overweight***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Guideline on the clinical evaluation of medicinal products for weight management- Addendum on weight control in children

Table of contents

Executive summary

This is the first revision of the *Guideline on clinical evaluation of medicinal products used in weight control - Addendum on weight control in children* (EMEA/CHMP/EWP/517497/2007).[1]

The Addendum should be read in conjunction with the Guideline on clinical evaluation of medicinal products used in weight management (EMA/CHMP/311805/2014).[2]

The Addendum provides guidance on the clinical investigation of medicinal products for weight management used in children and adolescents.

1. Introduction (background)

Overweight and obesity in children and adolescents have become a major health problem worldwide and their incidence is steadily increasing.[3] Changes to the addendum are introduced with the aim to align the addendum with the guideline for adults (where appropriate) and to reflect recent developments in this rapidly evolving field with respect to approval of new medicinal products for the treatment of childhood and adolescent overweight and obesity as well as clinical practice guidelines. When treating overweight and obesity in children and adolescents, there are not only specific ethical considerations, but also unique factors related to growth and development that should be thoughtfully considered.[4,5] Therefore it is requested to monitor body composition when feasible.

As overweight and obesity frequently persist in adulthood, they represent a risk factor for all obesity-related co-morbidities in later life. This emphasises the need for the development of effective treatments.

2. Scope

The focus of this paediatric addendum is on clinical investigation of treatment for weight management in children and adolescents.

The definition of overweight and obesity, suitable endpoints and specific methodological issues of clinical trials for treatment of weight management in children and adolescents are addressed.

3. Legal basis and relevant guidelines

This is an addendum to the *Guideline on clinical evaluation of medicinal products used in weight management* (EMA/CHMP/311805/2014).[2]

This addendum should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines.

All pertinent elements outlined in the current and future EU and ICH guidelines and regulations should be considered especially the following:

- ICH E11, Clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)
- Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/267484/2007)
- ICH E11A Guideline on pediatric extrapolation (EMA/CHMP/ICH/205218/2022)

- Reflection paper on investigation of pharmacokinetics in the obese population (EMA/CHMP/535116/2016)
- Clinical trials in small populations (CHMP/EWP/83561/2005)
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (CHMP/ICH/436221/2017)
- Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)
- Guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99)
- Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99) and Draft Guideline on non-inferiority and equivalence comparisons in clinical trials (EMA/301654/2025)

4. Definition of overweight and obesity in children and adolescents

A wide variety of definitions for childhood and adolescent overweight and obesity are in use. Recently, experts have advocated to differentiate clinical obesity from pre-clinical obesity.[6] Clinical obesity is defined as a chronic, systemic disease characterised by alterations in the function of tissues, organs, or the individual, resulting from excess adiposity. Pre-clinical obesity is seen as a condition with excess adiposity with preserved function of other tissues and organs. This distinction is important as the intensity of treatment is tailored to the extent of deleterious effects on tissue, organs and/or functionality and well-being of each individual. Therefore, trial subjects should be assessed in terms of impact of excess adiposity and be representative of the target population.

For the initial assessment of adiposity, the body mass index (BMI = bodyweight (kilogram)/ (height [metre]²) is used in adult populations and 25 and 30 kg/m² cut-off points are recognised internationally as a definition of adult overweight and obesity, respectively. BMI cut-offs based on pooled international data that link the accepted adult cut-off points to cut-off points related to age and sex for children should be used to define overweight and obesity in the paediatric population.[7, 8] Other anthropometric measures, in particular weight-to-height ratio (WtHR) may also be useful to identify excess adiposity in children or adolescents.[6]

5. Estimands and how to implement them in clinical trials

The scientific question(s) of interest, i.e. what the trial seeks to address, and consequently the target(s) of estimation (estimand) should be clearly specified. Trial planning, design, conduct, analysis, and interpretation must be aligned with the estimand. Reference is made to ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials (EMA/CHMP/ICH/436221/2017).

To adequately assess and understand the treatment effects, they need to be precisely described using the estimand framework as laid out in ICH E9 addendum (R1),[9,10] which, among other aspects, emphasises the importance of adherence to treatment and pre-specification of handling of intercurrent events. The nature of an intercurrent event dictates the strategy for how it should be handled. The estimand framework also highlights the importance of correctly addressing missing data, as well as carrying out sensitivity analysis to evaluate the robustness of the results.

5.1. Treatment condition

5.1.1. Non-pharmacological interventions

The previous attempt(s) of lifestyle therapy (nutritional, psychological and physical activity interventions etc.) without sufficient effect should be carefully recorded.

Lifestyle therapy should be offered as a background treatment for all interventions. The lifestyle therapy offered should be clearly described in the protocol both in terms of intensity and monitoring.

Lifestyle therapy should be offered to all participants in the trial. It is considered that the standardisation of food intake per se is not feasible.

A lifestyle therapy run-in phase is not mandatory but can be considered to harmonise the approach for lifestyle therapies that need to be implemented. The run-in phase should be short (no longer than one month), as participants will already have been exposed to various lifestyle therapies before initiation of drug treatment.

5.1.2. Pharmacological interventions

Trials should in general be randomised, double-blind and placebo-controlled. Although a placebo-controlled trial is more sensitive to show superiority, issues like drop out due to lack of efficacy and factual unblinding related to gastrointestinal adverse events are less of an issue in active-controlled than in placebo-controlled studies. As new treatments are becoming available, the use of placebo may pose ethical challenges as withholding active treatment may lead to substantial and potentially lasting increases in obesity severity. Imperfect blinding and knowledge of receipt of the intervention may also impact adherence to standard of care treatment.

An alternative to placebo-controlled trials is the use of active-comparator trials. Such trials typically aim to demonstrate non-inferiority, i.e. that an experimental treatment is not less effective than an active control by more than a predefined non-inferiority margin. However, these trials may require large sample sizes and may complicate the interpretation of efficacy and safety outcomes. In addition, in childhood and adolescent overweight and obesity, treatment effects are highly context-dependent, which poses challenges to the constancy assumption underlying non-inferiority trial designs. For these reasons, placebo-controlled trials remain the preferred option to allow for an accurate estimation of the efficacy and safety of new medicinal products. All trials should incorporate design features such as limiting the time of exposure to placebo, use of rescue medications, treatment withdrawal or tapering in the context of excessive weight loss. It should be prespecified in the protocol when tapering and use of rescue medication should occur and data on this is expected to be reflected in the summary of product characteristics (SmPC). Up-titration to the patient-relevant dosage and an upper dose limit with stop criteria for up-titration may be more appropriate than having different maintenance doses. Dose modifications should be possible for efficacy and tolerability (e.g. intolerable gastrointestinal symptoms).

5.2. Target populations

Because the underlying causes, health impacts, and effective treatment strategies for overweight and obesity differ markedly between children, adolescents and adults, age-specific approaches are required when designing and implementing weight management interventions.[11] Therefore, the results of studies in adults can normally not be extrapolated to adolescents, nor can the results from adolescents be expected to be possible to extrapolate to younger children.

Puberty significantly influences both the physiological consequences of overweight and obesity and the effectiveness and approach to their treatment, as changes in body composition, hormones, and metabolic processes during this developmental period affect weight trajectory and health outcomes.[8] Therefore, in this addendum, the following two categories are used to define subgroups of the paediatric population:

1. Pre-pubertal;
2. Pubertal: from Tanner stage 2.

The trial design (including the inclusion and exclusion criteria) and execution need to aim for a sufficiently diverse sample to allow generalisability to the target population for the indication under investigation. As the field is still very much evolving, Body Mass Index (BMI)-related metrics remain the most used measures to classify childhood and adolescent overweight and obesity.

Inclusion criteria: It is recommended that separate trials for pre-pubertal (up to Tanner stage 2) versus pubertal children (from Tanner score 2) are performed or at least the randomisation is stratified for this prognostic factor. This is based on the considerable physiological changes in body composition, metabolic responses and behaviour occurring during puberty.[12] Trials should be conducted in children or adolescents with overweight and at least one weight-related coexisting condition or with obesity and whom have a documented history of lifestyle therapies that did not achieve sufficient weight management. Children and adolescents of all ages for which the treatment is intended should be presented in sufficient large proportions in the study.

Exclusion criteria: Children and adolescents with monogenic or syndromic obesity should be excluded from pivotal trials when additional safety concerns are anticipated or when differences in terms of efficacy are expected. In such cases, dedicated clinical trials are warranted. Overlap of adaptation of medication for glucose control immediately after randomisation and initiation of the investigational medicinal product (IMP) should be avoided. This means that the upper HbA1c level at inclusion should be in line with treatment guidelines to ensure that type 2 diabetes mellitus patients with adequate glycaemic control will be enrolled.

5.3. Efficacy variables (or endpoints) to be obtained for each patient

The recommended primary endpoints in paediatric obesity trials are BMI-related metrics. Multiple additional BMI-related metrics should be reported as secondary endpoints to allow comparisons across trials.

Albeit BMI-related metrics are not ideal, as they do not differentiate between fat and lean mass and do not capture clinical implications of excess adiposity, they are still the most practical in use.

As primary endpoints, BMI-related metrics (expressed as percent change from baseline), BMI percent of the 85^{th}, 95^{th} percentile (or BMI percent of other cut-off points for overweight and obesity, depending upon which growth references are used) or percent of the median BMI can be used. Age- and sex-adjusted metrics should be used, with preference for the WHO charts. Other anthropometric measures such as waist circumference and WtHR should be included as secondary endpoints as they reflect the effect on visceral adiposity better than BMI. To confirm the change in adiposity, imaging techniques (e.g. dual energy x-ray absorptiometry (DXA) or magnetic resonance imaging) capable of quantifying body fat mass and distribution should be included when feasible as relevant secondary endpoints to ensure that any weight reduction is caused primarily by a reduction in fat content and not in lean body mass. In addition, muscular functionality tests may be included if feasible. Bioelectrical impedance is still insufficiently standardised and too variable for use in the context of clinical trials. Further relevant secondary endpoints, such as validated age-appropriate psychosocial and/or personal-

reported outcomes, metabolic, cardiovascular and mechanical biomarkers, should be considered. In particular, measures of quality of life should be included as secondary endpoints.

The population-level summary should be a difference in means at least for the BMI endpoints and a difference in proportions for the binary endpoints.

If another primary endpoint is used, it should be sufficiently justified and it is recommended to be discussed in advance within a CHMP scientific advice procedure.

5.4. Strategies to address intercurrent events

Different estimands may be warranted depending on the clinical question of interest and the resulting clinical trial design, e.g. binary or continuous endpoint, active or placebo-controlled trial, non-inferiority or superiority objective.

Relevant intercurrent events to be considered include, but are not limited to, treatment discontinuation, changes in medication such as use of additional or alternative weight management medications (e.g. metformin, insulin, GLP-1 receptor agonists, orlistat), changes in background therapy (e.g. changes in physical activity and diet) and changes in dose. For the management of intolerable GI symptoms, the dose may be delayed, down-titrated, or held, as needed. Of note, temporary study drug interruptions will be permitted if participants undergo a procedure unrelated to the study that requires temporary suspension of study treatment or experience adverse events that are expected to improve. Concomitant medication/interventions should be differentiated from prohibited drugs and specified under which conditions they might be used. Given that some approved antidiabetic medicinal products are associated with a weight-modifying effect in either direction, this potential effect should be anticipated as much as possible and a strategy to handle this intercurrent event defined and justified in the protocol. In addition, depending on the population selected, death might require incorporation into the estimand definition. Dose modifications, temporary study drug interruptions, treatment discontinuation, use of prohibited medications and death should be considered as intercurrent events. The frequency and timing of all intercurrent events need to be compared between treatment groups.

For superiority objectives, the intercurrent event of treatment discontinuation should be handled with a treatment policy strategy addressing the treatment effect regardless of discontinuing treatment. The number of patients who discontinue treatment is in general high in obesity trials and every effort should be made to keep patients who discontinue treatment within the study for further measurements. Similarly, a treatment policy strategy is relevant for changes in background therapies, which is equivalent to considering them as part of the treatment regimen of interest. Handling the use of alternative weight management medications/rescue medications that are not considered part of the treatment regimen of interest (i.e. therapies that could not be co-administered with the IMP), on the other hand, is challenging and there might not be the most appropriate strategy to address them as several strategies are relevant: a treatment policy strategy reflecting the outcome in clinical practice could be appropriate, but a hypothetical strategy, in which alternative medication is assumed not to have been an option, might be more relevant. If rescue medication is used more often in the comparator arm, the estimand using a treatment policy strategy might lead to the smaller treatment effect estimate than the one using a hypothetical strategy (and vice versa). It is recommended to prespecify expectations on the frequencies of important intercurrent events and by default compare the patterns between the arms at the analysis stage to understand whether an imbalance could have unexpectedly driven the conclusion. Supplementary analyses, possibly aiming at other targets of estimation, should be performed to assist in the interpretation of trial data.

For non-inferiority objectives, particular attention should be given to intercurrent events that might make the investigated treatments appear more similar or where participants are expected to do considerably better after the intercurrent event, for example initiating / changing additional medications (e.g., the background medication), or switching from, modifying, or discontinuing the assigned treatment. The intercurrent event of switching from the assigned treatment to the active comparator or new IMP should not be handled with a treatment policy strategy. This is especially important when the rates of intercurrent events differ between arms, and such events are more common on the test arm. In these settings, a continuous endpoint is seen as more sensitive and a hypothetical strategy for this class of intercurrent events may be preferable.

The choice of estimands should be justified and ideally discussed within the CHMP scientific advice.

6. Trial methodology

Pivotal trials should be conducted by physicians experienced in the management of childhood and adolescent overweight and obesity. They should be performed in centres with access to the relevant multidisciplinary teams that can provide expertise in drug monitoring, diet, psychological support, behavioural interventions and physical activity.

The confirmatory trial should ideally be stratified for important prognostic factors (e.g. BMI, sex, age/paediatric population, region, glucose lowering agents, prediabetic status), which in turn should be adjusted for in the statistical analysis models, and appropriate subgroup analyses should be pre-planned. A treatment phase of at least 6 months may be sufficient if a medicinal product has a known mechanism of action and data in the adult population are available. Treatments with a new mechanism of action or no data in other age groups may require a longer treatment period.

The use of placebo-controlled trials in obesity (particularly in long-term studies) may be associated with a high rate of dropouts. This has been the case in many recent studies and has complicated the evaluation of the results. For this reason, an effective non-pharmacological intervention is warranted, and the sponsor is urged to implement all possible measures to minimize the number of dropouts, even when randomised treatment is discontinued.

Choices made for statistical analysis, including the handling of missing data, should be aligned to an agreed target of estimation. The primary analysis will be associated with various assumptions which can be examined through a sensitivity analysis aligned to the same target of estimation. As with adults, the problem of treatment discontinuation is recognised in both the placebo and active treatment groups. Historically there have been high rates of premature subject withdrawal in trials of medicinal products used in the management of overweight and obesity. The effect estimates are strongly impacted by a large number of early treatment discontinuations or study withdrawals. Every effort should be made to follow-up these patients fully to be able to include them with a treatment policy strategy, if seen as appropriate. Missing data imputation should be performed in line with the proposed estimand definition. However, single-imputation inference tends to overstate precision because it omits the between-imputation component of variability, therefore, multiple imputation would be preferable (e.g. retrieved-dropout-based multiple imputation or reference-based multiple imputation in case of a treatment policy strategy for treatment discontinuation). Therefore, methods such as last observation carried forward (LOCF) and baseline observation carried forward (BOCF) are inappropriate, the later also because of a possible placebo effect. Tipping point analyses which explore the extent to which assumptions in respect for imputation or modelling for handling missing data would have to be violated before a positive result is lost could be conducted as sensitivity analysis to show how robust the results are to the handling of missing data. Patients should be seen on a regular basis

and their weight and height as well as metabolic, mechanical and mental issues monitored from baseline to final analysis.

After completion of the study, patients should be allowed to either switch to existing effective treatments or continue the experimental treatment in an open-label extension phase to assess effectiveness and tolerability in the context of longer-term exposure. The applicant should present measures to ensure long-term follow-up of possible adverse reactions and efficacy in the paediatric population. Subgroup analyses should be performed for all prognostic and possible predictive factors (e.g. BMI, prediabetic status, age/paediatric population, region, ethnic origin and sex) and possible interactions (with for example antihypertensives, glucose lowering and lipid modifying agents), especially including the stratification factors.

7. Assessment of safety

Safety aspects are dependent on the mechanism of action of the IMP and the available data in adults. Appropriate safety data should be collected during the entire drug treatment period, which will usually be from 6 months up to one year, and for the duration of the open-label extension. This data should notably encompass the adverse events related to lipid profile, liver function, cardiovascular system function and weight regain under treatment. For centrally acting anorectic agents, it is recommended that special attention and monitoring is afforded to neuropsychiatric events such as depression, sleep pattern and nightmares, assessment of self-esteem, anxiety, self-injury, aggression or suicidality. Patient Reported Outcomes and Patient Reported Experience Measures may be useful to assess the incidence of such events.

In growing children, height velocity should be monitored alongside standard safety assessments. Pubertal development should be evaluated using Tanner stages at baseline and at regular intervals (e.g., every 3–6 months). The method of assessment should be prespecified, preferably clinician-assessed or using validated self-assessment tools, to ensure consistency and reliability. For centrally acting anorectic agents the abuse potential should be considered and factored into trial design in an appropriate manner. This is especially important in the adolescent age group.

The possibility of an excessive pharmacodynamic effect, e.g. excessive weight loss, should be considered in the protocol and adequate guiding should be available if concerns about excessive weight changes, or mental health issues arise.

8. References

[1] EMA (2009) Guideline on Clinical Evaluation of Medicinal Products used in Weight Control (CPMP/EWP/281/96 Rev.1) Addendum on Weight Control in Children. Available from https://www.ema.europa.eu/en/clinical-evaluation-medicinal-products-used-weight-control-addendum-weight-control-children-scientific-guideline

[2] EMA (2017) Guideline on clinical evaluation of medicinal products used in weight management. Available from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-medicinal-products-used-weight-management-revision-1_en.pdf

[3] WHO (2025) Obesity and overweight.

[4] Kelly AS, Bahlke M, Baker JL, et al. (2024) Considerations for the design and conduct of pediatric obesity pharmacotherapy clinical trials: Proceedings of expert roundtable meetings. Pediatr Obes 19(11): e13161. 10.1111/ijpo.13161

[5] European Commission Expert Group (2017) Ethical considerations for clinical trials on medical products conducted with the paediatric population: Recommendations of the expert group on clinical trials for implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Available from https://health.ec.europa.eu/document/download/d721d6cb-687a-477f-b40f-8c7922e9ec9a_en

[6] Rubino F, Cummings DE, Eckel RH, et al. (2025) Definition and diagnostic criteria of clinical obesity. Lancet Diabetes Endocrinol 13(3): 221-262. 10.1016/S2213-8587(24)00316-4

[7] Ryder JR, Kelly AS, Freedman DS (2022) Metrics matter: Toward consensus reporting of BMI and weight-related outcomes in pediatric obesity clinical trials. Obesity (Silver Spring) 30(3): 571-572. 10.1002/oby.23346

[8] Cole TJ, Bellizzi MC, Flegal KM, Dietz WH (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 320(7244): 1240-1243. 10.1136/bmj.320.7244.1240

[9] EMA (2020) European Medicines Agency (2020) ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.

[10] Kahan BC, Hindley J, Edwards M, Cro S, Morris TP (2024) The estimands framework: a primer on the ICH E9(R1) addendum. BMJ 384: e076316. 10.1136/bmj-2023-076316

[11] Hoey H (2014) Management of obesity in children differs from that of adults. Proc Nutr Soc 73(4): 519-525. 10.1017/S0029665114000652

[12] Dunger DB, Ahmed ML, Ong KK (2005) Effects of obesity on growth and puberty. Best Pract Res Clin Endocrinol Metab 19(3): 375-390. 10.1016/j.beem.2005.04.005

Definitions

BMI: body mass index

BOCF: baseline observation carried forward

DXA: dual energy x-ray absorptiometry

IMP: investigational medicinal product

LOCF: last observation carried forward

SmPC: summary of product characteristics

WtHR: weight-to-height ratio