



Semaglutide in Routine Obesity Care: A Narrative Review of Effectiveness Outside the Trial Population

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Received: 22 January 2023; Accepted: 24 July 2023; Published: 24 November 2023

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Abstract

Randomised trials of semaglutide for obesity report mean weight reduction of roughly 15 to 16 per cent at 68 weeks. Routine practice reports considerably less. In a cohort of 7,881 adults treated outside a trial, mean weight reduction at one year was 8.7 per cent, and the reason is visible in the same dataset: those who stopped within three months lost 3.6 per cent, those who stopped between three and twelve months lost 6.8 per cent, and those who continued lost 11.9 per cent. Among patients who continued at a high maintenance dose, semaglutide achieved 13.7 per cent. Dose is the other half of the explanation, since 80.8 per cent of that cohort remained on a low maintenance dose, against 86 to 90 per cent reaching the full dose in the trials. Discontinuation ran at 42 per cent in one outpatient clinic against approximately 5 per cent over two years in a trial extension. A digital clinic pairing individualised dosing with intensive behavioural support reported 16.7 per cent at 64 weeks with only 28.8 per cent exceeding 1 mg weekly. The gap is one of delivery rather than of drug.

Keywords: Semaglutide; Obesity; Real-world effectiveness; Treatment persistence; Dose titration

Introduction

Semaglutide at 2.4 mg weekly produced mean weight reduction of approximately 15 to 16 per cent at 68 weeks across the phase 3 programme, a magnitude not previously achieved by pharmacological treatment for obesity [1,2,3]. Those results changed clinical expectations quickly and widely [4,27,33]. Weight regain follows withdrawal, and maintenance trials show the effect depends on continued treatment [12,16,18].

Effectiveness in routine care is a separate question from efficacy in a trial. Trial participants are selected, monitored frequently, supported by multidisciplinary teams and supplied with the drug at no cost, none of which describes an ordinary clinic [5,6,7]. Adherence and persistence to anti-obesity medication have been reviewed systematically and are poor across the class [32].

This review examines what semaglutide achieves outside those conditions, how large the difference is, and what accounts for it. The question matters because the answer determines

whether the shortfall is a property of the drug or of the service delivering it.

Material and Methods

Search strategy: PubMed and the archives of the major obesity, endocrinology and pharmacotherapy journals were searched for studies of semaglutide effectiveness outside randomised trials. Search terms combined semaglutide and glucagon-like peptide 1 receptor agonist with real-world, effectiveness, persistence, discontinuation, dose titration and weight loss. Reference lists of the phase 3 reports [1,2] and real-world reviews [6] were screened by hand for primary sources.

Eligibility: Studies were included if they reported weight outcomes in patients treated outside a randomised trial, characterised persistence or dose, or compared routine practice with trial results. Trial reports are cited as the comparator and are identified as such.

Data extraction and handling: Design, cohort, follow-up duration, the analysis population and the reported estimate were extracted as published. Whether an estimate describes all patients who started treatment or only those who continued is stated alongside every figure, because that distinction accounts for much of the apparent difference between settings. This review reports measured outcomes and makes no dietary, caloric or exercise recommendations. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What routine practice reports: A retrospective cohort using electronic health records identified 7,881 adults with overweight or obesity and without type 2 diabetes who started injectable semaglutide or tirzepatide between 2021 and 2023, of whom 6,109 received semaglutide. Among 6,477 with one-year data, mean weight reduction was 8.7 per cent [8,9].

Where the difference comes from: The same cohort separated outcomes by persistence. Patients discontinuing within three months lost 3.6 per cent, those discontinuing between three and twelve months lost 6.8 per cent, and those who did not discontinue lost 11.9 per cent (Figure 1) [8,9]. Dose mattered as much: 80.8 per cent of the cohort remained on a low maintenance dose, and patients who continued at a high maintenance dose lost 13.7 per cent on semaglutide and 18.0 per cent on tirzepatide (Figures 2 and 3) [8,9].

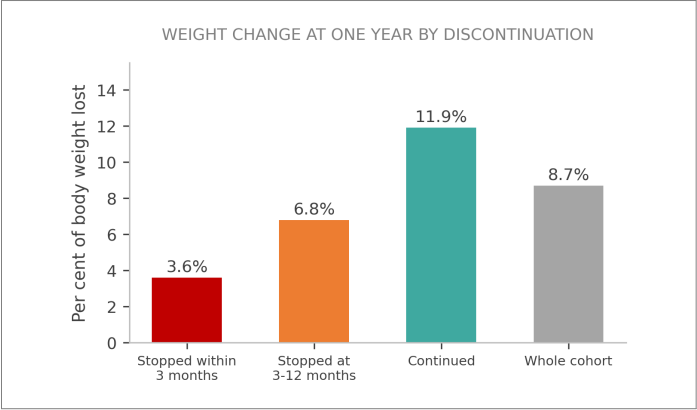


Figure 1: Weight change at one year by discontinuation status [8,9]

Table 1: Reported weight reduction by setting and by the population analysed [1,8,9,13]

Table 2: Differences between the trial setting and routine care [1,5,6,13]

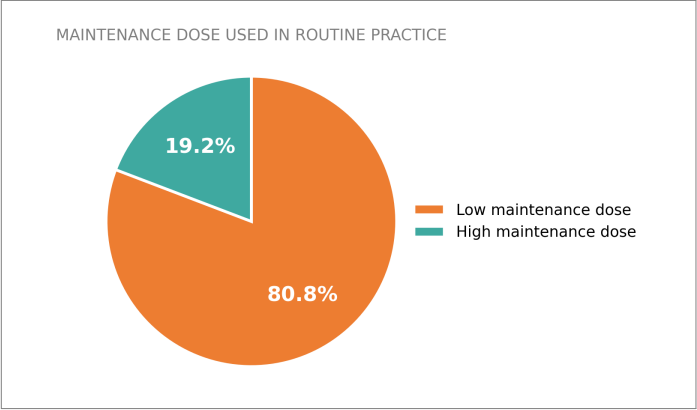


Figure 3: Maintenance dose reached in routine practice [8,9]

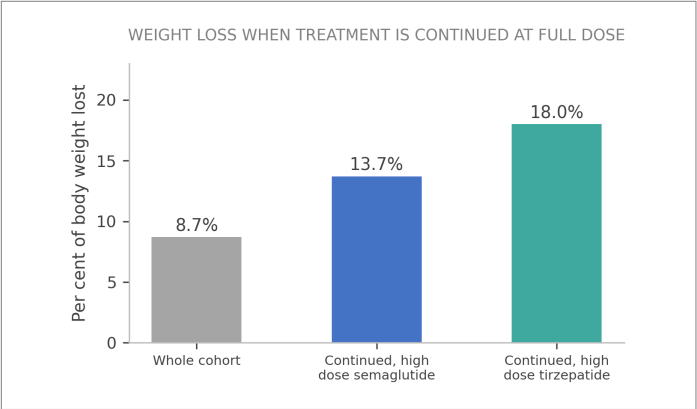


Figure 2: Weight loss among patients who continued treatment at a high dose [8,9]

How persistence compares with trials: One-year discontinuation was 17.1 per cent in the pivotal semaglutide trial and 14.2 to 16.4 per cent in the corresponding tirzepatide trial [8,10,11]. A community outpatient clinic reported 42 per cent discontinuation, against approximately 5 per cent over two years in a trial extension and 5 to 10 per cent across other extensions of the programme (Figure 4) [5,12]. Reports from outside academic centres describe discontinuation between 20 and 60 per cent within the first year [5,6].

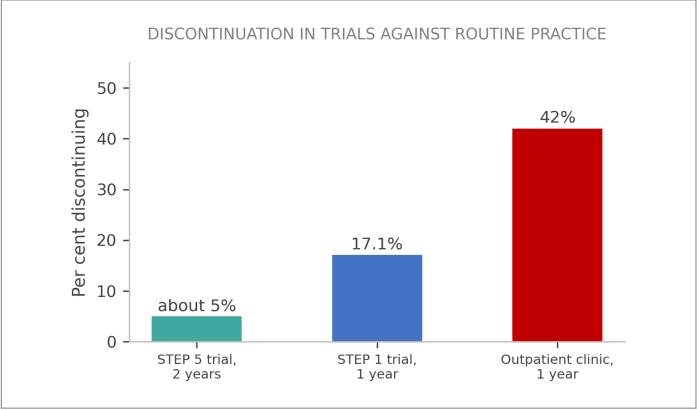


Figure 4: Discontinuation in trials against routine practice [5,8,12]

Setting	Analysis population	Weight reduction
Phase 3 programme	All randomised, 68 weeks	15% to 16%
Phase 3, if taken as intended	Hypothetical estimand	About 17%

Setting	Analysis population	Weight reduction
Routine practice cohort	All starters, 1 year	8.7%
Same cohort, continued	Did not discontinue	11.9%
Same cohort, continued at full dose	High maintenance dose	13.7%
Digital clinic with support	64 weeks	16.7%

What happens when support is added: A retrospective cohort of 2,694 participants in a digital weight-loss programme combining individualised semaglutide dosing with intensive behavioural therapy reported 16.7 per cent weight reduction at 64 weeks. The participants were 78 per cent women, mean age 46.8 years (SD 10.8) and mean body mass index 34.3 kg/m² (SD 4.8). Notably, only 28.8 per cent titrated above 1 mg weekly, against 86 to 90 per cent reaching 2.4 mg in the trials, and the investigators observed that their result resembled the trial estimate calculated on the assumption that all participants took the drug as intended (Figure 5) [13]. The distinction between those two ways of summarising a trial is formalised in regulatory guidance on estimands [28,29], and a trial pairing semaglutide with intensive behavioural therapy reported among the largest reductions in the programme [17].

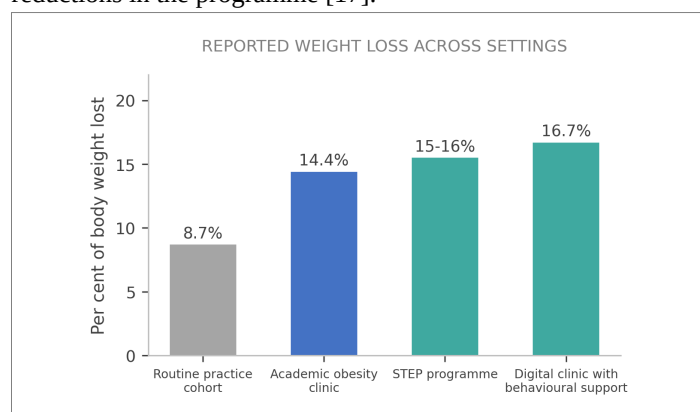


Figure 5: Reported weight reduction across settings [1,8,13,14]

An intermediate picture: A single-centre academic obesity clinic providing medication at no cost to the patient enrolled 2,855 people, of whom 2,306 received at least one prescription. Median weight loss was 9.4 per cent at six months and 14.4 per cent at twelve, positioned between the routine cohort and the trials [14]. A separate retrospective comparison of 2,396 patients found 8.83 per cent at six months with semaglutide among those adherent to treatment [15]. Other observational series report broadly similar figures across health systems [19,20,21,22,23,24].

Table 3: The questions this literature can and cannot answer [8,9,13]

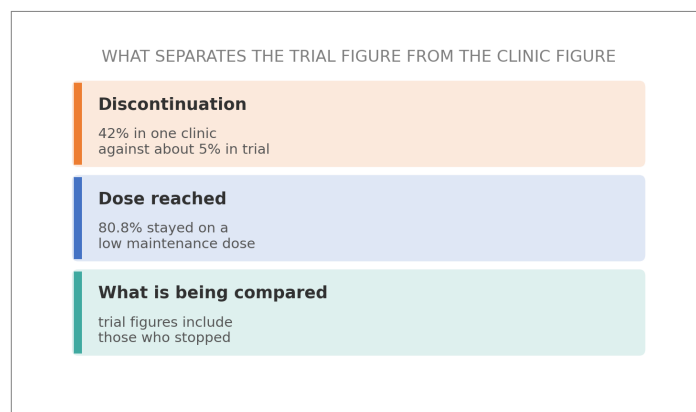


Figure 6: What separates the trial figure from the clinic figure [5,8,9,13]

Factor	Trial condition	Routine condition
Discontinuation at 1 year	About 17%	42% in one clinic; 20-60% reported
Reaching full dose	86% to 90%	19.2% on high maintenance dose
Drug supply	Provided without cost	Subject to cost and coverage
Follow-up	Scheduled and frequent	Variable; often none between visits
Behavioural support	Structured, multidisciplinary	Rarely available
Question	What the data support	
Does the drug work less well outside trials?	No; continued full-dose use approaches trial results	
Why is the average lower?	Discontinuation and low maintenance dosing	
Can routine care match trials?	One digital service reported 16.7% with intensive support	
Are the figures comparable?	Only if the analysis population is stated	

What continued treatment implies: Weight regain follows withdrawal, and the maintenance trials establish that the effect is contingent on continued exposure rather than durable after it [12,16,18]. That matters for interpreting persistence figures, since a patient who stops at three months has not received a shorter course of a curative treatment but has discontinued an ongoing one. It also means the clinically relevant question is not how much weight is lost by twelve months but how many patients are still taking the drug at that point [9,32].

Why patients stop: The principal cohort did not examine reasons for discontinuation, and its authors said so [8]. Other work points to gastrointestinal side effects, cost and interrupted supply, and reviews of adherence to anti-obesity medication describe poor persistence across the class rather than for semaglutide specifically [6,21,32]. Distinguishing between these matters because they call for different responses, and the evidence does not currently separate them [5,23].

Discussion

The headline comparison, 8.7 per cent against 15 to 16 per cent, invites the conclusion that the drug underperforms in the real world. The same dataset shows that is not what is happening. Patients who continued treatment lost 11.9 per cent, and those who continued at a high maintenance dose lost 13.7 per cent [8,9]. The pharmacology behaves as the trials described; what differs is how many people are still taking the drug at a therapeutic dose a year later.

Two mechanisms account for almost all of the gap. Discontinuation ran at 42 per cent in one outpatient clinic against about 5 per cent over two years in a trial extension, and 80.8 per cent of the routine cohort never reached a high maintenance dose against 86 to 90 per cent reaching the full dose in the trials [5,8,13]. Neither is a property of semaglutide. Both are properties of the system prescribing it, and both are in principle modifiable.

The third mechanism is more technical and frequently overlooked. Trial figures of 15 to 16 per cent are calculated across all randomised participants regardless of whether they stopped, while many routine-practice figures describe only patients still on treatment, or conversely describe everyone who ever started [1,8,15]. Comparing the two without saying which population is meant produces an apparent discrepancy that is partly arithmetic. The digital clinic study makes this explicit: its 16.7 per cent resembled the trial estimate calculated on the assumption that everyone took the drug as intended, rather than the headline figure [13].

That study is the most interesting result here and also the one most in need of caution. Sixteen point seven per cent at 64 weeks, achieved with only 28.8 per cent of participants exceeding 1 mg weekly, suggests that structured behavioural support can substitute for dose escalation [13]. But the cohort was self-selected, paying for a commercial service, 78 per cent women and with a mean body mass index of 34.3, which is lower than most trial populations. People who enrol in and pay for an intensive programme differ from people prescribed a drug at a routine appointment, and the comparison is not like for like.

The practical implication is narrow and reasonably firm. If the determinant of outcome is persistence and dose rather than the molecule, then the intervention that improves results is not a different drug but the support that keeps people on the one they have [5,6]. What the literature does not yet establish is which components of that support matter, how much is enough, or whether the effect survives outside services that selected for motivated participants. Guidance on pharmacological management of obesity predates most of this evidence [25,26,33], and long-term lifestyle comparisons remain the historical benchmark [34].

A final observation concerns what these cohorts can be used for. Effectiveness data of this kind are increasingly cited in coverage and reimbursement decisions, where an average of 8.7

per cent reads very differently from 15 per cent [6,25]. If most of that difference reflects discontinuation and under-dosing, then using the lower figure to judge the drug penalises it for a failure of the service around it. The same data could equally justify investing in the support that raises persistence [13,32].

It should also be said that none of these studies measures the outcomes that matter most over time. Cardiovascular benefit in this population has been demonstrated in a randomised trial with years of follow-up, not in twelve-month record-based cohorts [30,31]. Weight change is a reasonable proxy for comparing delivery models, and it is not the endpoint on which the value of the treatment ultimately rests.

Study limitations

The limitations belong to the underlying literature. Every effectiveness estimate here comes from a retrospective cohort using routinely collected records, so treatment assignment reflects clinical and patient choice and confounding by indication is unavoidable [8,15]. Comparisons between persistence groups are particularly vulnerable, since people who continue treatment differ systematically from those who stop, and early weight loss itself predicts continuation, so the direction of that association is not established [8,9]. Analysis populations differ between studies and are not always stated, which makes cross-study comparison unreliable [1,15]. Reasons for discontinuation were not explored in the principal cohort, so cost, side effects and supply cannot be separated [8]. The digital clinic cohort is self-selected, predominantly female and commercially operated [13]. Several source studies carry industry ties or author disclosures relevant to the products assessed [8,15]. Follow-up is one year or less against a chronic condition, whereas cardiovascular and mortality outcomes accrue over years [30,31]. And weight is recorded opportunistically in records rather than at protocol-defined visits [8,14].

Conclusion

Semaglutide prescribed in routine practice produces about 8.7 per cent weight reduction at a year, against 15 to 16 per cent in the trials, and the reason is not that the drug behaves differently. Patients who kept taking it lost 11.9 per cent, and those who kept taking it at a full dose lost 13.7 per cent. Four in five never reached a high maintenance dose, and discontinuation reached 42 per cent in one clinic against roughly 5 per cent in a trial extension. Part of the remaining difference is arithmetic, since trial and clinic figures are often calculated over different populations. The shortfall is therefore a problem of delivery, and the one service that matched the trials did so with intensive support rather than higher doses.

Acknowledgements

The authors thank the investigators whose cohorts and service evaluations are drawn together in this article, and the clinical teams whose prescribing and dispensing records made persistence measurable.

Funding

No dedicated funding from public, commercial or charitable sources supported the preparation of this review.

Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

- Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. "Once-weekly semaglutide in adults with overweight or obesity". *N Engl J Med* 384(2021):989-1002.
- Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. "Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial". *Nat Med* 28(2022):2083-2091.
- Davies M, Faerch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. "Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial". *Lancet* 397(2021):971-984.
- Muller TD, Bluher M, Tschop MH, DiMarchi RD. "Anti-obesity drug discovery: advances and challenges". *Nat Rev Drug Discov* 21(2022):201-223.
- Outpatient discontinuation investigators. "Semaglutide in a real-world outpatient setting: discontinuation patterns and weight maintenance". *J Obes Endocrinol* 1(2025):wjaf011.
- Real-world evidence review authors. "Real-world evidence on the utilization, clinical and comparative effectiveness, and adverse effects of newer GLP-1RA-based weight-loss therapies". *Diabetes Obes Metab* (2024).
- Rothwell PM. "External validity of randomised controlled trials: to whom do the results of this trial apply?". *Lancet* 365(2005):82-93.
- Gasoyan H, Pfoh ER, Schulte R, Sullivan E, Le P, Rothberg MB. "Changes in weight and glycated hemoglobin by pharmacotherapy discontinuation status". *JAMA Netw Open* 8(2025):e2516231.
- Gasoyan H, Rothberg MB. "Early- and later-stage persistence with anti-obesity medications: a retrospective cohort study". *Obesity* 32(2024):486-493.
- Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. "Tirzepatide once weekly for the treatment of obesity". *N Engl J Med* 387(2022):205-216.
- Rubino DM, Greenway FL, Khalid U, O Neil PM, Rosenstock J, Sorig R, et al. "Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial". *JAMA* 327(2022):138-150.
- Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, et al. "Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension". *Diabetes Obes Metab* 24(2022):1553-1564.
- Digital clinic investigators. "Treat to target in weight management with semaglutide: real-world evidence from an eHealth clinic". *Diabetes Obes Metab* (2025).
- Academic clinic investigators. "Real-world titration, persistence and weight loss of semaglutide and tirzepatide in an academic obesity clinic". *Diabetes Obes Metab* (2025).
- Comparative effectiveness investigators. "Comparative effectiveness of tirzepatide and semaglutide for obesity management in US clinical practice: a 6-month retrospective cohort study". *Int J Obes* (2025).
- Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, et al. "Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial". *JAMA* 331(2024):38-48.
- Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. "Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial". *JAMA* 325(2021):1403-1413.
- Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. "Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial". *JAMA* 325(2021):1414-1425.
- Danish cohort investigators. "Real-world use of semaglutide for weight management: patient characteristics and dose titration, a Danish cohort study". *Diabetes Obes Metab* (2024).
- Ghusn W, De la Rosa A, Sacoto D, Cifuentes L, Campos A, Feris F, et al. "Weight loss outcomes associated with semaglutide treatment for patients with overweight or obesity". *JAMA Netw Open* 5(2022):e2231982.
- Weiss T, Yang L, Carr RD, Pal S, Sawhney B, Boggs R, et al. "Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK". *BMJ Open Diabetes Res Care* 10(2022):e002517.

22. Squire P, Naude J, Zentner A, Bittman J, Khan N. "Factors associated with weight loss response to GLP-1 analogues for obesity treatment: a retrospective cohort analysis". *BMJ Open* 15(2025):e089477.
23. Real-world safety investigators. "A real-world study of the effectiveness and safety of semaglutide for weight loss". *Cureus* 16(2024):e59848.
24. Frontiers cohort investigators. "Real-world semaglutide in obesity cohort: effectiveness, safety and persistence across sex, BMI, and prior GLP-1RA treatment". *Front Endocrinol* (2026).
25. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. "American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity". *Endocr Pract* 22(2016):1-203.
26. Unanswered questions authors. "Semaglutide for weight loss: unanswered questions". *Front Endocrinol* 15(2024):1382814.
27. Bergmann NC, Davies MJ, Lingvay I, Knop FK. "Semaglutide for the treatment of overweight and obesity: a review". *Diabetes Obes Metab* 25(2023):18-35.
28. Wharton S, Astrup A, Endahl L, Lean MEJ, Satyrganova A, Skovgaard D, et al. "Estimating and reporting treatment effects in clinical trials for weight management: using estimands to interpret effects of intercurrent events and missing data". *Int J Obes* 45(2021):923-933.
29. International Council for Harmonisation. "ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials". European Medicines Agency (2020).
30. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. "Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials". *Lancet Diabetes Endocrinol* 9(2021):653-662.
31. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. "Semaglutide and cardiovascular outcomes in obesity without diabetes". *N Engl J Med* 389(2023):2221-2232.
32. Hong Y, Lee JH, Kim W. "Adherence and persistence to anti-obesity medications: a systematic review". *Obes Rev* 24(2023):e13593.
33. Gudzone KA, Kushner RF. "Medications for obesity: a review". *JAMA* 332(2024):571-584.
34. Look AHEAD Research Group. "Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study". *Obesity* 22(2014):5-13.

Citation: Serrano A, Verhoeven E, Makinen J. "Semaglutide in Routine Obesity Care: A Narrative Review of Effectiveness Outside the Trial Population". DOI: 10.5281/zenodo.22258301