National Institute for Health and Care Excellence

Health Technology Evaluation

Semaglutide for treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis [ID6458]
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Novo Nordisk	Novo Nordisk welcomes NICE's position on providing timely and relevant guidance to the system. However, Novo Nordisk believes that the evaluation of this topic is [redacted] Therefore, Novo Nordisk proposes that semaglutide is evaluated as a single technology appraisal to ensure that appropriate guidance and its implementation is provided at the time of launch. Novo Nordisk will keep NICE updated on its UK launch of semaglutide for the treatment of MASH so that a timely evaluation via the STA process can be considered for a future date.	Thank you for your comments. The routing has been updated to a single technology appraisal for semaglutide.

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	Madrigal Pharmaceuticals	Madrigal Pharmaceuticals believes that the MTA is not an appropriate route of appraisal for resmetirom and concerns regarding the MTA process have already been delivered to NICE by email on 17th April 2025. However, Madrigal Pharmaceuticals remains fully committed to working with NICE to support a fair and transparent assessment of resmetirom. Madrigal Pharmaceuticals respectfully ask that NICE carefully reflect on the legal, scientific, and operational implications of this route change, and ensure that resmetirom is evaluated on a level playing field, consistent with the principles enshrined in NICE's own manuals and UK administrative law. The main Madrigal concerns are also listed here: **Mid-process change from STA to MTA** without prior consultation disrupts planning and undermines fairness. **Legal and procedural uncertainty** may breach principles of legitimate expectation under UK administrative law. **Risk of unjustified delay**—a six to nine-month postponement to resmetirom's launch could significantly impact patient outcomes. Please see "regulatory timelines" section, regarding marketing authorization approval date. **Public health implications**—delayed access could affect patients with F2/F3 fibrosis in the UK to the only approve treatment. **Economic modeling concerns**—mismatched evidence maturity undermines cost-effectiveness evaluations.	Thank you for your comments. The routing has been updated to a single technology appraisal for semaglutide.

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		Appeal to revert to STA and adopt a proportionate, fair, and transparent approach to resmetirom's evaluation.	
	Royal College of General Practitioners	Some disadvantages to a multiple technology appraisal from primary care perspective as semaglutide is already being prescribed in primary care in diabetes management and appraisal may be different in terms of initiation and monitoring/be more likely to be used in subgroups with MASLD fibrosis (i.e. those with T2D/prediabetes/obesity indications)	Thank you for your comments. The routing has been updated to a single technology appraisal for semaglutide.
	The British Association for the Study of the Liver (BASL)	High importance and appropriate evaluation route.	Thank you for your comment.
	UK Clinical pharmacy Association	More appropriate as two single tech appraisals, due to differing mechanisms of action. More GLP-1 agonists in pipeline for MASH, such as tirzepatide, which may lead to lack clarity in funding decisions between GLP-1s if semaglutide combined in appraisal with a non-GLP1 agonist, unless carefully worded. There are factors that may potentially reduce concordance/alignment between appraisal outcomes for each technology, affecting application of the appraisal to practice: differing inclusion/exclusion criteria of the clinical trials for the two technologies, different modes of action, different routes of administration.	Thank you for your comments. The routing has been updated to a single technology appraisal for semaglutide.

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		More appropriate to include semaglutide in a multiple technology appraisal with tirzepatide, but with semaglutide likely available in UK in advance of tirzepatide, single technology appraisal for each is preferable.	
	British Liver Trust	This is an important topic for NICE evaluation – patients are in desperate need of effective treatments for MASLD/MASH	Thank you for your comment.
Wording	Novo Nordisk	The wording in the draft remit suggests that there is one marketing authorisation for both products. Novo Nordisk proposes the following change to wording. Current wording: To appraise the clinical and cost effectiveness of resmetirom and semaglutide within its marketing authorisation… Proposed wording: *To appraise the clinical and cost effectiveness of resmetirom and semaglutide within their respective marketing authorisations…* Novo Nordisk suggests that within the draft remit section, it is specified that these technologies are for 'treating moderate to advanced liver fibrosis (without cirrhosis) caused by metabolic dysfunction-associated steatohepatitis (MASH).' Novo Nordisk proposes for the inclusion of the following points within the draft scope table:	Thank you for your comment. The remit has been updated.

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		1. The BMI subgroups should also be included in the subgroup box as BMI influences liver fibrosis progression. 2. A subgroup with and without the presence of type 2 diabetes (T2D) should also be included in the subgroup box as T2D influences liver fibrosis progression. **3.** The inclusion of non-hepatic benefits as outcomes for semaglutide due to its wider metabolic benefits which impact on liver fibrosis progression. The following should also be included as outcomes e.g. Change in weight from baseline Change in HbA_{1c} from baseline Change in cardiovascular markers from baseline e.g. HDL, LDL and SBP.	
	Madrigal Pharmaceuticals	The remit need to be changed at least for resmetirom. The remit should be changed to: Resmetirom for treating noncirrhotic MASH with moderate to advanced fibrosis	Thank you for your comment. The remit has been updated for semaglutide.
	Royal College of General Practitioners	It seems appropriate although the clinical and cost effectiveness comparator which is predominantly lifestyle intervention is not currently standardised in delivery across primary or secondary care with locally commissioned availability/different offers/uptake. Also need to consider long natural history of MASLD from stage 2/ 3 fibrosis to significant clinical liver/CV/other outcomes . With high prevalence/low liver outcome rates in both groups going to be difficult to show clinical /cost effectiveness using long term outcomes and will likely have to rely on	Thank you for your comment. The outcomes have been updated for semaglutide.

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		surrogate clinical outcomes - most of which require repeat liver biopsies (change in fibrosis, MASH activity etc). This limits the real life applicability of this outcome data to the small percentage of those in secondary care with biopsy proven disease. The vast majority of the population with F2/F3 MASLD are in the community/not or only briefly under secondary care and will never have had a biospy.	
	The British Association for the Study of the Liver (BASL)	Yes [the remit wording is appropriate].	Thank you for your comment.
	UK Clinical pharmacy Association	Current use of 'and' for resmetirom and semaglutide may be easily misunderstood as advocating dual therapy – should be 'or'. Patients with cirrhosis have been excluded from clinical trials for these agents so for clarity 'without cirrhosis' should be included in the title for clarity assuming also excluded from evaluation.	Thank you for your comment. The remit has been updated for semaglutide.
	British Liver Trust	Yes [the remit wording is appropriate].	Thank you for your comment.
Timing issues	Novo Nordisk	At this present time, there is no planned launch date for semaglutide for the treatment of MASH in the NHS due to the uncertainty of the launch date. Novo Nordisk proposes that semaglutide is evaluated as a single technology appraisal to ensure that the guidance and its implementation is provided at the time of launch. Novo Nordisk will keep NICE updated on its UK launch of semaglutide for the treatment of MASH so that a timely evaluation via the STA process can be considered for a future date. Based on this there is no relative urgency for guidance on this topic.	Thank you for your comments. The routing has been updated to a single technology appraisal for semaglutide.

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	Madrigal Pharmaceuticals	Resmetirom is the only treatment for MASH included in the EASL Guidelines. Given the progressive nature of MASH, even modest delays could have real and serious consequences—particularly for the patients with moderate to advanced fibrosis stages (F2 and F3) who are at heightened risk of disease progression.	Thank you for your comment.
	Royal College of General Practitioners	Not urgent. Need to better identify and define the highest risk population who will benefit from these treatments by working on pathways of care between primary/secondary care.	Thank you for your comment.
	UK Clinical pharmacy Association	There are currently no licensed and effective existing pharmacological therapies, but high and increasing prevalence and disease burden/heath resource utilisation for this patient group, so this is a high priority. Timely evaluation is crucial to ensure appropriate resource allocation in a reconfiguring NHS.	Thank you for your comment.
	British Liver Trust	Fairly urgent. There is a clear unmet need for patients.	Thank you for your comment.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novo Nordisk	Novo Nordisk proposes the following should be added to the background information for clarity on page 1: Current wording: **Using MASLD is preferred because it is more specific about the main associated risk factors of excess weight and metabolic diseases.**	Thank you for your comments. The wording around symptoms has been updated for semaglutide.

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		MASLD is usually seen in people with type 2 diabetes, obesity or other cardiometabolic risk factors such as raised blood pressure or high levels of cholesterol or triglycerides in the blood.[2] MASLD includes a group of conditions of increasing severity *Proposed wording:* *Using MASLD is preferred because it is more specific about the main associated risk factors of excess weight and metabolic diseases. The definition of MASLD includes the presence of hepatic steatosis and at least one cardiometabolic risk factor (type 2 diabetes, obesity, raised blood pressure, low HDL (high-density lipoprotein cholesterol) and high triglycerides).[2] MASLD includes a group of conditions of increasing severity[1,2]:* Current wording: **Metabolic dysfunction-associated steatohepatitis or MASH (fibrosis stage 0 or 1), where there are distinct changes in tissues of the liver (hepatocellular ballooning and lobular inflammation) but no or very little scarring and it can be reversed. MASH in the new name for non-alcohol related steatohepatitis (NASH).** *Proposed wording:* *Metabolic dysfunction-associated steatohepatitis or MASH (fibrosis stage 0 or 1), where there are distinct changes in tissues of the liver (hepatocellular ballooning and lobular inflammation) but no or very little scarring and it can be reversed. MASH in the new name for non-alcohol related steatohepatitis (NASH). The nomenclature was changed to be less stigmatising for people living with MASH and reflect the metabolic nature of the condition.*	

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		Current wording: **Fibrosis, moderate or advanced (stage 2 or 3), where persistent inflammation causes scar tissue around the liver and nearby blood vessels, but the liver is still able to function normally.** *Proposed wording:* *MASH with moderate or advanced (stage 2 or 3) fibrosis, is where persistent inflammation causes scar tissue around the liver and nearby blood vessels, but the liver is still able to function normally.* **Current wording:** **In the early stages of MASLD there are not usually any symptoms. Occasionally, people with MASH or fibrosis may experience dull or aching pain over the ribs on the lower right side, fatigue, unexplained weight loss, and weakness. Symptoms of cirrhosis are more severe and include yellowing of the skin and eyes (jaundice), itchy skin, and swelling in the legs, ankles, feet or abdomen.** *Proposed wording:* *In the early stages of MASLD there are not usually any symptoms. Occasionally, people with MASH or fibrosis may experience dull or aching pain over the ribs on the lower right side, fatigue, unexplained weight loss, and weakness. Often, steatosis in the liver is identified incidentally on imaging. Symptoms of cirrhosis are more severe and include yellowing of the skin and eyes (jaundice), itchy skin, and swelling in the legs, ankles, feet or abdomen.* **Current wording:** **MASLD is estimated to affect up to 1 in 5 people in the UK.[2] Rates are increasing with rising levels of obesity. Global estimates suggest that**	

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		around 10 to 30% of people with isolated fatty liver progress to steatohepatitis (seen in MASH) and advanced liver disease, but the risk is much higher in the presence of type 2 diabetes where up to 65% of people have steatosis (fatty liver).[1] People with MASH have a higher rate of liver-related and cardiovascular mortality than the general population.[1] *Proposed wording:* *MASLD is estimated to affect up to 1 in 5 people in the UK.[2] Rates are increasing with rising levels of obesity. Global estimates suggest that around 10 to 30% of people with isolated fatty liver progress to steatohepatitis (seen in MASH) and advanced liver disease, but the risk is much higher in the presence of type 2 diabetes where up to 65% of people have steatosis (fatty liver).[1] However, due to lack of knowledge, vague symptoms and no licensed treatments, MASH remains underdiagnosed. People with MASH have a higher rate of liver-related and cardiovascular mortality than the general population.[1] Importantly, in the earlier stages of MASH with fibrosis, cardiovascular mortality is higher than liver-related mortality, however when cirrhosis occurs, the liver-related mortality increases.*	
	Royal College of General Practitioners	Comment on accuracy. Title and reference to MASH throughout the background information. MASH is a histological diagnosis and most people with MASLD fibrosis will not have had a liver biopsy. Therefore MASH is rarely coded in primary care records and although it is correct that to have progressed to liver fibrosis there has been liver inflammation, this is not usually a 'stage' that is defined/coded. statement around symptoms: *'Occasionally, people with MASH or fibrosis may experience dull or aching pain over the ribs on the lower right side, fatigue, unexplained weight loss, and weakness. Symptoms of cirrhosis are more severe and include yellowing*	Thank you for your comments. The wording around symptoms has been updated for semaglutide.

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		of the skin and eyes (jaundice), itchy skin, and swelling in the legs, ankles, feet or abdomen. ' Where is the evidence from that those with F2/F3 can have the symptoms mentioned? I have not seen this evidence or and clinical experience that liver fibrosis can cause weight loss for e.g.? Also - cirrhosis is also usually fairly asymptomatic - perhaps presenting with the earlier symptoms you mention for MASH/fibrosis but only when 'decompensated' with jaundice, itch, ascites etc - think this could be made clearer	
	The British Association for the Study of the Liver (BASL)	MASH often coexists with moderate or advanced fibrosis, rather than existing as a pre-fibrosis stage. Fibrosis may develop in absence of histological MASH. MASH and fibrosis should therefore not be depicted in a linear or stepwise manner.	Thank you for your comment.
	UK Clinical pharmacy Association	Accurate. Note 'NASH' terminology used under 'The technologies' heading, first paragraph.	Thank you for your comment. The wording has been updated for semaglutide.
	British Liver Trust	Although GPs should manage earlier stage disease we often hear from patients that in reality this does not happen. Further education is needed for GPs to effectively manage early stage disease. It is important that MASH is not considered in isolation and that treatment should be personalised based on indicative liver disease stage and other comorbidities	Thank you for your comment.
Population	Novo Nordisk	Novo Nordisk proposes the following change to the wording on page 3 in the Populations table:	Thank you for your comment. The population wording has

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		Current wording: Adults with significant liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH) *Proposed wording:* *Adults with moderate to advanced liver fibrosis cause by metabolic dysfunction-associated steatohepatitis (MASH).*	been updated for semaglutide.
	Madrigal Pharmaceuticals	It should be changed to: Adults with noncirrhotic MASH with moderate to advanced fibrosis (consistent with stages F2 to F3)	Thank you for your comment. The population wording has been updated for semaglutide.
	Royal College of General Practitioners	See above - think should be changed to *Adults with significant liver fibrosis caused by metabolic dysfunction-associated steatotic liver disease (MASLD)*	Thank you for your comment. The population wording has been updated for semaglutide.
	The British Association for the Study of the Liver (BASL)	Yes [the population is defined appropriately].	Thank you for your comment.
	UK Clinical pharmacy Association	Define 'significant' liver fibrosis using i.e. METAVIR/Ishak staging. Currently doesn't define whether cirrhosis included, while excluded from clinical trials.	Thank you for your comment. The population wording has

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			been updated for semaglutide.
	British Liver Trust	Yes [the population is defined appropriately].	Thank you for your comment.
Subgroups	Novo Nordisk	Novo Nordisk believes the subgroups suggested seem reasonable. However, Novo Nordisk proposes that additional subgroups should be included. Given the significant overlap with patients living with obesity, BMI subgroups should be considered separately to the full licensed population in the submission. This is due to wider non-hepatic benefits on metabolic factors which can influence the rate of progression of MASLD and MASH in these patients. Therefore, Novo Nordisk proposes that semaglutide is evaluated in F2 and F3 patients by BMI subgroup. This is in line with the recommendations from NICE's HTA Lab proposed in March 2025 on MASH models as a patient's BMI level is likely impact their rate of liver fibrosis progression.	Thank you for your comments. BMI and type 2 diabetes subgroup has been added for semaglutide.
	NHS England	The technologies are seen to have greatest benefit and impact for those patients with advanced (F3, F4) fibrosis. It can be also argued that younger patients are in greater need due to their life expectancy and the prospect of progressing to cirrhosis.	Thank you for your comments.

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		The cost and clinical effectiveness in patients at F0-F2 is less clear, and there are more significant challenges in identifying these patients who are more likely to be asymptomatic. Disease progression is a key consideration but at this time there is not sufficient or compelling evidence on this. Anecdotal evidence suggests patients will progress from one disease stage to the next after approximately seven years. A study highlights that a significant placebo response in MASH trials is influenced by biopsy-related variability and natural disease fluctuations, which can complicate the assessment of treatment outcomes (Rowe et al., 2022). There is currently no effective mechanism to identify patients in the absence of a structured screening process. A standalone screening approach is unlikely to be practical or feasible in this context. Therefore, consideration must be given to how screening can be effectively integrated into existing primary care pathways. However, integrating this process into primary care presents a significant capacity challenge, given current workload and system constraints. Given the anticipated significant eligible population sizes and resultant capacity challenges for delivery, implementation within a 90-day timeframe is not deemed feasible and a funding variation will likely be submitted to NICE.	

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	Royal College of General Practitioners	Subgroups by liver fibrosis stage will be hard to define other than in small number with liver biopsies. If using non-invasive liver fibrosis tests - e.g. serum tests (Fib4 for e.g) or fibroscan to define groups then will not be able to cut them off into exact F2/F3 groups accurately. ? See above - is it worth considering T2D as a separate subgroup? This group may already be on semaglutide as part of their T2D management and if not a diagnosis of MASLD fibrosis and starting semaglutide for a liver indication is likely to be clinically and cost effective beyond liver outcomes. This group if already on semaglutide for T2D may also form a separate subgroup for consideration of the clinical/cost effectiveness of resmetirom?	Thank you for your comment. A Type 2 diabetes subgroup has been added for semaglutide.
	The British Association for the Study of the Liver (BASL)	Treatment of stage 3 fibrosis is likely preferable (and more cost-effective) to treatment of stage 2 & 3 so, if possible, should be considered separately i. because many people with stage 2 fibrosis do not progress to clinically significant liver end-points and ii. it is not possible to identify stage 2 liver fibrosis reliably using non-invasive tests, while non-invasive tests to identify patients with stage 3 fibrosis perform better.	Thank you for your comments.
	UK Clinical pharmacy Association	Cirrhosis, if included in appraisal, to be distinguished and considered separately as such patients less likely to benefit and therefore benefit to non-cirrhotic patients may be underestimated. Conversely patients with diabetes to be distinguished and considered separately with regards to semaglutide, as more likely to benefit from dual indication for diabetes.	Thank you for your comments. The population includes moderate to advanced liver fibrosis but without cirrhosis. A Type 2 diabetes subgroup has been added for semaglutide.

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	British Liver Trust	Our understanding is that Resmetirom can be used from early stage fibrosis (F1) to severe fibrosis (F3) and that semaglutide is for F2 and F3. It is important from a patient perspective that treatment decision needs to be defined by the use of non-invasive technology (NIT) (rather than biopsy). Treatment of more advanced disease (F3) is likely to be more cost effective initiative as this can be measured more reliably by NIT.	Thank you for your comments.
Comparators	Novo Nordisk	NICE guideline 49 (NG49) recommends that pharmacological treatment with pioglitazone or vitamin E may be considered for adults with NAFLD and advanced liver fibrosis in secondary care settings, typically after and alongside lifestyle modification interventions. However, neither is widely used nor has UK marketing authorisation for treating MASLD. The anticipated marketing authorisation for semaglutide, and available evidence supports use on top of standard of care, which includes lifestyle modifications, diet and pioglitazone and vitamin E, based on local clinical guidelines for the treatment of MASLD and MASH.	Thank you for your comment. The comparators in the scope for semaglutide remain broad. The company can justify any differences from these in its submission to NICE.
	Madrigal Pharmaceuticals	While vitamin E and pioglitazone have been studied in MASH, the evidence supporting their efficacy in non-cirrhotic MASH patients with significant fibrosis (consistent with stages F2–F3) remains weak and inconsistent. **Clinical guideline positioning:** Neither vitamin E nor pioglitazone are formally approved for MASH treatment. Their use is considered off-label, and major guidelines (e.g., AASLD, EASL) only recommend them in select cases with significant limitations (Chalasani et al., 2018). Given these factors, neither therapy represents a standard-of-care comparator in the NICE submission. Moreover, our analysis of CPRD data indicates that [redacted] of patients with MASH	Thank you for your comment. The comparators in the scope for semaglutide remain broad.

		in the UK are currently treated with either of these two agents, highlighting their limited real-world use in this population. • **Vitamin E:** The PIVENS trial, a pivotal study in non-diabetic patients, showed that vitamin E improved some histological markers of MASH but failed to demonstrate significant fibrosis regression compared to placebo (Sanyal et al., 2010). While it showed modest improvements in inflammation and hepatocellular ballooning, these effects were not sufficient to establish it as a definitive treatment for F2–F3 fibrosis, and long-term benefits remain unclear. • **Pioglitazone:** While some studies have reported MASH resolution benefits, its effects on fibrosis are inconsistent. In PIVENS, pioglitazone did not significantly improve fibrosis, and its benefits were observed primarily in non-diabetic patients (Sanyal et al., 2010). Additionally, safety concerns such as weight gain, edema, and potential cardiovascular risks have limited its adoption as a first-line treatment for MASH (Chalasani et al., 2018). Semaglutide's impact on MASH is **indirect**, making it an inappropriate comparator. MASH is a progressive liver disease driven by liver-specific mechanisms such as dysregulated lipid metabolism, inflammation, and fibrosis. Therefore, therapies that directly target these hepatic pathways are more suitable for altering disease progression. In contrast, treatments focused on systemic metabolic effects may offer indirect benefits but do not address the core liver-specific processes—an important consideration when evaluating treatment efficacy in patients with established liver disease. • **Mechanistic differences:** Resmetirom is a liver-targeted thyroid hormone receptor-β agonist designed to directly address MASH by promoting hepatic fat metabolism and reducing fibrosis progression. In contrast, semaglutide primarily induces weight loss and improves metabolic parameters, which may secondarily influence MASH outcomes. This distinction is crucial as it underscores that semaglutide cannot be considered a direct comparator (Newsome et al., 2021).	

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		Challenges in indirect treatment comparisons (ITC): Conducting an ITC between resmetirom and semaglutide presents fundamental challenges under NICE's MTA framework—not due to differences in patient populations, which are broadly similar—but because of key differences in trial design and outcome assessment methods. While both trials enroll patients with MASH, the duration of follow-up and the methodology used for liver biopsy reading vary substantially. These inconsistencies introduce structural heterogeneity that cannot be adequately adjusted for using standard statistical methods. According to NICE, such differences increase uncertainty and may undermine the validity of an ITC, as reliable comparisons require consistency not only in populations but also in study design and endpoint measurement. As such, semaglutide may not be considered a methodologically appropriate comparator to resmetirom in this setting.In summary, vitamin E and pioglitazone have limited and inconsistent efficacy in non-cirrhotic MASH patients with F2–F3 fibrosis and very minor adherence in the UK, while semaglutide's impact on MASH is secondary to its weight-loss effects. From both a clinical and economic modeling perspective, excluding these agents as comparators ensures that the NICE evaluation of resmetirom remains aligned with real-world treatment paradigms and accurately captures its value proposition.	
	NHS England	Consideration of bariatric surgery Off label products may be a comparator in a small number of patients Magnetic resonance elastography for assessment of fibrosis	Thank you for your comment. Bariatric surgery has been added to the background section on treatment options.

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	Royal College of General Practitioners	Yes - although as above the comparator is not standardised in availability or delivery across the NHS at present.	Thank you for your comment.
	The British Association for the Study of the Liver (BASL)	Given that more than 50% of patients with MASH and liver fibrosis have T2DM and most are obese, these interventions should, where possible, be compared to use of GLP-1 RAs for existing indications (T2DM and obesity) and models where access to GLP-1 RAs for patients with existing indications is enhanced.	Thank you for your comment. The comparators in the scope for semaglutide remain broad.
	UK Clinical pharmacy Association	Lifestyle intervention is an appropriate comparator. Significant heterogeneity in existing therapeutic options may complicate analysis. Unlicensed use of pioglitazone and vitamin E is not uniformly adopted across the NHS due to unlicensed nature and uncertain clinical benefit/ADRs and predominant use in advanced liver fibrosis ≥F3. Those with pre-existing diabetes most likely to have had prior pioglitazone therapy. Bariatric surgery is also a potential comparator. Survival vs liver transplant should be explored.	Thank you for your comment. The comparators in the scope for semaglutide remain broad. Bariatric surgery has been added to the background section on treatment options.
	British Liver Trust	Yes [all relevant comparators have been included].	Thank you for your comment.
Outcomes	Novo Nordisk	Novo Nordisk believes that the current outcomes listed do not capture all relevant outcome measures for a patient living with MASLD and MASH. As noted in the draft NICE HTA Lab report on MASH models (NICE HTA Lab, 2025), due to the metabolic nature of the condition and the interplay between MASH, diabetes, obesity and cardiovascular disease, non-hepatic benefits are also important outcomes since they will likely have an impact on costs	Thank you for your comments. The outcomes for semaglutide have been updated. They now include major adverse liver outcomes, and

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		and the QALY estimates. Therefore, the following additional outcomes should be considered: • Change in weight from baseline • Change in HbA_{1c} from baseline • Changes in cardiovascular disease risk factors e.g. HDL, LDL and SBP. The draft scope omits important detail on what the relevant MASH markers are. Important markers are alanine transaminase (ALT) and aspartate transaminase (AST), as these are clinically important markers of disease progression. Changes in non-invasive test (NIT) scores such as Enhanced Liver Fibrosis (ELF) test and change in liver stiffness values assessed by transient elastography should also be included as outcomes. Due to the inherent challenges of liver biopsy, these non-invasive tests are increasingly being used in the diagnosis and monitoring of MASH. As such, they are relevant outcomes to include in the assessment.	outcomes for weight and metabolic effects. Changes in non-invasive tests are covered by the outcomes “resolution of MASH” and “change in fibrosis” that are already included in the scope.
	NHS England	Outcomes listed are appropriate but to note changes in MASLD activity score is less useful outcome, it could be replaced with resolution of MASH. Outcomes that could be added: • Working years of life gained/ lost • A combined end-point (resolution of MASH and improvement of fibrosis) • 2 stage reduction in fibrosis	Thank you for your comment. The outcomes have been updated to include resolution of MASH for semaglutide. Changes in non-invasive tests are covered by the

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		• Improvement in non-invasive tests results (ELF and FibroScan) For semaglutide the additional metabolic health benefits.	outcomes “resolution of MASH” and “change in fibrosis” that are already included in the scope.
	Royal College of General Practitioners	*change in NASH (or MASH) markers* *change in NAFLD (or MASLD) activity score* *change in fibrosis stage* Appropriate but debate about if this actually captures a health benefit - short term surrogate outcomes. Also depending on how these are measured/standardised need to know if this only includes histological markers of above or non-invasive tests? If the former then then population will be very selected/limited. *liver transplantation* *hepatocellular carcinoma* *overall survival* Appropriate but unlikely to be any data on these very long term outcomes requiring modelling with lots of uncertainty in input. *adverse effects of treatment* *health-related quality of life.* Important and appropriate	Thank you for your comments. The outcomes have been updated for semaglutide.

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	The British Association for the Study of the Liver (BASL)	Most deaths in this patient group are caused by cardiovascular disease but cardiovascular risk factors should be optimised in this patient group in any case. Change in NASH (or MASH) markers are a) of dubious validity vs liver biopsy) and b) are unlikely to correlate with clinically relevant outcome measures. Change is MASLD activity score is a short-term outcome measure used in clinical trials whereas change in fibrosis stage is probably the most relevant surrogate marker. The focus should be on major adverse liver outcomes (MALOs). You include hepatocellular carcinoma and liver transplantation but should also try to include features of hepatic decompensation including: development of ascites, hepatic encephalopathy and variceal bleeding.	Thank you for your comments. The outcomes have been updated and now include major adverse liver outcomes for semaglutide.
	UK Clinical pharmacy Association	Appropriate.	Thank you for your comment.
	British Liver Trust	Could also include progression (or not progressing) to more advanced decompensated liver disease (ascites, portal hypertension, variceal bleeding and hepatic encephalopathy)	Thank you for your comments. The outcomes have been updated and now include major adverse liver outcomes for semaglutide.

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Equality	Novo Nordisk	Given the rate of progression of liver fibrosis is linked to BMI, Novo Nordisk proposes to use lower BMI thresholds (usually reduced by 2.5 kg/m^2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African Caribbean family backgrounds as a treatment threshold for patients living with MASLD/MASH and obesity.	Thank you for your comment. This has been noted on the Equality Impact Assessment for semaglutide.
	NHS England	There are known differences in MASH prevalence between ethnic groups (Office for Health Improvement & Disparities, 2024). It is not year clear how patients would be clinically prioritised if demand for the technology is greater than the NHS capacity to deliver treatment. However, consideration is likely to be focused on disease state and setting of care. It should also be noted that existing local variation in primary care practice and diagnostic capacity is likely to impact the number of patients identified and could lead to potential geographical inequity in access to treatment.	Thank you for your comment. This has been noted on the Equality Impact Assessment for semaglutide. Information from the source cited has been included in the scope as follows: 'Rates of premature death from MASLD are higher for people living in more deprived areas of England'.
	The British Association for the Study of the Liver (BASL)	Ethnic differences in criteria for diagnosing obesity should be included.	Thank you for your comment. This has been noted on the Equality Impact Assessment for semaglutide.

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	UK Clinical pharmacy Association	The factors already identified under scoping for *Metabolic dysfunction-associated steatotic liver disease: assessment and management (NG49)* apply equally to this technology appraisal and should be aligned. An additional factor includes the current use of specialised centres within the Operational Delivery Network for delivery of advanced therapies for other liver diseases, including direct acting antivirals for hepatitis C and obeticholic acid/elafibranor for Primary Biliary Cholangitis and bulevirtide for hepatitis D. Restriction to the ODN 'hubs' for obeticholic acid/elafibranor and bulevirtide sometimes reduces access to these therapies if a patient needs to travel over a wide geographical area. This disproportionately affects those with advanced age or disability, as well as those of lower socioeconomic status, which is therefore more likely to disadvantage ethnic minorities. ODN hub and spoke network model (as per direct acting antivirals) would therefore be the preferred model for improving access to these technologies. If this is not more widely commissioned, then approval of these technologies is likely to result in worse outcomes for those with protected characteristics compared to the wider population with MASH.	Thank you for your comments. These have been noted on the Equality Impact Assessment for semaglutide.
	British Liver Trust	MASLD disproportionally affects those from the most deprived communities/disadvantaged groups. This contributes to significant health inequalities Some ethnic groups are more likely to develop MASLD (eg. S Asian population and Latino). There is some evidence Black people who develop MASH are more likely to progress to liver cirrhosis,	Thank you for your comment. This has been noted on the Equality Impact Assessment for semaglutide.
Other considerations	The British Association for	Stopping rules and definitions of non-response.	Thank you for your comment.

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	the Study of the Liver (BASL)		
	UK Clinical pharmacy Association	Analysis of comparative efficacy data between the appraised agent, if available, to guide pathway placement/sequential/combination therapy.	Thank you for your comment.
Questions for consultation	Novo Nordisk	How are people with liver fibrosis caused by MASH who might be eligible for treatment with the technologies identified in NHS practice? MASH is associated with vague symptoms if at all, and therefore patients do not tend to present requesting screening for MASH. Patients are more likely to have persistently deranged liver function tests prompting ultrasound/hepatology referral or might have fatty liver incidentally found on imaging. Upon referral, hepatologists will perform additional testing which might be transient elastography, an ELF test or decreasingly, a liver biopsy to evaluate and diagnose MASH with fibrosis. GPs and endocrinologists managing high-risk patients (e.g. those also living with obesity) in their clinics could also identify patients with high risk of advanced fibrosis using a Fib-4 test. In this case, if a Fib-4 score is <1.3, due to the high negative predictive value of the test, patients are generally kept in primary care. If the Fib-4 is >1.3, hepatologists perform either an ELF test, transient elastography or decreasingly, a liver biopsy, to evaluate and diagnose MASH with fibrosis. How is the disease activity of metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH routinely assessed in the NHS? Which scales are used in clinical practice in the NHS to stage liver fibrosis? Traditionally, disease activity of MASLD and MASH is determined through a liver biopsy. However, this is invasive, there is variability in interpretation, and	Thank you for your comments.

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		is not a scalable test for the estimated population living with MASLD/MASH. Therefore, there is a move towards non-invasive testing however there isn't a consensus on which tests are best and is dependent on local resources. Generally, Fib-4 is used to screen for high risk of advanced fibrosis in at-risk populations and transient elastography is used to determine liver stiffness. If there is diagnostic uncertainty, liver biopsy is still considered and performed. In terms of monitoring disease activity, there is no consensus on the best way to do this, although HCPs tend to consider regular monitoring with transient elastography as well as monitoring of metabolic factors (weight, HbA_{1c}, blood pressure etc) to determine metabolic improvement. Where do you consider the technologies will fit into the existing care pathway for liver fibrosis caused by MASH? Please select from the following, will the technologies be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care MASH services in the NHS are heterogenous and in some cases are part of a multidisciplinary team combined with diabetes and weight management services. Novo Nordisk expects that semaglutide would be prescribed in either primary or secondary care with follow up in primary care. At present, there is no consistent approach to monitoring patients with MASH. Some hepatologists advocate for monitoring using transient elastography at 6 or 12 month frequencies. Some also suggest transient elastography, liver function tests, and metabolic factors (improvement in weight, HbA1c, etc) as a holistic approach to monitoring patients. Therefore, we understand that currently, monitoring takes place in secondary care with a mix of transient elastography and liver function tests.	

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		For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Liver-directed therapies (i.e. resmetirom) will likely be initiated and continued in secondary care with hepatologists, due to the mechanism of action of these drugs. However, medicines with a wider metabolic action (i.e. upstream from the liver), will likely either be initiated in secondary care with hepatologists and continued in primary care, or initiated and continued in primary care. We expect vitamin E and pioglitazone use to remain in secondary care as they are off-licence treatment options, albeit to a lesser extent as they are not commonly used. Would the technologies be candidates for managed access? Semaglutide is unlikely to be a candidate for managed access. Do you consider that the use of the technologies can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Yes. MASH has complex interrelationships with multiple metabolic disorders, such as T2D, obesity, and cardiovascular disease (Targher et al., 2021). In the presence of MASH insulin resistance becomes more pronounced, and hepatic fat accumulation further impairs insulin signalling, further reinforcing the cycle (Gastaldelli and Cusi, 2019). The liver's role as a central metabolic hub means that MASH-related dysfunction can significantly impact whole-body metabolism and contribute to hepatic and cardiovascular complications (Petersen et al., 2021; Hardy et al., 2020).	

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		The cardiovascular impact of MASH is particularly significant, as MASH independently increases cardiovascular risk beyond traditional risk factors (Adams et al., 2017). Recent evidence also suggests that MASH may influence glucose homeostasis through mechanisms independent of insulin resistance, including altered gluconeogenesis and glycogen storage (Birkenfeld and Shulman,2020). This intricate metabolic interplay highlights the value of developing comprehensive treatment approach that targets multiple metabolic pathways simultaneously. Semaglutide has wider metabolic benefits with treatment effects on hyperglycaemia, weight and cardiovascular disease. Therefore an economic model that allows for the capture of these wider metabolic effects should be used, such as the model structure published by Gal et al, 2023, which is in line with the recommendations of the NICE HTA Lab's draft consensus document on MASH economic modelling (NICE HTA Lab, 2025). This is because these complications and comorbid outcomes, rather than MASH itself, typically drive QoL impacts and healthcare costs. QoL data specific to MASH health states is limited. Therefore the health-related benefits of semaglutide are unlikely to be fully captured in the QALY estimate. This is because the risk equations, which predict the complications of MASH and the health state utility values for these later stage conditions, are not studied in a MASH-specific patient population (Johansen et al, 2020). In the absence of MASH-specific patient population utilities, values from other hepatic conditions may be required to inform these health states. Therefore, while Novo Nordisk believes that the current evidence is sufficient to inform the cost effectiveness of semaglutide, there is likely to be an underestimate in the QALY benefit.	

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		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. QoL estimates from other hepatic conditions such as hepatitis C for advanced liver fibrosis. QoL estimates for patients living with T2D, cardiovascular disease and obesity without MASH. Please indicate if any of the treatments in the scope, including pioglitazone, are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. Pioglitazone and Vitamin E are two treatments that are included in NICE guidance as off-license treatments for MASH and restricted to secondary care use. As they are off license, they are used in practice differently than advised in their SmPC. However, in speaking to hepatologists, these are very infrequently prescribed.	
	Madrigal Pharmaceuticals	Which treatments are considered to be established clinical practice in the NHS for liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH)? **Answer: As of now, there are no approved pharmacological treatments indicated nor established as standard clinical practice in the NHS**	Thank you for your comments.

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		specifically for liver fibrosis caused by MASH (Metabolic dysfunction-associated steatohepatitis). How are people with liver fibrosis caused by MASH who might be eligible for treatment with the technologies identified in NHS practice? **Answer: In NHS practice, people with liver fibrosis due to MASH are typically identified in primary care through elevated liver enzymes or incidental findings on ultrasound. GPs may use non-invasive tests that are available to them, such as FIB-4, for initial risk stratification. If the score is elevated or indeterminate, patients are referred to secondary care for further testing with FibroScan or ELF, which help determine the severity of fibrosis. Those with advanced fibrosis may be considered for treatment by resmetirom and lifestyle interventions, following the approach outlined in NICE guideline NG49.** How is the disease activity of metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH routinely assessed in the NHS? Which scales are used in clinical practice in the NHS to stage liver fibrosis? **Answer: In NHS clinical practice, the assessment of disease activity in MASLD and MASH typically begins in primary care when elevated liver enzymes or incidental findings of steatosis on imaging prompt calculation of the FIB-4 score. This non-invasive tool stratifies patients by fibrosis risk using age, AST, ALT, and platelet count. Patients with intermediate or high FIB-4 scores are referred to secondary care for further evaluation using transient elastography (FibroScan) or the Enhanced Liver Fibrosis (ELF) test. While some regions integrate FIB-4 into diabetes annual reviews, proactive screening in high-risk groups (e.g., those with obesity, metabolic syndrome, or type 2 diabetes)**	

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		remains inconsistent across the NHS, leading to variation in implementation of care pathways. Have all relevant comparators for the technologies been included in the scope? **Answer: Please see our comments on section "Comparators".** Are there any subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately? **Answer: The published results from the Phase 3 MAESTRO-MASH trial indicate that there were no meaningful differences in outcomes across the patient subgroups analyzed in the study.** Where do you consider the technologies will fit into the existing care pathway for liver fibrosis caused by MASH? Please select from the following, will the technologies be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. **Answer: We believe pathway C is fit with resmetirom specifications** Would the technologies be candidates for managed access? **Answer: Yes**	

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		Do you consider that the use of the technologies can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **Answer: Yes, the use of resmetirom, an oral, liver-targeted therapy, may offer substantial health-related benefits beyond what is typically captured in QALY calculations:** **1- Resmetirom is an oral once-daily medication, which is more convenient and may improve adherence and patient satisfaction, especially in a population that may already be managing multiple comorbidities. This is important when the comparator in this MTA is semaglutide as a subcutaneous injection, may be associated with injection-related anxiety, training needs, and reduced adherence—all of which are unlikely to be fully captured in QALY estimates.** **2- Oral therapies reduce the need for training, sharps disposal, and potentially fewer primary care or nurse interactions—resulting in cost savings and reduced resource burden, benefits often excluded from QALY-based evaluations.** Please indicate if any of the treatments in the scope, including pioglitazone, are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any	

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		treatments in the pathway used differently than advised in the Summary of Product Characteristics. **Answer: Please see our comments on section "Comparators".**	
	NHS England	NHS England considered the questions posed regarding the draft scope. Questions not covered in the above table are set out below: *Which treatments are considered to be established clinical practice in the NHS for liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH)?* • Currently there is **no licensed treatment** that has shown to improve clinical outcomes in patients MASLD and liver fibrosis. The current treatment focusses on advice for lifestyle changes (based on the evidence that weight loss could potentially prevent disease progression or even improve fibrosis) and treatment of the metabolic comorbidities. • Lifestyle intervention with calorie restriction and physical activity (for MASLD) – weight reduction achieved by calorific restriction, either with or without increased physical activity, leads to improvements in MASLD biomarkers, including liver enzymes, steatosis, MASH, and fibrosis. • Bariatric surgery (for MASH) – effectively promotes weight loss and its maintenance; the effects on body weight largely exceed the 10% weight loss target associated with clearance of liver fat, resolution of MASH and reversal of fibrosis. However, there is only a small eligible population that could benefit.	Thank you for your comments.

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		• NICE NG49 outlines the lifestyle changes and **off-label** pharmacological treatments that can manage MASLD and advanced liver fibrosis. • Pioglitazone or vitamin E can be considered for adults with advanced liver fibrosis (i.e. MASH ≥F3), whether they have diabetes or not (in secondary or tertiary care settings only), and vitamin E can be considered for children with advanced liver fibrosis (i.e. MASH ≥F3) in tertiary care settings only, and in young people in secondary or tertiary care settings. Whilst these options are available, they are not widely used in practice (estimated less than 5% of eligible population is receiving these interventions). *How are people with liver fibrosis caused by MASH who might be eligible for treatment with the technologies identified in NHS practice?* • <u>There are currently no recommendations for case finding approaches for at risk patients. NG49 considered this but did not find in favour, given the current changes in MASLD / MASH care this may need to be revisited.</u> • With disease being typically asymptomatic at earlier stages, there are no standardised detection triggers for liver disease in primary care, nor are there consistent diagnostic pathways. Identification is typically through incidental findings to other investigations (e.g. abnormal LFTs or ultrasound being conducted for another reason) or identification of risk factors prompting further investigation. However, there is substantial potential to reduce duplication and costs in primary care through the development of standardised pathways across England.	

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		• Non-invasive tools such as MAFLD Fibrosis Score, Fibrosis (FIB)-4 Score (FIB-4) FibroScan and the Enhanced Liver Fibrosis (ELF) test are used in primary care to assess level of fibrosis. • A liver biopsy is used in a small subset of patients when there is diagnostic or disease staging uncertainty. *How is the disease activity of metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH routinely assessed in the NHS?* *Which scales are used in clinical practice in the NHS to stage liver fibrosis?* • For the purposes of this response inflammation is the definition by which disease is considered and stage /extent of fibrosis the focus for treatment not activity. • <u>Detection can also arise through profiling other risk factors (such as cardiovascular disease, lipid management and obesity) in primary care when adopting a more proactive and preventative strategy. As such the alignment of MASLD / MASH pathways to these existing pathways will be key in case finding.</u> • Non-invasive tools such as MAFLD Fibrosis Score, Fibrosis (FIB)-4 Score (FIB-4) FibroScan and the Enhanced Liver Fibrosis (ELF) test are used in primary care to assess level of fibrosis. • NICE CKS recommends referring people identified as being at high risk of advanced liver fibrosis for transient elastography or liver biopsy. • NICE DG48 recommends use of FibroScan as an option for assessing liver fibrosis or cirrhosis outside secondary and specialist care to improve access to testing for underserved groups, providing certain	

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		conditions are met and it is used in accordance with national guidelines. • NICE guideline NG49 covers how to identify adults, young people and children with MASLD who have advanced liver fibrosis and are most at risk of further complications. This can only be assessed with a liver biopsy. There are some non-invasive tests that assess the combination of steatohepatitis (activity) and significant fibrosis (termed as at-risk MASH) but these are not particularly accurate. *Please select from the following, will the technologies be:* *A. Prescribed and routine follow up in primary care* *B. Prescribed in secondary care with routine follow-up in primary care* *C. Prescribed and routine follow up in secondary care* *D. Other (please give details)* • The answer is C. However, it was indicated that dose titration for semaglutide can happen in primary care. • Option C could then be followed by B and in terms of long management of the patient possibly should progress to A over time. *Would the technologies be candidates for managed access?* • If these technologies are shown to provide significant clinical benefits for patients, particularly demonstrating that they are a step change in patient outcomes, are shown to be plausibly cost-effective and the appraisal committee have clinical uncertainties that a period of data	

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		collection in managed access could resolve then there is the potential for managed access *Do you consider that the use of the technologies can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?* • There can potentially be societal benefits as liver disease is the second commonest cause of death during working age. *Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits* • Data collected from randomised control trials (RCTs) *Please indicate if any of the treatments in the scope, including pioglitazone, are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.* • Pioglitazone is used off-label for MASH and is licensed to treat type 2 diabetes. Several RCTs and a meta-analysis have consistently shown an improvement in biochemistry and histology after administration of	

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		pioglitazone at doses of 30-45 mg/day versus placebo, without a clear effect on fibrosis regression even after prolonged (3-year) therapy (Tacke et al., 2024) • Vitamin E is also used off-label for MASH, and is licensed to treat vitamin E deficiency. In the PIVENS trial (n=247), at a dose of 800 IU/day, vitamin E significantly improved MASH compared with placebo (49% vs. 19%), as well as reducing steatosis and lobular inflammation, without significant effects on fibrosis (41% vs. 31%; average change in score −0.3 vs. −0.1) RP (Petroni et al., 2021). • However, as noted in Q1 Pioglitazone and vitamin E are very rarely used in the NHS for off label treatment of MASH.	
	Royal College of General Practitioners	*How are people with liver fibrosis caused by MASH who might be eligible for treatment with the technologies identified in NHS practice?* This is the big issue - those that might be eligible for treatment are not diagnosed in any structured or proactive way in the primary care setting. Referral practices and pathways of care differ across the UK. Research currently underway to define the best way to identify those with MASLD with fibrosis in the community /onward referral. At present the identified population may have come from a number of sources and may/may not be under secondary care. Coding for these patients also likely to be an issue - might be coded as 'fatty liver', 'NAFLD' (before new nomeclature) or cirrhosis but lots who have had high Fib4 scores/have had Fibroscans indicating liver fibrosis may not be coded as 'liver fibrosis' and v unlikely will have 'MASH' codes as noted above. Therefore defined population for looking at cost effectiveness /outcomes likely to come from a small tertiary care population.	Thank you for your comments.

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		How is the disease activity of metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH routinely assessed in the NHS? Which scales are used in clinical practice in the NHS to stage liver fibrosis? In primary care MASLD would usually be 'triaged' using Fib4 or similar non-invasive serum score. Some areas may also have acces to requesting ELF test and some areas may have direct access to Fibroscan. Cut offs for these tests and referral criteria into secondary care vary by region. *Where do you consider the technologies will fit into the existing care pathway for liver fibrosis caused by MASH?* As discussed above care pathways for MASLD (would again call it this rather than MASH) are not currently standardised/well defined across the UK. Generally primary care would currently detect MASLD after some incidental liver bloods done for another reason or a fatty liver found on US (again done for another reason). Some more proactive detection in high risk groups (e.g. T2D) is now happening in pockets across the country. Once MASLD is diagnosed most primary care would do a Fib4 or similar NIT to look for risk of liver fibrosis and then refer on based on this (or abnormal fibroscan if have access to this) . I would anticipate that the above technologies would currently fit into this care pathway at the stage of confirmation of liver fibrosis on a combination of NITs (serum and Fibroscan). In principle this could be done in primary care (particularly for semaglutide) but in reality due to inexperience with these medications/lkely managed access due to high prevalence of MASLD and need for ongoing disease activity monitoring to access effectiveness this will initially be done in a secondary care part of the	

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		care pathway. There may be an option for shared care agreements once treatment is initiated and established (especially for semaglutide where primary care already have prescribing experience) *Please select from the following, will the technologies be:* *B. Prescribed in secondary care with routine follow-up in primary care* *C. Prescribed in secondary care with routine follow-up in secondary care* Would anticipate initially C but that could move to a shared care model with B over time. *For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.* The setting for prescribing and follow up of lifestyle interventions (the main comparator) would most likely be primary care which differs from the intervention. Again this varies across the nation with some MASLD liver clinics having an MDT approach including physio/dietician/ endocrine input follow up for intensive lifestyle modification but this is by no means across the patch.	
	UK Clinical pharmacy Association	Which treatments are considered to be established clinical practice in the NHS for liver fibrosis caused by metabolic dysfunction-associated steatohepatitis (MASH)? - As above. How are people with liver fibrosis caused by MASH who might be eligible for treatment with the technologies identified in NHS practice?	Thank you for your comments.

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		- Ad hoc primary or secondary care investigation following signs/symptoms, often incidental findings in response to bloodwork or imaging, or drug monitoring (e.g. methotrexate FibroScan monitoring). Some through viral hepatitis case finding, drug and alcohol treatment/withdrawal services. How is the disease activity of metabolic dysfunction-associated steatotic liver disease (MASLD) and MASH routinely assessed in the NHS? Which scales are used in clinical practice in the NHS to stage liver fibrosis? - Assessment through liver ultrasound and FibroScan, occasionally through biopsy. Scored via Child-Pugh or MELD/UKELD, some use of Fib-4, staged according to Ishak/METAVIR. Have all relevant comparators for the technologies been included in the scope? - As above Are there any subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately? - Expected that those treated early in disease course are likely to benefit more than those with advanced fibrosis Are the outcomes listed appropriate? - As above Where do you consider the technologies will fit into the existing care pathway for liver fibrosis caused by MASH?	

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		- Based on trial data, expect semaglutide to be made available for those failing weight/lifestyle management interventions, with resmetirom offered as an alternative in those patients who require oral over subcutaneous therapy. Please select from the following, will the technologies be: ~~A. Prescribed in primary care with routine follow-up in primary care~~ B. Prescribed in secondary care with routine follow-up in primary care ~~C. Prescribed in secondary care with routine follow-up in secondary care~~ D. Other (please give details): - Based on likely need for imaging and access to FibroScan technology initially, expect that patients may be initiated in secondary care. However patient numbers may place severe burden on secondary care so expect widescale delivery to require primary care involvement and monitoring/drug supply, potentially utilising 3-5 yearly FibroScan in secondary unless access to this technology becomes more widely available in primary care. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. - Pioglitazone and vitamin E (where available) typically prescribed and monitored in primary care. Would the technologies be candidates for managed access? - Yes, priority according to disease stage/comorbidity due to likely high cost associated with treating all eligible patients nationally and impact on services given little existing pharmacological management currently.	

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		Do you consider that the use of the technologies can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? - Reduced utilisation of liver transplant via reduced disease progression and development of cirrhosis, thereby improving health outcomes in broader liver disease population. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. - UK Transplant Registry data on liver transplant for MASH cirrrosis. Please indicate if any of the treatments in the scope, including pioglitazone, are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. - No comment. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the technologies will be licensed;	

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		• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the ccommittee to identify and consider such impacts. - As above. NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation). As above	
Additional comments on the draft scope	The British Association for the Study of the Liver (BASL)	Consider whether you are treating MASLD as a *disease* or as a *risk factor* for developing clinically significant liver disease (cirrhosis, HCC). If a disease, you would stop if no response to therapy. If a risk factors, you would continue long term in the target population (like statins).	Thank you for your comments.
	UK Clinical pharmacy Association	Will the appraisal include assessment of combination therapy with both agents? This appraisal is for semaglutide SC only – will this be revisited should the license be extended to oral formulations currently in use for diabetes? Failure to re-appraise following licence extensions is a common barrier to	Thank you for your comments. The scope has been updated to a single technology

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		commissioning and achieving broader patient access, which will impact on some with protected characteristics (such as age/disability) who might struggle to self-administer injections.	appraisal for semaglutide.
	British Liver Trust	At the moment there is wide variation in case-finding strategies in primary care and many areas do not have systematic routine liver testing of those people who are at risk (eg people with Type 2 diabetes and those who are overweight). There needs to be a consistent and agreed use of **non-invasive tests** to ensure accurate indicative fibrosis staging (eg LFT/Fib 4/ELF/FibroScan). There needs to be agreed and consistent cut offs. There are currently not enough FibroScans in the community. There needs to be a 'shared care' approach with a combination of specialist and GP-led approaches that integrate lifestyle interventions so that treatment pathways are cost-effective and widely implementable. Treatments can start with specialists and then transfer to primary care for ongoing management – however at the moment there is a lack of knowledge and confidence amongst GPs. Treatment should be integrated as part of care of other metabolic diseases – looking at the patient as a whole. Some patients may benefit from combining treatments – both resmetirom and semaglutitude. Need to clearly define when and how to assess whether the treatment is working and when to withdraw treatment.	Thank you for your comments. We note that changes in non-invasive tests are covered by the outcomes "resolution of MASH" and "change in fibrosis" that are already included in the scope.