Review

JOURNAL OF HEPATOLOGY

Standardisation of diet and exercise in clinical trials of NAFLD-NASH: Recommendations from the Liver Forum

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Keywords: Lifestyle modifications; Placebo effect; Endpoints; Fibrosis; Clinical studies.

Received 22 August 2019; received in revised form 29 March 2020; accepted 20 April 2020; available online 27 April 2020

Summary

Lifestyle modification is the foundation of treatment recommendations for non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The design of clinical trials in NASH may be impeded by the lack of a systematic approach to identify and evaluate how lifestyle changes and/or modifications influence clinical trial outcomes and associated endpoints. Furthermore, there are additional uncertainties regarding the methods that can be utilised to better characterise and quantify lifestyle variables – which can influence disease activity and alter trial endpoints – to allow for comparisons of trial outcomes across different phases of research and/or within drug-classes. This summary by the Liver Forum's Standard of Care Working Group reviews currently available clinical data, identifies the barriers and challenges associated with the standard of care in NAFLD/NASH clinical trials, defines available assessments of lifestyle changes, and proposes approaches to better understand and define the influence of diet and exercise on NASH treatment in the context of different pharmacologic interventions. The ultimate objective is to propose tangible solutions which enable investigators, sponsors, and regulatory authorities to meaningfully interpret clinical trial outcomes and the impact of lifestyle modification on such outcomes as they pertain to phase I-IV clinical trials.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, affecting 25–30% of the adult general population in industrialised countries.[1] NAFLD is a spectrum of disease ranging in severity from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH).[2,3] Patients with NASH are at increased risk of fibrosis progression and its associated negative clinical outcomes.[4] Given the high prevalence of NAFLD, the increased risk of morbidity and mortality associated with NASH, and the absence of approved therapies, the development of treatments for NASH is of great interest. The recommended standard of care (SOC) for NASH is lifestyle modification, with the goal of optimising weight and insulin sensitivity. Lifestyle modification will remain key to managing NASH even after medical interventions become available.

Improvements in lifestyle can have immediate and sometimes significant effects on the liver in patients with NAFLD, and may contribute to the high rate of "placebo response" observed in NASH trials.[5,6] In the drug development/regulatory context, a high placebo response rate necessitates larger trials to guarantee sufficient power to detect a significant difference between placebo and intervention arms, results in difficulty interpreting outcomes and makes cross-trial comparisons challenging. Ideally, clinical trial protocols should provide uniform guidance on lifestyle modifications to better account for placebo responses.[5] The inconsistent utilisation of tools to measure and quantify lifestyle modification in NASH clinical trials makes this potential confounder difficult to account for and thus, difficult to control. Lastly, the lack of an appropriate lifestyle recommendation that is applicable to different patient populations in different geographic regions is a concern that should be prospectively addressed. In clinical research for NASH, a significant improvement in the placebo arm might prevent the detection of a beneficial effect of the intervention (*e.g.*, drug) being studied. Failure to document what lifestyle recommendations were provided/followed prevents a comprehensive examination of factors that may impact placebo response rates.

Treatments for NASH will need to be generalisable to the real-world setting where not all patients are able or willing to adhere to diet/exercise instructions, as with the clinical experience in diabetes and cardiovascular disease. Thus, the field of NASH needs to find a suitable approach to

address changes in lifestyle without necessarily implementing a "lifestyle intervention" as part of clinical trials. We need to better understand the effect of promising interventions on the underlying pathophysiology in the context lifestyle changes.

In this paper, we review the documentation of lifestyle recommendations in completed and ongoing trials, and look at the importance of evaluating diet and physical activity. We conclude with recommendations for a "minimal set of measures" to help standardise lifestyle recommendations for the field by providing clarity on clinical trial designs that minimise the need for lifestyle interventions beyond the intervention being tested. These recommendations will increase the ability to interpret treatment effects, within a trial, and facilitate better comparative studies or combination trials. This publication builds on the Standardisation of Baseline Parameters article previously published by the Liver Forum.[7]

Founded in 2014, the mission of the Liver Forum is to advance the regulatory science for the treatment of NASH and liver fibrosis by identifying barriers and gaps in the field, and addressing them through a multi-stakeholder consensus building process.[8] The Liver Forum SOC Working Group was created to focus on the issue of inconsistent recommendations and documentation of lifestyle in NASH clinical trials, with the aim of developing consensus recommendations for a standardised approach. The working group is comprised of experts from academic medicine, regulatory agencies, pharmaceutical and diagnostic companies, and patient organisations.

Methods

The SOC Working Group was divided into 2 subgroups: i) the lifestyle modification subgroup, and ii) the comorbidity management subgroup. This summary focuses strictly on lifestyle modification as defined by diet and exercise. Recommendations for minimising confounding factors as they pertain to management of comorbidities will be undertaken by the comorbidity management subgroup.

The SOC Working Group had spirited discussions as to whether or not lifestyle modification should be integral to the study design of longitudinal clinical trials for NAFLD/NASH. The Working Group assessed the state of the science in clinical trials for NAFLD/NASH, reviewed current practices and guidelines in clinical trials of diabetes and obesity, and made recommendations for approaches to manage lifestyle recommendations within the context of NASH clinical trials.

As a first step, we reviewed randomised, placebo-controlled NAFLD/NASH trials (RCTs) registered in *clincialtrials.gov* for study designs. Trials not registered in *clinicaltrials.gov*, but available through PUBMED, were also evaluated. We stratified studies based on the methodology applied to lifestyle modification within the trial, such as recommendations, monitoring, and compliance. Data from historical studies detail the existing lifestyle modification approaches, or lack thereof, which serve as the foundation of deliberations in the SOC Working Group and the recommendations detailed within this position paper.

Need for standardisation of diet and exercise recommendations in clinical trials of NASH

The current AASLD and EASL guidelines recommend weight loss, achieved by hypocaloric diets in conjunction with increased physical activity, for treatment of NAFLD/NASH.[9,10] While lifestyle modification consisting of diet, exercise, and weight loss is advocated to treat patients with NAFLD/NASH,[9,10] such modifications are difficult to sustain long-term.[11] Moreover, weight loss alone may not suffice for the majority of patients, particularly those with advanced hepatic fibrosis. In addition, there are challenges to the implementation of lifestyle recommendations. Currently, the manner of delivering lifestyle recommendations, and specifications of these recommendations, are at the discretion of an investigator, risking site-specific differences and confounding of study outcomes. Although standardised lifestyle recommendations ensure that all study participants are given the same recommendation for the duration of the trial, such recommendations may introduce a recruitment and retention bias, potentially resulting in selection of a study cohort which is not representative of the larger population of patients with NASH and a study outcome that is not broadly generalisable. Additionally, if recommendations are too rigorous, they may lead to difficulties in the interpretation of study results by introducing additional confounders: the recommendation itself as an intervention/treatment, and the degree of patients' adherence to the recommendation. Conversely, if no recommendations for lifestyle modification are provided then the deferral to the discretion of a site investigator may risk introducing site-specific differences in the primary outcome of a trial. Site-specific differences can influence the outcome of a multicentre study and make it difficult to interpret study results. For example, the implementation of rigorous lifestyle recommendations at high enrolling sites, or sites with an imbalance of patients in the trial arms due to low enrolment rates and/or multiple stratification factors (*e.g.*, diabetes, fibrosis stage, vitamin E) can result in differential treatment effects. Furthermore, while randomisation should equalise the effects of lifestyle equally across treatment and placebo arms, cultural and regional differences in dietary intake and physical activity options and/or availability limit the ability to standardise lifestyle for diverse populations, as well as in global trials.

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https://doi.org/10.1016/j.jhep.2020.04.030

Key point

Change in lifestyle can impact NAFLD and may contribute to the high rate of "placebo response" observed in NASH trials, potentially preventing the detection of a beneficial effect of the intervention being studied.

Key point

Clinical trial protocols should provide uniform guidance on lifestyle modifications.

In clinical trials where a behavioural component (*i.e.*, diet or exercise) is being monitored, participation may introduce the Hawthorne effect,[12] where patients either consciously or unconsciously alter their behaviour as a response to being observed. For example, patients with NAFLD/NASH may change their diet or increase physical activity due to knowledge of these factors being actively monitored, leading to a different outcome from patients who are not otherwise enrolled or monitored under a research protocol.[13] Unfortunately, changes in physical activity and/or behaviour have not been systematically measured in the context of NASH studies. While activity is a variable for consideration, similarly, the level of physical inactivity is an important measure to ascertain, as this may also influence outcomes.[14]

Lessons learned from applying lifestyle recommendations to clinical trials in NASH

Across studies which have informed both recommendations for clinical care of NAFLD/NASH, as well as served as the framework for current clinical studies, the protocol for lifestyle modification as part of the lifestyle recommendations in clinical trials is either not captured, not well defined, or not fully described. A review of 46 clinical trials available on PUBMED and *clinicaltrials.gov* showed that 52% of randomised and investigator-initiated controlled trials did not describe lifestyle modification at all, 22% had an undefined recommendation of diet and/or exercise, and 26% had nutritional counselling and/or exercise recommendations. Lack of this basic information on a granular level makes interpretation of results challenging, particularly when early phase studies otherwise fail to demonstrate a therapeutic response over placebo treatment arms. When coupled with ethnic and regional differences in adopting lifestyle changes after counselling, clearly defining the presence or absence of such changes will facilitate our ability to optimally design trials, ensure adequate sample size, and consider lifestyle changes as covariates or confounders in the statistical handling of pre-specified outcomes of the intervention(s) being studied.

Key point

While no single optimal diet or exercise recommendations currently exist, stable and sustainable lifestyle modification is encouraged for clinical studies.

The importance of elucidating the potential impact of lifestyle recommendations on clinical endpoints is highlighted by a recent systematic review and meta-analysis of placebo groups from 39 histology-based RCTs of adults with NASH.[5,15] As previously reported, 25% of patients in the placebo groups (95% CI 20%–30%) had an improvement in NAFLD activity score (NAS) by ≥2 points, and 21% had improved fibrosis scores.[5] Table 1 details the broad heterogeneity of approaches to lifestyle recommendations in NASH trials published to date. This heterogeneity, combined with the variance in placebo response rates, supports the rationale of proposing strategies to *guide, determine, or quantify* lifestyle recommendations for clinical trials in NASH. This is particularly important in short-term proof-of-concept, dose-finding trials. A recent meta-analysis of 22 RCTs (11 with lifestyle recommendations only) consistently showed evidence of improvement in biomarkers of liver disease in NAFLD in the short to medium term.[16] However, no evidence was found of between-group differences in weight, glucose, homeostatic model assessment of insulin resistance, alanine aminotransferase (ALT), or fatty liver index in the long-term follow-up. Endpoints particularly impacted by minor changes in lifestyle recommendations are transaminases and liver fat content.[15,16] Lifestyle recommendations in NASH clinical trials can be grouped into 3 main categories: i) integrated nutritional counselling and/or exercise recommendations, ii) undefined recommendations of diet and exercise, and iii) no mention of diet or exercise.

In studies that have integrated nutritional counselling and/or physical activity recommendations, the placebo response rate has ranged from 11% reduction in hepatic fat content via proton magnetic resonance spectroscopy at 16 weeks[17] to non-significant changes in mean fibrosis stage at 96 weeks.[18] Some of these studies utilised run-in periods, where participants were interviewed by a dietician and instructed not to change their current diet or exercise levels for 4 weeks.[15,19] After which, daily caloric intake was reduced and reinforced during follow-up visits. Other trials instituted specific diets that were reinforced by 3-day food diaries,[20,21] and encouraged physical activity by providing pedometers.[17] The existing studies that introduce dietary recommendations, nutritional counselling, and/or physical activity have demonstrated that although recommendations were made, no quantifiable measures of adherence to dietary or physical activity recommendations were reported.

There are several studies that report using standardised recommendations, without clarifying the standard for which those recommendations are provided.[22–25] These studies are categorised as undefined recommendations of diet and exercise. Recommendations for diet and/or exercise in studies that had undefined standards of lifestyle modification were left to the discretion of investigators, local, or regional practices for what is considered “healthy” and SOC. While healthy lifestyle approaches are routinely recommended for patients with NASH, there are no quantifiable or structured measures to capture what “healthy” is, resulting in potentially large variability in the implementation of recommendations within trials.

Despite integrating specific, or undefined lifestyle recommendations, most NASH studies (52%) do not mention diet and/or exercise recommendations, further creating a sizeable gap in the

Table 1. Different lifestyle approaches across clinical studies in NASH.

Clinicaltrials.gov NCT #	PMID #	Intervention	Diet/Exercise approaches detailed	Compliance	Key placebo response (Compared to baseline)
NCT00633282	26252777	Pioglitazone Berberine	Diet: study participants were instructed to subtract 500 kcal from daily mean calorie intake when entering the treatment. Activity: Medium intensity aerobic exercise for more than 150 minutes per week with a heart rate of 50–70% of the maximal heart rate; or higher-intensity aerobic exercise for more than 90 minutes per week with heart rate around 70% of the maximal heart rate.	Measured by pedometers and a 3-day food diary at 4 times during the trial, and reviewed by a dietician. Compliance of the lifestyle group, lifestyle plus pioglitazone, and lifestyle plus berberine was 92.5%, 95.8%, 94.5% respectively.	After 16 weeks: −14.1 IU/L mean change in ALT, −6.5 IU/L mean change in AST, and 11.4% reduction in hepatic fat content via H-MRS.
NCT01373554	28225186	Oltipraz Placebo	The dietitian at each site instructed all participants to keep a low-fat hypocaloric diet by reducing their intake by 500 kcal/day.	n.a.	At 24 weeks: −3.2% absolute change in liver fat, −0.6% reduction in liver fat, −25.3 mean change in ALT, −10.9 mean change in AST.
NCT00303537	19811343	Metformin Placebo	General advice about a healthy lifestyle, *i.e.* physical activity at least 30 min daily and a diet low in fat, particularly saturated fat, and refined carbohydrates.	n.a.	At 6 months: 38% of placebo group improved steatosis, 13% improved ballooning necrosis, 33% improved lobular inflammation, 50% improved NAS, and 17% improved fibrosis.
n.a.	24407920	Ezetimibe Placebo	An hour of nutritional counselling by an experienced dietitian before starting the 6 month treatment period. In addition, they were given a standard energy diet (125.5 kJ/kg per day; carbohydrate 50–60%, fat 20–30%, protein 15–20%) and exercise (5–6 metabolic equivalent estimations for 30 min daily) counselling before the study.	n.a.	At 6 months: Steatosis decreased 1.42 ± 0.15 to 1.17 ± 0.17, NAS decreased 3.25 ± 0.53 to 2.82 ± 0.59, minimal changes in AST and ALT.
NCT00227110	17135584	Pioglitazone	During the 4-week run-in period, the subjects were interviewed by the research dietitian and instructed not to change the calorie content of their diet or their level of physical activity. 6 months of treatment with a hypocaloric diet (a reduction of 500 kcal per day in relation to the calculated daily intake required to maintain body weight).	n.a.	At 6 months: 21% decrease in AST, 34% decrease in ALT, 38% improvement in steatosis, 24% improvement in ballooning necrosis, 29% improvement in lobular inflammation, 38% improvement in combined necroinflammation, and 33% improvement in fibrosis.
n.a.	18445142	Insulin-sensitizing agents	The management was focused in the following areas: establishment of an appropriate diet and exercise program including walking (initially as 300 steps/day for 3 days, thereafter adding 500 steps at 3-day intervals until a level of 10 000 steps was attained) and jogging (20 min twice a day). A conventional diet of 25 kcal/kg · ideal body weight (kg) and an exercise program. Three meals per day containing 60% carbohydrate, 25% fat and 15% protein were provided for each individual.	n.a.	At 48 weeks: AST improved from 39.3 ± 11.1 to 30.0 ± 8.6, ALT improved 66.9 ± 28.9 to 42.0 ± 16.2.
n.a.	21180541	Metformin and standard therapy *vs.* Standard therapy alone	Dietician counselling referred a DASH (Dietary Ap-proaches to Stop Hypertension) diet emphasizing fruit, vegetables and lowering saturated fat and cholesterol. Patients advised to attempt to complete 30 minutes of aerobic exercise 4 times per week.	Study participants were seen 2 weeks after enrolment and at 6-week intervals thereafter where BMI was measured and compliance with exercise regimen was assessed.	At 12 months: ALT levels decreased by 40.7 IU/L, AST levels decreased by 20.1 IU/L, NAS decreased 4.6 to 3.4, and steatosis decreased 2.23 to 1.58.

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Table 1. (*continued*)

Clinicaltrials.gov NCT #	PMID #	Intervention	Diet/Exercise approaches detailed	Compliance	Key placebo response (Compared to baseline)
NCT00590161	**21748765**	**Pentoxifylline Placebo**	**Individualized nutritional counselling for adequate caloric intake and recommended lifestyle modifications.**	**Assessed by direct questioning of the subjects over course of the study.**	**At 1 year: 13.8% of placebo group showed a decrease of ≥ 2 points in the NAS and 15% improved fibrosis; mean change in steatosis score: −0.04, lobular inflammation: 0, and liver fibrosis: +0.4.**
n.a.	**26831610**	**Relmisartan Placebo**	**Moderate exercise consisting of 30 min of walking daily with dietary advice to avoid fatty foods and excessive sugar-containing diet.**	**n.a.**	**At 1 year: 20% of patients improved NAS by ≥ 2, mean change of −1.10 ± 0.57 in NAS, −0.30 ± 0.48 fibrosis.**
n.a.	**29085788**	**Pentoxifylline Placebo**	**Moderate exercise (30 minutes of walking/day) and dietary advice (avoidance of fatty foods as well as diet containing excessive sugar).**	**n.a.**	**At 1 year: 30% of patients improved NAS ≥ 2, mean change in NAS 0.90 ± 0.99, steatosis improved from 2.30 ± 0.68 to 1.40 ± 1.08.**
NCT00994682	**27322798**	**Pioglitazone Placebo**	**Patients were instructed by a dietician to keep physical activity and diet constant during the run-in phase (mean duration, 1 month). Participants were prescribed a hypocaloric diet (500–kcal/d deficit from the calculated weight maintaining diet) through dietary counselling.**	**n.a.**	**At 18 months: 17% had a ≥2-point improvement in NAS without worsening of fibrosis, 19% had resolution in NASH, 22% had an improvement in inflammation, 24% had improvement in ballooning, 25% had improvement in fibrosis, and 4% had a reduction in hepatic triglyceride content.**
n.a.	**28419124**	**Losartan Placebo**	**Standard advice with regard to diet, exercise and weight maintenance, which was the recommendation to undertake 150 minutes of exercise/per week, combined with a reduction in intake of 500 kcal per day.**	**n.a.**	**At 96 weeks: Mean fibrosis stage decreased 2.41 (0.87) to 2.35 (1.06).**
NCT00470171	n.a.	UDCA Placebo	Patients encouraged to lose weight if overweight, to exercise, and to consume a healthy diet. No specific dietary counselling was implemented.	Lifestyle information (physical activity, alcohol consumption, and possibly others) was collected at baseline and completion of the study.	n.a.
NCT01811472	n.a.	LCQ908 Placebo	Patients were required to remain on their American Heart Association (AHA) diet for the entire duration of the study.	n.a.	At 24 weeks: 0% mean change in liver fat, −5.3 IU/L ALT, −1.8 IU/L AST.
NCT02006498	28419855	Silymarin Placebo	Lifestyle advice and regular advice on dietary intake and physical activity by senior study physicians.	n.a.	At 48 weeks: 26% achieved ≥30% improvement in the NAS, 6% had fibrosis reductions of 1 point or more.
NCT01237119	26608256	Liraglutide Placebo	All patients received standard National Health Service care recommendations on lifestyle modifications, including exercise, weight reduction, and dietary modification.	Health-related quality-of-life scores (Medical Outcomes Study 36-Item Short-Form Health Survey version 2 [SF-36v2] physical and mental components), and daily dietary consumption.	At 48 weeks: 9% had resolution of non-alcoholic steatohepatitis, 14% had improvement in fibrosis, 64% improved NAS, 32% improved hepatocyte ballooning, 45% improved steatosis, 55% improved lobular inflammation, −10.2 IU/L ALT, −8.6 IU/L AST mean change.

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Table 1. (*continued*)

Clinicaltrials.gov NCT #	PMID #	Intervention	Diet/Exercise approaches detailed	Compliance	Key placebo response (Compared to baseline)
NCT00492700	18503774 19877169	Rosiglitazone Placebo	Patients instructed to lose weight if they were obese or overweight, to follow a healthy diet, and to exercise at least twice a week. No specialized nutritional counselling was implemented.	No information on diet or physical activity was collected throughout the study.	At 1 year: placebo group has a 10% improvement in steatosis, 0.09 reduction in NAS score, 0.32 increase in ballooning, 0.13 reduction in intralobular inflammation, 0.25 reduction in fibrosis stage, 0.09 reduction in perisinusoidal fibrosis.
NCT02217475	28833331	Cenicriviroc Placebo	The study protocol relied on local standard of care for implementing diet and lifestyle intervention in randomised subjects.	n.a.	At 1 year: 19% of placebo group achieved ≥2-point improvement in NAS, 6% resolution of steatohepatitis, and 10% no worsening of fibrosis.
NCT00267670	21677329	Pentoxifylline Placebo	No specific dietary or exercise recommendations were given to either treatment group. Diet and exercise were encouraged and monitored in all subject.	n.a.	At 1 year: 12% reduction in ALT, 10% reduction in AST, Delta values: −0.6 steatosis grade, 0.3 lobular inflammation, 0 hepatocyte ballooning, 0.4 fibrosis score, −0.3 NAS.
NCT00586911	19824078	Betaine Placebo	All participants were given appropriate nutritional and weight-loss advice. No additional weight loss strategies were offered.	n.a.	At 1 year: mean changes in ALT −10.9 (44.5), AST−0.3 (44.7), −1.0 (2.6) NAS, 0.7 (1.24) steatosis grade, 0.28 (1.23) lobular inflammation, 0.4 (1.6) fibrosis stage.
NCT01265498	25468160	UDCA Placebo	Standardised recommendations on healthy eating habits, weight reduction, exercise, and the management of hypertension, hypercholesterolaemia, and diabetes when indicated.	n.a.	At 72 weeks: 13% had resolution of NASH, 19% improved fibrosis, NAS decreased −0.7, 31% improved ballooning, 35% improved lobular inflammation, 38% improved steatosis, 13% improved portal inflammation.
NCT00063622	20427778	Pioglitazone Vitamin E Placebo	Standardised recommendations concerning lifestyle modification (dietary modification, weight loss, exercise administered in a consistent manner at all 8 clinical centres).	n.a.	At 96 weeks: 19% of placebo group improved NASH, 31% improved steatosis, 31% improved fibrosis, 35% improved lobular inflammation, 29% hepatocyte ballooning, 21% had resolution of NASH.
NCT02077374	30430605	IDN-6556 Placebo	Subjects who planned to make a significant lifestyle change to their diet or exercise regimen during the study were to be excluded.	3 subjects (1 randomised to placebo, 2 randomised to emricasan) had a weight change of greater than 5 pounds (−9 lbs. in the placebo subject, and −18 and +14 lbs in the emricasan subjects).	At 28 days: median −9.4 IU/L ALT, −5.2 IU/L AST.
NCT00501592	23727264	Obeticholic acid Placebo	n.a.	n.a.	At 43 days: mean change +4.0 IU/L AST, +11 IU/L ALT, 0.3 ELF score, 6.7 HA, 0.5 Pro C-3, 46.3 TIMP.
NCT01094158	24815326	Aramchol Placebo	n.a.	n.a.	At 3 months: 6.39% reduction in liver fat content, mean change −10.4 IU/L ALT, −5.83 IU/L AST.
NCT02856555	30059671	GS-0976 Placebo	n.a.	n.a.	At 12 weeks: Median decrease of 8% in MR-PDFF, median 12.5% decrease in MRE-stiffness.

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Table 1. (*continued*)

Clinicaltrials.gov NCT #	PMID #	Intervention	Diet/Exercise approaches detailed	Compliance	Key placebo response (Compared to baseline)
NCT01277094	24795254	RO5093151 Placebo	Dietary consumption was captured in some patients and assessment of changes in diet and exercise were scheduled for the baseline visit and the visits at the weeks 4, 8, and 12.	n.a.	At 12 weeks: Mean liver fat decreased 0.07%, mean change in liver fat content −0·02%, mean change +1.17 IU/L ALT, +1.78 IU/L AST.
NCT02633956	n.a.	Obeticholic Acid and Statins	n.a.	n.a.	At 16 weeks: −53.33 mg/dl mean change in LDL concentration.
NCT02546609	29696666	NS-0200 Placebo	n.a.	n.a.	At 16 weeks: −10 relative change in MRI-PDFF; in placebo subjects with ALT below the median value of 50 IU/L exhibited a 20.5% decrease in MRI-PDFF.
NCT01260246	28104990	Sitagliptin Placebo	n.a.	n.a.	At 24 weeks: AST improved from 39 ± 19 at baseline to 42 ± 23, ALT 46 ± 36 at baseline to 48 ± 28, Fibrosis 2.2 ± 0.8 to 2.0 ± 1.0, NAS 4.2 ± 1.5 to 3.8 ± 1.9.
NCT01066364	22431131	Colesevelam Placebo	n.a.	n.a.	At 24 weeks: Mean reductions in MR-PDFF 2.7%, ALT 13.7, AST 6.7.
NCT02442687	n.a.	JKB-121 Placebo	n.a.	n.a.	At 24 weeks: −3.09 mean change in MRI-PDFF, −20.9 IU/L mean change in ALT.
NCT01766713	25482832	Ezetimibe Placebo	n.a.	n.a.	At 24 weeks: MRI-PDFF decreased from 18.5%–16.4%, ALT decreased from 45.5 to 42.0, AST 31.0 to 32.0; 27.8% had NAS improvement ≥ 2.
NCT01963845	27151177	Sitagliptin Placebo	n.a.	n.a.	At 24 weeks: 13.9% reduction in liver fat via MRI-PDFF, 11.5 mean reduction in ALT, 5.0 mean reduction in AST, 3.8 increase in FIBROSpect II Index.
NCT00680407	n.a.	Silymarin Placebo	n.a.	n.a.	At 48–50 Weeks: 12% of placebo group improved NAS ≥2-point.
NCT01154985	24818764	EPA-E Placebo	n.a.	n.a.	At 12 months: Median change of −1 in NAS, −8 IU/L AST, −20 IU/L ALT.
NCT01694849	26874076	GFT505 Placebo	n.a.	n.a.	At 1 year: 12% resolved NASH without fibrosis worsening.
n.a.	20683947	High-dose UDCA Placebo	n.a.	n.a.	At 18 months: Overall Histology score decreased −0.97, NAS −1.03, AST −14.30 IU/L, and ALT −38.15 IU/L.
n.a.	14999696	UDCA Placebo	n.a.	n.a.	After 24 months: mean difference −20.7 IU/L AST, −31.6 IU/L ALT, −0.3 steatosis, −0.1 inflammation, −0.0 fibrosis, −0.1 hepatocyte ballooning, Mallory's hyaline −0.2.
NCT02068339	n.a.	Oltipraz Placebo	n.a.	n.a.	n.a.
NCT03400163	n.a.	BMS-986036 Placebo	n.a.	n.a.	n.a.
NCT02316717	n.a.	IMM-124E Placebo	n.a.	n.a.	n.a.
NCT00668070	n.a.	ASP9831 Placebo	n.a.	n.a.	n.a.

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Table 1. (*continued*)

Clinicaltrials.gov NCT #	PMID #	Intervention	Diet/Exercise approaches detailed	Compliance	Key placebo response (Compared to baseline)
NCT00740610	n.a.	GS-9450 Placebo	n.a.	n.a.	n.a.
NCT02421094	n.a.	GR-MD-02 Placebo	n.a.	n.a.	n.a.
NCT02290106	n.a.	Pitavastatin Placebo	n.a.	n.a.	n.a.

Coding: Bold text = integrated nutritional counselling and/or exercise recommendations; Underlined text = undefined recommendations of diet and exercise; Neither bold nor underlined = no mention of diet and exercise. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; HA, hyaluronic acid; H-MRS, proton magnetic resonance spectroscopy; MRI-PDFF, MRI-proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; Pro C-3, N-terminal type III collagen propeptide; RCTs, randomised controlled trials; SOC, standard of care; TIMPs, tissue inhibitor of metalloproteinases; UDCA, ursodeoxycholic acid.

interpretation of study results. It is not surprising that placebo responses across these studies vary: a mean change in aspartate aminotransferase and ALT at 12 and 16 weeks of −6 to +4 IU/L and −10 to +11 IU/L; a reduction in liver fat as measured by MRI-proton density fat fraction at 24 weeks of 2 to 14%; and improvement in NAS ≥2 points at 1 year in 12–19% of patients.[26–34] Overall, the variability and lack of transparency in lifestyle recommendations in NASH trials strongly suggest that strategies are needed to *guide*, *determine, or quantify* lifestyle recommendations to facilitate study result interpretation.

Tools used to measure diet and exercise behaviour in NASH clinical studies

Measuring diet and exercise behaviour in NASH clinical studies is necessary to evaluate the impact and/or influence of lifestyle modification on clinical outcomes; however, few clinical studies have incorporated proper strategies to capture this information or use it in data analysis. Capturing diet and exercise behaviour may identify target cohorts that will or will not benefit from a particular therapy, and hence, distinguish responders from non-responders. For example, drugs that impact muscle insulin resistance might confer a better response if a patient exercises or is on a particular diet. Introducing tools to measure diet and exercise could introduce reporting bias and Hawthorne effects among respondents, resulting in a change in dietary intake and exercise behaviour, which is otherwise different from pre-study behaviour. Furthermore, such tools may encumber the conduct of clinical studies by burdening participants and study personnel (with associated costs). However, measurement tools could be of significant value when assessing changes from baseline, impact on clinical variables, or evaluating potential confounders. Such tools can promote adherence and provide objective measures of diet and exercise behaviours not otherwise captured. With regards to physical activity, one alternative could be to use pedometers, which provide the most basic estimate of physical movement quantified as steps. Since walking is one of the most frequently reported forms of physical activity,[35] pedometers are likely to capture the majority of physical activity behaviours among patients with NASH. However, a pedometer's display may influence participants to perform more physical activity in order to meet or exceed certain goals (*i.e.* 10,000 steps); a similar influence would be expected to occur in the control arm. Alternatively, a pedometer can be used to either increase physical activity through a display visible by a participant or allow the participant to remain blinded to their performance metrics by providing no visible data. While the number of steps taken can provide an overview of general physical activity, the intensity and

quantity of physical activity can be provided by wearable multi-axial accelerometers (*e.g.* Fitbit®, smart watches). Multi-axial accelerometers are becoming more widely used to track activity levels in several chronic disease populations.[36]

Dietary food questionnaires including the Block98 food frequency questionnaire (FFQ)[37] have previously been utilised in the NASH CRN PIVENS study.[24] The Block98 FFQ has been validated in broad populations and provides assessment of nutritional and caloric intake data. Other studies have used a 3-day food diary to track patient dietary intake. Such tools are dependent on accurate patient recall. Together, self-reported questionnaires and pedometers can provide insight into the dietary and physical activity behaviours of NAFLD participants in a trial. Increasing technological capabilities may provide a more accurate assessment of lifestyle behaviour, but scientific accuracy, regulatory issues, and technical aspects need to be carefully assessed before using these tools in a clinical trial.

Key point

To address heterogenous approaches to lifestyle in clinical trials, we recommend: i) evaluation at screening for current diet and exercise habits, ii) lifestyle stability prior to screening for baseline measures, iii) counselling on improving diet and physical activity and iv) documentation of lifestyle throughout the trial.

Lessons learned from clinical trials in diabetes and obesity: Regulatory authority perspective

Recent diabetes lifestyle recommendations[38] highlight the importance of individualised assessment of eating patterns, preferences, and metabolic goals (*e.g.* considering personal preference, tradition, culture, religion, health beliefs and goals, economics) since evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people with diabetes.

For exploratory phase II diabetes trials, the FDA recommends sponsors include a 6–8 week run-in period prior to randomisation to allow for diabetes education and optimisation of compliance with diet and exercise.[39,40] This run-in period is also intended to allow for stabilisation of parameters of metabolic control (*e.g.,* glycated haemoglobin [HbA1c]), so that the magnitude of the effect of different doses can be accurately estimated. The EMA also recommends a run-in period when evaluating HbA1c as a primary endpoint to wash-out patient exposure to previous glucose lowering agents.[41] Absence of this run-in period can result in overestimation of the real-world treatment effects. In addition, placebo run-in periods in phase III studies can help screen out non-compliant participants.

Key point

Standardised approaches to lifestyle modification in clinical studies require consideration of program timelines, feasibility, practicality and financing.

The FDA 1996 Guidance for the Clinical Evaluation of Weight Control Drugs[42] advocated that RCTs include a 6-week behavioural weight reduction run-in period designed to: i) identify placebo responders and ii) avoid unnecessary treatment with drugs in those who could lose weight through diet and exercise.[43] During the 2004 FDA Endocrinologic and Metabolic Drugs Advisory Subcommittee Meeting,[44] most panellists were in favour of abolishing the run-in period since most patients entering obesity RCTs had unsuccessfully tried diet and exercise programmes. There was concern from the committee regarding how to interpret the data at the completion of trials using run-in periods, and it was suggested that removing the 6-week run-in period would render the results more generalisable and simplify the measure of effect as placebo-subtracted weight loss from baseline. The final suggestion by the committee was to remove the run-in design and encourage companies to include a stabilisation or screening period to ascertain baseline values of weight and identify comorbidities. The most recent draft guidance from the FDA makes no mention of run-in periods. However, the FDA guidance highlights that lifestyle modification, consisting of changes in patterns of dietary intake, exercise, and other behaviours is considered the cornerstone of obesity management and recommends that lifestyle modification programmes be continued following randomisation and emphasised at appropriate intervals throughout the trials. Additionally, lifestyle modification programmes used in preapproval trials should be applicable to individual patients prescribed the product post-approval (*i.e.,* programmes should strike an appropriate balance between effectiveness and simplicity). There is no specific request to limit enrolment to those patients who previously had an unsuccessful dietary intervention. In contrast, the 2016 Guideline on Clinical Evaluation of Medicinal Products used in weight management from the EMA[45] highlights that eligible patients for pharmacological management of weight loss should be those for whom at least 1 trial of an appropriate weight-reducing diet has proven to be insufficient. Further, all patients should be given similar instructions, advice and encouragement with regard to diet and behaviour modification and exercise.[45] Overall, clinical trials in diabetes and obesity suggest the importance of stable lifestyle habits/practices prior to screening, as well as the need to improve delivery, adherence and reporting of lifestyle recommendations.

Recommendations

In general, the SOC Working Group recommends that clinical trial participants i) be evaluated at screening for current diet and exercise habits, ii) should have lifestyle stability prior to screening for baseline measures to minimise the impact of lifestyle on study outcomes and iii) be individually counselled on improving diet, increasing physical activity, and decreasing sedentary behaviour; iv) these practices should be appropriately documented throughout the trial including prior to, at the start, during, and at the end of the trial.

Lifestyle stability is in part reflected by the requirement for weight stability (with varying definitions across trials). A stable weight – defined as a weight change of ≤5% of body weight in the

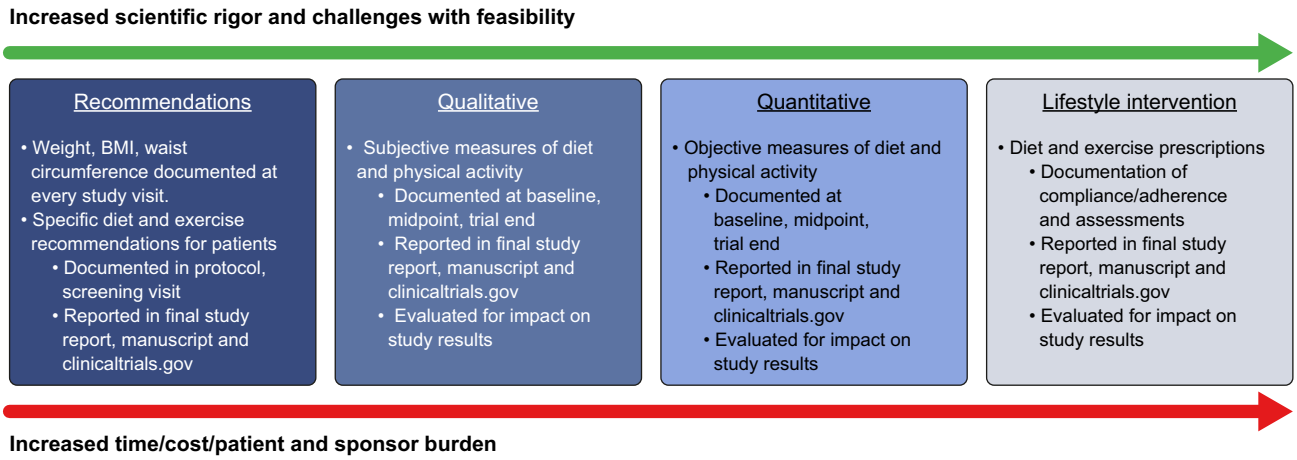

Fig. 1. Standardising diet and exercise in clinical trials of NAFLD/NASH: a proposed clinical trial design block diagram for consideration of SOC in treatment arms of NASH clinical trials. The block diagram depicts increasing factors for consideration in study design with the goal to reduce confounding factors and lend the ability to interpret and compare primary outcomes across different studies. BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SOC; standard of care.

3–6 months prior to the baseline (biopsy and/or non-invasive measures) assessment that serves as comparison for evaluating treatment efficacy – should be required. Second, patients should have a history of at least 1 (unsuccessful) attempt to reduce weight. Third, in the 3–6 months prior to screening for baseline measures no substantial attempt to change lifestyle should have been initiated. In line with the recent recommendations in the fields of obesity and diabetes, and as this might induce changes that impact on eligibility, a run-in period is not systematically recommended, but can be utilised as part of a trial design to provide a new "on-study" baseline after implementing lifestyle recommendations and prior to initiation of the investigational study, thereby minimising confounding and defining the changes that lifestyle counselling may (or may not) have on the study participant and the larger study cohort.

There are a wide-range of diet and exercise options for those with NAFLD, and while no single optimal diet or exercise recommendations currently exist, participants should be encouraged to adopt lifestyle modifications that are sustainable over the long-term. Patients should be encouraged to adopt a dietary approach in accordance with the 2016 EASL guidelines on NAFLD(10), which promote unprocessed foods and the elimination of sugar sweetened beverages. At the discretion of the investigator or sponsor, a more specific recommendation of distinct macronutrient composition or dietary type may be provided to participants as long as compliance is assessed in a standardised manner. Dietary approaches can be adjusted for global variations in dietary practices and preferences; however, regardless of the dietary approach selected, it is essential that the selected approach be included in the trial protocol and that all trial sites follow the same approach. Patients should also be encouraged to meet the minimal recommendations of physical activity (150–180 minutes of moderate intensity exercise per week) whenever possible, with the education and understanding that even recommendations below the minimum have been demonstrated to decrease liver fat in the short-term.[46] If patients are unable to be physically active, unable to meet minimal recommendations, or have specific limitations to physical activity, this should be documented whenever possible. While we acknowledge the additional burden of obtaining this information on sites as well as patients, understanding whether standard lifestyle recommendations influence primary outcomes of clinical trials will be critical to interpreting study results.

General physical activity measures can be subjectively assessed using a validated questionnaire, such as the general physical activity questionnaire, and/or more objective methods including pedometers and tri-axial accelerometers to evaluate physical activity and sedentary behaviour in short-term trials. These measures may aid in capturing changes in physical activity behaviour prior to enrolment and over the course of the trial. It is also critical that lifestyle recommendations are implemented consistently across trial sites to avoid the occurrence of a site effect. Although enforcement of lifestyle recommendations is impractical, capturing data on compliance with such recommendations will provide insights and increase transparency, allowing investigators, sponsors and/or regulatory authorities to more accurately ascertain and interpret study outcomes.

More specifically, at the current time, we recommend a block method (Fig. 1) to facilitate basic standardisation of NASH clinical trials around the globe and to reduce potential bias within these trials. The selection of which recommendations to employ, whether the standard recommendation,

Table 2. Standard of care lifestyle recommendations.

Recommendation	Early phase	Late phase
Minimum	Document at each study visit: • Weight • BMI • Waist Circumference Diet recommendations provided • Specific recommendations written in the protocol and implemented consistently across trial sites, documented in screening visit, reported in final manuscript and on clinicaltrials.gov Physical activity recommendations provided • Specific recommendations written in the protocol land implemented consistently across trial sites, documented in screening visit, reported in final manuscript and on clinicaltrials.gov	Document at each study visit: • Weight • BMI • Waist Circumference Diet recommendations provided • Specific recommendations written in the protocol and implemented consistently across trial sites, documented in screening visit, reported in final manuscript and on clinicaltrials.gov Physical activity recommendations provided • Specific recommendations written in the protocol and implemented consistently across trial sites, documented in screening visit, reported in final manuscript and on clinicaltrials.gov
Qualitative		Assessment of physical activity habits using self-reported measures by validated questionnaires • Documented at baseline, midpoint, trial end, evaluated for impact on study results, reported in final manuscript. Assessment of dietary habits using self-reported measures by validated questionnaires • Documented at baseline, midpoint, trial end, evaluated for impact on study results, reported in final manuscript.
Quantitative		Assessment of participants' physical activity habits using pedometers, tri-axial accelerometers, or other similar wearable devices to be worn at predetermined intervals. • Documented at baseline, midpoint, trial end, evaluated for impact on study results, reported in final manuscript. Assessment of participants' dietary habits using validated food frequency questionnaire to be assessed at predetermined intervals. • Documented at baseline, midpoint, trial end, evaluated for impact on study results, reported in final manuscript.
Lifestyle intervention		Specific dietary prescription led by a registered dietician or similar accompanied with validated instruments for measuring change in diet. • Regular follow-up with a dietician to evaluate compliance and adherence to prescriptions. • Assessments documented according to time-point, evaluated for potential impact on study results, and reported in the final manuscript and clinicaltrials.gov. Specific exercise prescription led by an exercise physiologist or similar accompanied with validated instruments for measuring change in exercise behaviour. • Regular follow-up with an exercise physiologist to evaluate compliance and adherence to prescriptions. • Assessments documented according to time-point, evaluated for potential impact on study results, and reported in the final manuscript and clinicaltrials.gov. Lifestyle intervention may not be practical for most clinical studies.

qualitative, quantitative, or interventional in nature, will depend on numerous factors including patient/investigator/sponsor burden, cost, study objectives, length of trial, and phase of trial. Lifestyle recommendations for early and late-phase clinical trials are summarised in Table 2.

Conclusions

The notable placebo response rate identified in early phase studies of NAFLD/NASH made it difficult to assess the potential efficacy of novel and emerging therapeutics. The lack of standardised approaches to lifestyle recommendations in these trials is likely contributing to the observed favourable placebo effect and impracticable cross-trial comparisons. Observed changes in NAFLD/NASH disease activity in patients administered placebo may also be attributable to disease variation or variables currently known to influence NAFLD, which have yet to be quantified. Identifying and defining differences in treatment response across clinical studies necessitates a more standardised approach to assess and/or quantify both diet and physical activity. The Liver Forum SOC Working Group acknowledges that the development of tools for phase III clinical studies, which factor in ethnic, geographic and genetic differences, is challenging; however, insights on the influence of lifestyle differences and the impact of associated placebo response rates in NAFLD/NASH studies will further inform industry, regulatory authorities and future third-party payers.

Future directions

For therapeutic clinical studies, a minimum recommendation for defining lifestyle and its

influence on treatment outcomes is encouraged. Such clinical trials may evaluate baseline diet and exercise with cross-sectional assessment of change at various time-points over the duration of a study in placebo *vs.* treatment groups. However, programmes should strike an appropriate balance between effectiveness and practicality. Any proposed approach will require thoughtful consideration of the impact on the study, associated timelines and financing. Future strides intended to establish and quantify the effect of lifestyle modification in clinical studies of patients with NAFLD and NASH are associated with both risks (time, costs, encumbrance) and benefits (data quality, minimisation of placebo response).

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; FFQ, food frequency questionnaire; HA, hyaluronic acid; H-MRS, proton magnetic resonance spectroscopy; MRI-PDFF, MRI-proton density fat fraction; NAFL, non-alcoholic fatty liver; NAFLD, NAFL disease; NAFLD activity score; NASH, non-alcoholic steatohepatitis; Pro C-3, N-terminal type III collagen propeptide; RCTs, randomised controlled trials; SOC, standard of care; TIMPs, tissue inhibitor of metalloproteinases; UDCA, ursodeoxycholic acid.

Financial support

In the past 24 months, The Forum for Collaborative Research has received unrestricted educational or research support from the following: 3-V Biosciences; Abbott Molecular; AbbVie; Advanced Biological Laboratories; Afimmune; Aicuris; Allergan; Aligos Therapeutics; Altimmune; AMRA Medical; Arbutus Biopharma; Arrowhead Pharmaceuticals; Assembly Biosciences; Astellas; Astra-Zeneca; Biogen; Boehringer Ingelheim; Bristol-Myers Squib; Celgene; Chimerix; Cirius Therapeutics; Cocrystal Pharma, Inc.; Conatus Pharmaceuticals, Inc.; ConSynance; Covance; DDL Diagnostics; CTI Clinical Trial and Consulting Services; Cirius Therapeutics Inc.; ContraVir; Cymabay; DeuteRx; DiaPharma; DS Biopharma; Durect; EA Pharma Co., Ltd.; Echosens; Eli Lilly and Company; Enanta Pharmaceuticals, Inc.; Enyo Pharma; e.scopics; Exalenz; Ferring Pharmaceuticals; Fractyl; Galectin Therapeutics; Genentech; Genesis Imaging Services; Genfit; Genkyotex; Gilead Sciences; GlaxoSmithKline; Glympse Bio; Hepatitis B Foundation; HepQuant; HighTide Therapeutics; HistoIndex Pte Ltd; Humedics GmbH; ICON Clinical Research; Immuron; Intercept Pharmaceuticals; Inventiva; Ironwood Pharmaceuticals; Janssen; LabCorp; Madrigal Pharmaceuticals; Mallinckrodt Pharmaceuticals; MEDIAN Technologies; MediciNova; Medivir; Merck Laboratories; Metacrine; Microbiotix; Mirum; Morphic Therapeutic; Mylan; NGM Biopharmaceuticals; Nimbus Therapeutics; Nitto Denko Technical Corp; Nordic Bioscience; Northsea Therapeutics; Novartis; Novo Nordisk Inc.; Nusirt; OWL Metabolomics; Perspectum Diagnostics; Pfizer; Pliant Therapeutics; PPD Inc.; ProSciento; Quest Diagnostics; Raptor Pharmaceuticals; Resonance Health; Resoundant; Roche Molecular Systems; Roivant Sciences; RuiYi; SeraCare; Shire; Springbank Pharma; Somalogic; Syneos Health; Takeda; TARGET PharmaSolutions; Teva Pharmaceuticals; ViiV Healthcare; VLVBio; Zafgen; and Zealand Pharma.

This work was also supported in part by the Duke Divisions of Gastroenterology and Integrative Medicine and NIH Grant U01DK061713. These funding sources had no role in the analysis, and interpretation of data, the writing of the manuscript or the decision to submit the article for publication.

Conflict of interest

SF: Consultancy and/or speaker for Gilead, MSD, BMS, Roche, Bayer, Aktelion, Janssen, Intercept, Genfit, Inventiva, GSK, Boehringer Ingelheim, Galmed, Genentech, Galapagos, Aligos, MedImmune, Novartis, Novo Nordisk. CF: Employee of Covance. MN: Advisory board or a speaker for Allergan, Gilead, Intercept, Pfizer, Novartis, Blade, EchoSens North America, OWL, Simply Speaking, and Abbott; Research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Novartis, Shire and Zydus; Minor shareholder or has stocks in Anaetos and Viking. MBH: Employee of Zealand Pharma, former employee of Novo-Nordisk. JS. Consultancy AbbVie, Boehringer Ingelheim, BBN Cardio, BMS, Echosens Galamed, Genfit, Gilead Sciences, Intercept Pharmaceuticals, IQVIA, MedImmune, Novartis, Novo Nordisk, Pfizer; Research Funding: Gilead Sciences, Yakult Europe B.V.; Travel Support: Janssen; Lecture: Falk Foundation, Takeda, Merck, Norgine. MFA: Consultancy and/or speaker for BMS, Intercept, Inventiva, Novo Nordisk, Allergan, TaiwanJ, NGM Bio, Pfizer Research, Prometic. Research support from Conatus, Intercept, Allergan, Novartis, Genfit, Galmed, Galactin, Madrigal, BMS, NGM Bio, Novo Nordisk, Poxel, Durect, Inventiva, Enyo, and Enanta. All other authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: OG, CF, MN, MBH, ES, JMS, KB, SO, VM, SF, MFA. *Drafting the work or revising it critically for important intellectual content:* OG, CF, MN, MBH, ES, JMS, KB, SO, VM, SF, MFA. *Final approval of the version to be published:* OG, CF, MN, MBH, ES, JMS, KB, SO, VM, SF, MFA. *Agreement to be accountable for all aspects of the work in ensuring that questions related to the*

accuracy or integrity of any part of the work are appropriately investigated and resolved: OG, SF, MFA.

All authors of the Liver Forum Standard of Care Working Group, irrespective of participation in the writing group, had the opportunity to review and comment on the final manuscript for publication.

Disclaimer

The content of this paper represents the considerations and reflections of the authors, and not the views of the Food and Drug Administration, Bundesinstitut fuer Arnzeimittel und Medizinprodukte, or the European Medicines Agency.

Acknowledgment

The authors thank Dr. Lara Dimick-Santos for providing valuable feedback and input into the development of the manuscript, as well as the entire Standard of Care: Lifestyle Management Working Group (Appendix).

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.030.

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