Expert Opinion

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Platform trials to overcome major shortcomings of traditional clinical trials in non-alcoholic steatohepatitis? Pros and cons

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Summary

Non-alcoholic fatty liver disease is a condition that affects 25% of the population. Non-alcoholic steatohepatitis (NASH) is a progressive form of the disease that can lead to severe complications such as cirrhosis and hepatocellular carcinoma. Despite its high prevalence, no drugs are currently approved for the treatment of NASH. The drug development pipeline in NASH is very active, yet most assets do not progress to phase III trials and those that do reach phase III often fail to achieve the endpoints necessary for approval by regulatory agencies. Amongst other reasons, the methodological and operational features of traditional clinical trials in NASH might impede optimal drug development. In this regard, platform trials might be an attractive complement or alternative to conventional clinical trials. Platform trials use a master protocol which enables evaluation of multiple investigational medicinal products concurrently or sequentially with a single, shared control arm. Through Bayesian interim analyses, these trials allow for early exit of drugs from the trial based on success or futility, while providing participants better chances of receiving active compounds through adaptive randomisation. Overall, platform trials represent an alternative for patients, pharmaceutical companies, and clinicians in the quest to accelerate the approval of pharmacologic treatments for NASH.

The landscape of clinical trials in NASH

Non-alcoholic fatty liver disease (NAFLD) is a medical condition characterised by an excessive accumulation of lipids in the liver (*i.e.*, hepatic steatosis) that is not related to alcohol abuse or other secondary causes. It is a growing societal concern as it currently affects around 25% of the general population and is expected to affect one-third of the world population by 2030.[1] Approximately 25% of those who have NAFLD develop the progressive form of the disease, non-alcoholic steatohepatitis (NASH), which is characterised by inflammation and cell injury, and can lead to the development of fibrosis.[2] NASH is highly prevalent in individuals with metabolic syndrome, such as those living with type 2 diabetes or obesity. The initial stages of NASH are asymptomatic and thus the condition can silently evolve to cirrhosis, hepatocellular carcinoma or liver failure.[3]

Despite being a prevalent condition entailing a great global burden of disease, no pharmacological treatments have been approved for NASH. Therefore, clinical management relies on lifestyle modification and weight loss.[3–7] Although no drugs have been approved, there are multiple ongoing clinical trials testing an expansive array of molecules with various mechanisms of action.[8,9]

The EU Patient-cENtric clinical tRIal pLatforms (EU-PEARL) consortium, created under an IMI2 (Innovative Medicines Initiative) project, aims to boost the use of platform trials to improve the efficiency of drug development, while focusing on the needs of trial participants. One group within EU-PEARL is laying the foundations for a platform trial for NASH. In this *Expert Opinion*, we aim to discuss how platform trials might improve upon current NASH drug development, as well as pointing out some challenges that are particular to such trials.

Limitations of current NASH clinical trials

Despite the NASH drug pipeline being one of the most vibrant in the current drug development landscape, a substantial proportion of trials do not progress from phase II to phase III, and most phase III trials have failed to reach their primary endpoints.[10] The conduct of clinical studies in NASH poses unique challenges (*e.g.*, diagnosis of NASH, heterogeneity of the disease, and uncertainties regarding the monitoring of therapeutic efficacy). Also, there are a number of intertwined reasons why no drugs have yet achieved approval from regulatory agencies in the US (FDA) or Europe (EMA),[11] and some of these issues could be overcome with a more uniform clinical trial design.

A major cause of inefficiency of current drug development strategies concerns the diagnosis of NASH. Although fatty liver disease is prevalent, there is low awareness amongst healthcare

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professionals of its progression to NASH, fibrosis and cirrhosis, leading to the underdiagnosis of NASH in clinical practice.[12] Consequently, referral pathways to liver specialists are far from optimal in many settings. Moreover, a liver biopsy is necessary to confirm the diagnosis and stage the disease.[13] Hence, histological confirmation of NASH is required in clinical trial settings. This requirement accounts for a substantial proportion of the high screening failure rates seen in NASH trials (60-70% on average), adding complexity and extra costs. In addition, although liver biopsy is generally safe when performed by expert hands, it is nonetheless an invasive procedure that might be painful and uncomfortable, and patients might refuse it. With respect to clinical trials, individuals may be reluctant to undergo this invasive procedure repeatedly (*e.g.*, at the screening phase and at end of treatment; or to repeat screening for a subsequent trial, as biopsy results are only considered valid for 6 months), particularly if the trial design does not offer a high likelihood of clinical benefit.

A number of non-invasive biomarkers for NASH have been proposed,[14,15] yet they are far from perfect at diagnosing and staging the disease. Consequently, another reason for the failure of classical NASH clinical trials is the difficulty in assessing the efficacy of investigational medicinal products (IMP) on the basis of imperfect clinical endpoints. Regulatory approval is largely based on histopathological endpoints for trials from phase IIb onwards. Achieving such endpoints, *i.e.* improvement in fibrosis without worsening of steatohepatitis and vice versa, is very demanding and can be methodologically challenging.[16,17] The main methodological limitations of liver biopsy include two current hindrances and one potential drawback in the short-to-medium term. The former concern the large sampling variability and the lack of inter-observer agreement in the cross-sectional analyses of the same liver samples, especially in terms of ballooned hepatocyte identification.[18] This might be less of an issue in longitudinal pre- and post-treatment biopsies, if read systematically in a homogeneous way by the same team of pathologists, as it would have a less significant effect on the evaluation of a certain drug's efficacy over time. However, it certainly affects how patients are included in or excluded from clinical trials, as the results of histological assessment by local pathologists frequently differ from those obtained by pathologists from the trials' central laboratory. Additionally, how the pathological assessment is performed and the overall quality of reading is difficult to ensure across individual trials. On the flip side, as the group of pathologists providing services to central laboratories is relatively small, limiting assessments to liver biopsy might impede real world evaluation outside clinical trials once drug approval occurs. In summary, the limitations associated with liver biopsy make histological efficacy endpoints difficult to reach; hence, drugs that just halt disease progression or have rather weak (but not necessarily insignificant) effects may not be powerful enough to hit these stringent endpoints, potentially leading to trial failure. Enrolling patients in NASH trials is also complex and demanding, and the relative lack of power necessitates large sample sizes, which altogether render the whole process slow, costly and inefficient.

The third and main limitation is that phase III/IV NASH trials are long-term trials requiring assessments of both histological endpoints and clinical outcomes. Maintaining a participant in a placebo arm for such a long period can be a serious challenge. Since there is no drug-based standard of care for NASH, patients in the placebo arm only receive counselling on lifestyle habits, yet the necessary weight loss to improve NASH (*i.e.*, 7–10%) is seldom achieved and very rarely maintained over the medium term.[6] Moreover, the use of drugs that have shown promising results in early phase clinical trials, such as glucagon-like peptide 1 receptor agonists and sodium/glucose cotransporter 2 inhibitors, is becoming common amongst individuals with NASH and type 2 diabetes mellitus but might add a potential confounding effect in more advanced trials. Another potential problem is that if a drug obtains regulatory approval for NASH it should be incorporated into the trial as standard of care; however, this cannot be done once the trial has started and, as phase III/IV trials are very long, preventing patients allocated to the standard of care arm from receiving a newly approved drug for the duration of the trial would be problematic.

Platform trials as an alternative to traditional 1:1 clinical trials

Platform trials are a type of adaptive master protocol trial (Fig. 1). Master protocols are designed to evaluate more than one treatment in more than one patient type or disease in the same trial.[19] A master protocol encompasses the overall clinical trial design components and operational aspects related to all sub-protocols and interventional specific appendices, which contain the information about the IMP, such as doses and treatments, as well as background information. Indeed, master protocols have been successfully used in oncology,[20–23] Alzheimer's, amyotrophic lateral sclerosis, influenza, pneumonia, and, more recently, in the development of strategies against COVID-19,[24,25] among others.

The main differences between traditional trials and platform trials are shown in Table 1. One of the main advantages of platform trials is that there is a single, common, placebo comparator arm. This reduces the sample size requirements for each new IMP entering the platform and allows most trial participants to be allocated to active rather than control arms. In addition, their adaptive design means that arms of IMP that prove inefficacious in interim analyses can be discontinued, increasing the chances of participants being allocated to arms testing potentially more efficacious compounds.[26] There have already been some initial experiences with trials testing multiple interventions (single and combinatorial drugs) in NASH compared to a single control group by both a single pharmaceutical company[27] and as a collaboration between companies.[28]

A platform trial also has the potential to accelerate the completion of trials and, therefore, the transition to later-stage trials. Thus, given the potential benefits in terms of efficiency and participants' needs, there is a strong rationale for conducting platform-based trials. A common benefit for participants, IMP owners (*i.e.*, those owning the patent of the molecule being tested in the platform trial, usually pharmaceutical or biotechnology companies, but potentially public and academic institutions too), and sponsors (*i.e.*, the institutions or individuals responsible and liable for the platform trial) is the methodological approach used in platform trials, usually based on Bayesian techniques.[29,30] Such an approach provides a mathematically rigorous guide for making decisions under complex scenarios, which provides a useful framework for determining when there is a low likelihood that an IMP will achieve a minimally efficacious threshold and needs to be discontinued from the trial early or, more often, when it can move

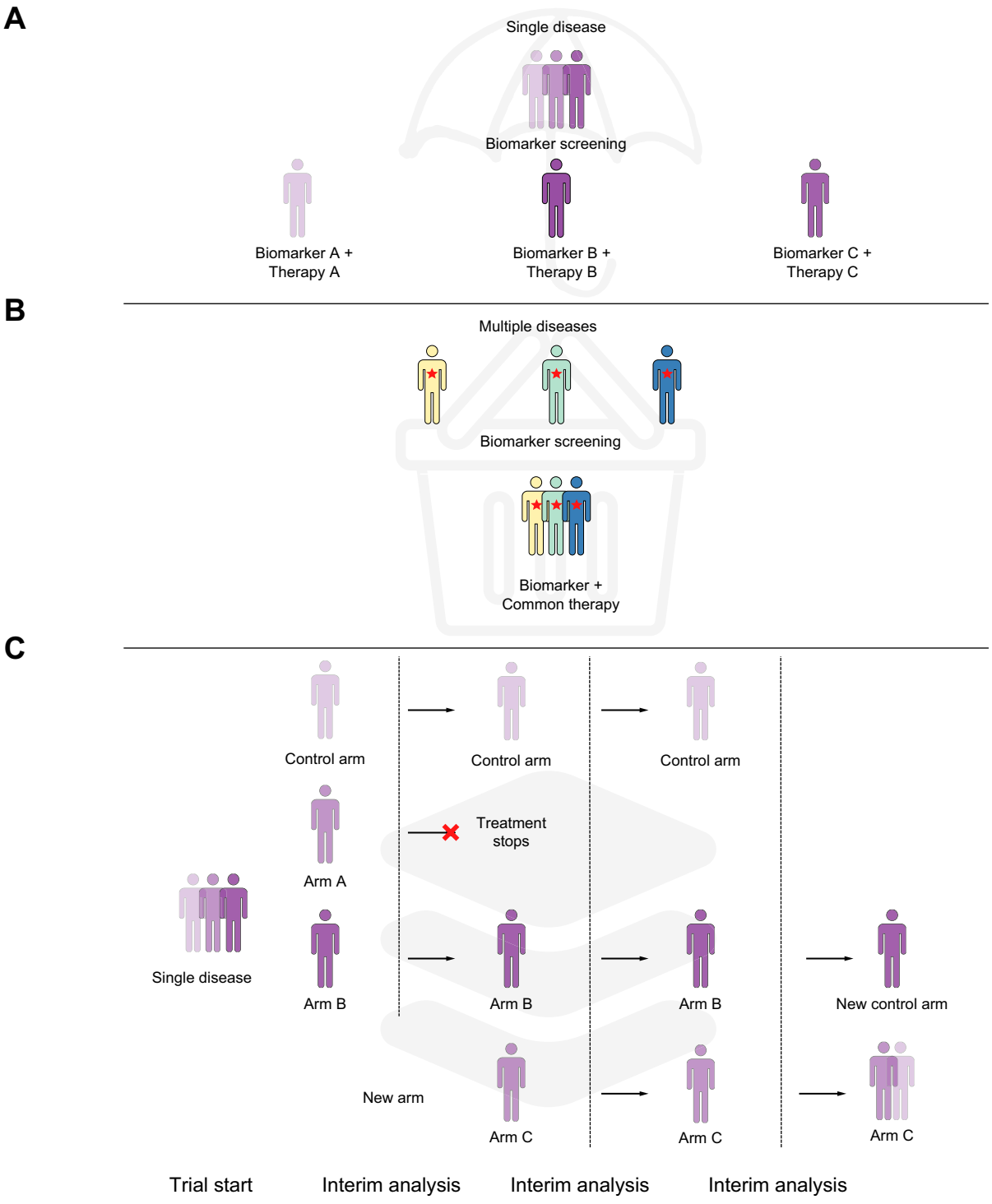

Fig. 1. Master protocol types. The figure depicts three types of master protocols. (A) Umbrella trials evaluate a single disease with different subgroups to select the optimal type of treatment for each subgroup. (B) Basket trials treat two or more diseases with common biomarker expression and use one single therapy. (C) Platform trials have a common randomised trial structure, and their main characteristic is that subtrials involving one or several therapeutic arms can enter and exit the study continuously based on an algorithm. Moreover, platform trials use a common control group or placebo and can last many years. When a drug is proven effective, it becomes the new standard of care. Comparisons are conducted between each therapeutic arm and placebo/standard of care and between therapeutic arms within each subtrial, *e.g.* monotherapy *vs.* combination therapy or various dosages of the same drug. In a platform trial for non-alcoholic steatohepatitis, besides the histologic inclusion criteria in case of phase IIb trials onwards, patients will need to fulfil certain criteria regarding age, BMI and type 2 diabetes, among others; interim and final analyses will take into account patients' baseline characteristics and stratification will be performed for major categories.

Table 1. Differences between traditional clinical trials and platform trials.

Traditional clinical trials	Platform trials
Test a single active compound *vs.* control	Test multiple active arms *vs.* a single control arm
Trial logistics to be implemented for each individual trial	Ongoing platform for long-term, continuous testing
Sponsor is the IMP owner	Sponsor is often an academic or non-profit organisation
All decisions made by the pharmaceutical or start-up company	Governance bodies make decisions related to treatment arms
Drugs enter only at the beginning of the trial	Drugs enter and exit the trial depending on interim analysis
Protocol for each trial	Master protocol for all the trials and ISA for each drug

IMP, investigational medical product; ISA, interventional specific appendices.

forward in the clinical research pipeline. These periodic interim analyses performed during the platform trial are based on analyses where the hypothesis is tested between the treatment arms within each subtrial *vs.* placebo following decision rules adopted according to pre-specified efficacy and futility thresholds. This reduces costs and saves time, rendering trial adaptability beneficial to all stakeholders involved in the platform.

The benefits for participants in NASH platform trials are multiple. The presence of only one control arm means a smaller group of participants will not receive active treatment. Moreover, the more IMPs that are added to the platform, the higher the probabilities of receiving an active treatment. Also, if an arm is discontinued due to lack of efficacy, patients can potentially be allocated to other arms after a wash-out period. In addition, when a treatment is proven effective it might rapidly progress to the next stage of development. Another advantage is the use of a common screening platform where a participant will be screened for the platform and, depending on which selection criteria are fulfilled (along with participant preferences), the chances that he or she can be included in an arm of the platform trial will be greatly enhanced without having to repeat the procedures for screening. This will optimise the screening process and considerably increase the likelihood of a patient being selected for one of the trials in the platform.

The sponsor of a NASH platform trial will likely be an academic institution, consortium, or a non-profit entity. Platform trials are nonetheless attractive to IMP owners since they increase operational efficiency due to the use of a single infrastructure, trial design and protocol to evaluate several compounds simultaneously. In a platform trial, there is a centralised governance structure that handles the various subtrials embedded in the platform trial, including a scientific committee and data safety monitoring committee, as well as standardised clinical, laboratory, biomarker or imaging assessment to reduce the start-up time. Also, in the setup of the platform trial, there are central laboratories and reading centres to increase data quality and reduce variability. In the case of a platform trial in NASH that embeds phase IIb trials onwards (thus requiring liver biopsy as per current regulatory requirements), a central pathology laboratory and histopathology review committee will be paramount to implement a smooth and high-quality pathway to process and homogenously interpret liver biopsies, enhanced by artificial intelligence tools. This is particularly relevant for reliable, reproducible and accurate pathological reading of the screening and follow-up biopsies.[13] A central imaging committee will also review imaging reports (*e.g.* MRI-based assessments of liver fat content or liver stiffness) to provide more uniform and consistent data. Of course, it is important to allow IMP owners access to their data but also to fire wall data such that each shall not be able to access data from other IMP owners.

Last but not least, platform trials offer an opportunity to reduce timelines and financial cost for the IMP owner. Under a platform trial with a common infrastructure, personnel and master protocol, each treatment arm should cost less than it would in a classical clinical trial. IMP owners have the opportunity to access and utilise a pre-existing infrastructure when new therapies enter the study. This is in contrast with the classical trials where each new treatment needs to have an independent setup for sites, patients and all the operational activities related to the trial.

Potential shortcomings of platform trials in NASH

The setup of a platform trial is not without challenges. Regulatory and operational aspects, data sharing, publishing policies and legal liability are some of the topics that can reduce the enthusiasm of different stakeholders. Adaptability and openness to innovation are key features of a platform trial which are largely due to scientific decisions relying on a scientific committee that will not respond to a specific IMP owner's priorities but rather to the cutting-edge quality standards posed by the scientific community. This might suppose, for instance, that a NASH platform trial will, subject to validation, rapidly include non-histological biomarkers derived from large research consortia (*e.g.*, LITMUS[31] and NIMBLE[32]) as secondary endpoints or apply machine-learning/artificial intelligence tools to reduce variability between liver biopsy readings. However, it is unlikely that regulatory authorities will give up histological endpoints in the foreseeable future.

Platform trials can appear complex to patients who are familiar with the classical paradigm of participating in one trial at a time which would usually run until completion. Some patients may feel uncomfortable with not knowing what treatment they may be assigned to. This is why it is so important to carefully inform patients about the implications of the setup of a platform trial, including screening particularities and how patient preferences should be embedded in the enrolment process. Since individuals with NASH can currently only benefit from pharmacological interventions in the context of clinical trials, the information, communication and participation pathways for patients should be periodically evaluated. Engaging with the patient community in a platform trial may make it more appealing.[33]

From the sponsor's perspective, there are considerable logistical challenges, including the requirement for a large clinical network able to recruit patients for several ongoing subtrials. This requires the involvement of a global clinical research organisation, complex pathways of sample shipments to laboratories, the coordination of various decision boards, and tackling US- and European-specific regulatory requirements on data privacy,

sponsorship, and clinical trial regulation. Liability and overall conduct might also be of concern since an academic institution might not have the appropriate legal and clinical operations teams to handle the enormous complexity of a global clinical trial. A legal framework able to ensure that novel drugs entering the platform trial are properly assessed and capable of optimising timelines for contract development and intellectual property issues is essential. The sponsor will also be responsible for ensuring that the patient-centricity of the trial is achieved and maintained. This means that patient representatives should be able to engage in the design of the master protocol, participate in platform trial boards, and be part of audits. Principal investigators with experience in NASH might not be so enthusiastic in the initial steps of the platform trial until the efficiency and advantages for trial participants are made evident, because it can be expected that trial initiation and informed consent procedures will be more complex in a platform trial compared to a single-drug trial. We also think that in order to be viable *vs.* competing traditional trials, platform trials should align their investigator fees with those of standalone trials. It is conceivable that the overall gain in speed and efficacy from a platform trial *vs.* individual, separately conducted, trials might be a strong incentive to participate for investigators committed to NASH research. Ensuring the prior points, although most of the activities will be outsourced, will require significant coordination capacity and strong commitment by the institutions hosting the platform trial headquarters.

From the IMP owners' side, having major decisions on trial conduct being taken by the governing board of the platform trial may raise concerns and generate some pushback at the initial stages. For instance, some reticence may arise regarding the use of interim analysis based on Bayesian methods to decide if an arm is terminated before the trial is fully completed. Issues regarding data ownership will be discussed and measures applied in a transparent way while ensuring data privacy amongst IMP owners on the platform. Also, commercial and innovation strategies might widely differ between big pharma and small or medium biotech companies, *e.g.* while the latter likely own a single IMP and might want to "fail early and cheap", the former might have planned the whole drug pipeline strategy for several years and prefer to control their own data in spite of it being more expensive and slower. Another relevant aspect to be considered is that there is currently a race to be the first company to obtain regulatory approval with an indication for NASH, and this might impact the interest of IMP owners in drug development (not specific for platform trials) in NASH once the first drug for NASH is approved by the FDA/EMA.

Despite these potential barriers, there is enough proof-of-concept in medical areas other than NASH showing that platform trials work and are attractive for all implied stakeholders. This sets the stage for testing them in this chronic liver disease as well.

Conclusions

Master protocols, and particularly platform trials, are a promising tool to advance the pipeline of NASH pharmacological treatment by ensuring faster and more efficient trials that provide consistent evidence in shorter periods than standalone trials, allowing for a faster transition between trial phases. The high prevalence of the disease coupled with a continuously emerging field of new compounds are key to developing platform trials, from which various stakeholders – sponsors, IMP owners and patients – will soon benefit.

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Abbreviations

IMP, investigational medicinal products; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

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Conflicts of interest

JMP reports having received consulting fees from Boehringer-Ingelheim, MSD and Novo Nordisk. He has received speaking fees from Gilead, Intercept, and Novo Nordisk, and travel expenses from Gilead, Rubió, Pfizer, Astellas, MSD, CUBICIN, and Novo Nordisk. He has received educational and research support from Madrigal, Gilead, Pfizer, Astellas, Accelerate, Novartis, Abbvie, ViiV, and MSD. Funds from European Commission/EFPIA IMI2 853966-2, IMI2 777377, H2020 847989, and ISCIII PI19/01898. FT lab' work has been supported by the German Research Foundation (DFG, CRC/TR 362) and research grants from Gilead, Allergan, Bristol-Myers Squibb and Inventiva. QMA is Coordinator of the EU IMI-2 LITMUS consortium, which is funded by the EU Horizon 2020 programme and EFPIA. This multi-stakeholder consortium includes industry partners. He reports research Grant Funding: Allergan/Tobira, AstraZeneca, Boehringer-Ingelheim, Glaxo SmithKline, Glympse Bio, Intercept, NovartisPharma AG, Pfizer Ltd. Consultancy: 89Bio, Abbvie/Allergan, Akero, Altimentiv, Altimmune, AstraZeneca, Axcella, Blade, BMS, BNN Cardio, Boehringer-Ingelheim, Cirius, CymaBay, EcoR1, E3Bio, Eli Lilly & Company Ltd., Galmed, Genentech, Genfit SA, Gilead, Grunthal, HistoIndex, Indalo, Intercept Pharma Europe Ltd., Inventiva, IQVIA, Janssen, Johnson & Johnson, Madrigal, MedImmune, Medpace, Merck, Metacrine, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk A/S, PathAI, Pfizer Ltd., Poxel, ProSciento, Raptor Pharma, Roche, Servier, Shionogi, Terns, The Medicines Company, Viking Therapeutics. Speaker: Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Fishawack, Genfit SA, Gilead, Integritas Communications, Kenes, Medscape. Royalties: Elsevier Ltd. DNA works for Janssen. MSK is an employee of and a shareholder in Novo Nordisk A/S. PM works for Novartis. JG has received consulting fees from Boehringer-Ingelheim, speaking fees from Echosens and travel expenses from Gilead and Abbie. Funds from ISCIII PI18/00947 and PI21/00691. VR consults for and Intercept, Novo Nordisk, Galmed, Poxel, NGM, Madrigal, Enyo, Sagimet, 89 Bio, Prosciento, Terns, and Theratechnologies, and received grants from Intercept and Gilead.

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Authors' contributions

Conceptualization: JMP, FT, QA, NDP, MSK, PM, FK, JG, VR; Drafting of the first version of the manuscript: JMP, FT, NDP, VR; Revision: PM, FK, JG; Approval of the final version of the manuscript: JMP, FT, QA, NDP, MSK, PM, FK, JG, VR; Coordination: JMP, NDP, VR.

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Supplementary data

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References

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[1] Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, et al. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2019;69:2672–2682.
[2] Liu W, Baker RD, Bhatia T, Zhu L, Baker SS. Pathogenesis of nonalcoholic steatohepatitis. Cell Mol Life Sci 2016;73:1969–1987.
[3] Ratziu V, Francque S, Sanyal A. Breakthroughs in therapies for NASH and remaining challenges. J Hepatol 2022;76:1263–1278.
[4] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367–378.e5.
[5] Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010:121–129.
[6] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–357.
[7] Oseini AM, Sanyal AJ. Therapies in non-alcoholic steatohepatitis (NASH). Liver Int 2017;37:97–103.
[8] Attia SL, Softic S, Mouzaki M. Evolving role for pharmacotherapy in NAFLD/NASH. Clin Transl Sci 2021;14:11–19.
[9] Fraile JM, Palliyil S, Barelle C, Porter AJ, Kovaleva M. Non-alcoholic steatohepatitis (NASH) – a review of a crowded clinical landscape, driven by a complex disease. Drug Des Devel Ther 2021;15:3997–4009.
[10] **Rinella ME**, **Tacke F**, **Sanyal AJ**, **Anstee QM**. participants of the AASLD/EASL Workshop. Report on the AASLD/EASL joint workshop on clinical trial endpoints in NAFLD. J Hepatol 2019;71:823–833.
[11] Ratziu V, Friedman SL. Why do so many NASH trials fail? Gastroenterology 2020 May 18. S0016-5085(20)30680-30686.
[12] Loomba R, Wong R, Fraysse J, Shreay S, Li S, Harrison S, et al. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. Aliment Pharmacol Ther 2020;51:1149–1159.
[13] Brunt EM, Kleiner DE, Carpenter DH, Rinella M, Harrison SA, Loomba R, et al. NAFLD: reporting histologic findings in clinical practice. Hepatology 2021;73:2028–2038.
[14] Masoodi M, Gastaldelli A, Hyötyläinen T, Arretxe E, Alonso C, Gaggini M, et al. Metabolomics and lipidomics in NAFLD: biomarkers and non-invasive diagnostic tests. Nat Rev Gastroenterol Hepatol 2021;18:835–856.
[15] **Selvaraj EA**, **Mózes FE**, **Jayaswal ANA**, Zafarmand MH, Vali Y, Lee JA, et al. Diagnostic accuracy of elastography and magnetic resonance imaging in patients with NAFLD: a systematic review and meta-analysis. J Hepatol 2021;75:770–785.
[16] Davison BA, Harrison SA, Cotter G, Alkhouri N, Sanyal A, Edwards C, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. J Hepatol 2020;73:1322–1332.
[17] Brunt EM, Clouston AD, Goodman Z, Guy C, Kleiner DE, Lackner C, et al. Complexity of ballooned hepatocyte feature recognition: defining a training atlas for artificial intelligence-based imaging in NAFLD. J Hepatol 2022;76:1030–1041.
[18] Roskilly A, Shearer J, Parker R, Rowe IA. vHigh rates of ineligibility for participation in trials of new therapies in non-alcoholic steatohepatitis: a systematic review. Eur J Gastroenterol Hepatol 2020;32:1023–1029.
[19] Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med 2017;377:62–70.
[20] Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther Nat Publishing Group 2009;86:97–100.
[21] **Herbst RS**, **Gandara DR**, **Hirsch FR**, **Redman MW**, LeBlanc M, Mack PC, et al. Lung Master Protocol (Lung-MAP) - a biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. Clin Cancer Res 2015;21:1514–1524.
[22] **Kaplan R**, **Maughan T**, Crook A, Fisher D, Wilson R, Brown L, et al. Evaluating many treatments and biomarkers in oncology: a new design. J Clin Oncol 2013;31:4562–4568.
[23] Sydes MR, Parmar MKB, Mason MD, Clarke NW, Amos C, Anderson J, et al. Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. Trials 2012;13:1–14.
[24] Vanderbeek AM, Bliss JM, Yin Z, Yap C. Implementation of platform trials in the COVID-19 pandemic: a rapid review. Contemp Clin Trials 2022;112:106625.
[25] Meyer EL, Mesenbrink P, Dunger-Baldauf C, Fülle HJ, Glimm E, Li Y, et al. The evolution of master protocol clinical trial designs: a systematic literature review. Clin Ther 2020;42:1330–1360.
[26] Park JJH, Siden E, Zoratti MJ, Dron L, Harari O, Singer J, et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. Trials 2019;20:1–10.
[27] Loomba R, Noureddin M, Kowdley KV, Kohli A, Sheikh A, Neff G, et al. Combination therapies including cilofexor and firsocostat for bridging fibrosis and cirrhosis attributable to NASH. Hepatology 2021;73:625–643.
[28] Alkhouri N, Herring R, Kabler H, Kayali Z, Hassanein T, Kohli A, et al. Safety and efficacy of combination therapy with semaglutide, cilofexor and firsocostat in patients with non-alcoholic steatohepatitis: a randomised, open-label phase II trial. J Hepatol 2022;77:607–618. S0168-8278(22)00235-5.
[29] Saville BR, Connor JT, Ayers GD, Alvarez J. The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. Clin Trials 2014;11:485–493.
[30] Giovagnoli A. The bayesian design of adaptive clinical trials. Int J Environ Res Public Health 2021;18:1–15.
[31] Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) LITMUS Project (litmus-project.eu) Last accessed August 30, 2022.
[32] Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE) | The Foundation for the National Institutes of Health (fnih.org) Last accessed August 30, 2022.
[33] Warner K, See W, Haerry D, Klingmann I, Hunter A, May M. EUPATI guidance for patient involvement in Medicines research and development (R&D); guidance for pharmaceutical industry-led Medicines R&D. Front Med (Lausanne) 2018;5:270.