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Review article: The need for more efficient and patient-oriented drug development pathways in NASH—setting the scene for platform trials

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Summary

Background and Aims: Non-alcoholic steatohepatitis (NASH) constitutes a significant unmet medical need with a burgeoning field of clinical research and drug development. Platform trials (PT) might help accelerate drug development while lowering overall costs and creating a more patient-centric environment. This review provides a comprehensive and nuanced assessment of the NASH clinical development landscape.

Methods: Narrative review and expert opinion with insight gained during the EU Patient-cEntric clinicAl tRial pLatforms (EU-PEARL) project.

Results: Although NASH represents an opportunity to use adaptive trial designs, including master protocols for PT, there are barriers that might be encountered owing to distinct and sometimes opposing priorities held by these stakeholders and potential ways to overcome them. The following aspects are critical for the feasibility of a future PT in NASH: readiness of the drug pipeline, mainly from large drug companies, while there is not yet an FDA/EMA-approved treatment; the most suitable design

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(trial Phase and type of population, e.g., Phase 2b for non-cirrhotic NASH patients); the operational requirements such as the scope of the clinical network, the use of concurrent versus non-concurrent control arms, or the re-allocation of participants upon trial adaptations; the methodological appraisal (i.e. Bayesian vs. frequentist approach); patients' needs and patient-centred outcomes; main regulatory considerations and the funding and sustainability scenarios.

Conclusions: PT represent a promising avenue in NASH but there are a number of conundrums that need addressing. It is likely that before a global NASH PT becomes a reality, 'proof-of-platform' at a smaller scale needs to be provided.

1 | NASH: A BURGEONING YET ELUSIVE DRUG DEVELOPMENT FIELD

The increasing number of individuals with non-alcoholic fatty liver disease (NAFLD), including its progressive form non-alcoholic steatohepatitis (NASH), and the associated burden on healthcare costs have led to an increased focus on developing therapies for NASH.[1] Thus far, most therapies have been targeted to modifying one of the three major pathophysiological processes: steatosis, inflammation or fibrosis.[2,3] However, the complex nature of NASH makes it likely that a multimodal agent or a combination of agents may be necessary for maximal benefit. Despite several promising therapeutic targets being identified in animal models or through in vitro assays, the translation of these insights using pharmacological approaches in the clinic has been limited. In 2019, the Phase 3 data for the most advanced clinical programme, obeticholic acid, was submitted to the United States Food and Drug Administration (FDA), but received a complete response letter indicating that additional data would be necessary to assess its overall safety and efficacy.[4] A new drug application with further data with obeticholic acid from the REGENERATE study was submitted by Intercept in late December 2022 and FDA accepted it in late January 2023.[5] Three other agents, selonsertib, elafibranor and cenicriviroc, failed to meet their Phase 3 primary endpoint(s),[5-7] leading to the discontinuation of their development efforts in NASH. There are four other agents currently in Phase 3 (i.e. aramchol, resmetirom, semaglutide and lanifibranor) that may be completed by 2024. However, the vast majority of therapies are in early stages of development; according to clinicaltrials.gov, there are approximately 85 NASH interventional studies active or recruiting participants across Phases 1 through 3 with over 50 in Phase 2 and over 20 in Phase 1. Given the numerous failures and lengthy development time, novel approaches to clinical development need to be considered to accelerate the development of effective therapies.

In a recent opinion article, we discussed the main pros and cons of adaptive designs and platform trials (PT) in particular, to become a feasible and useful tool to advance the field of drug development in NASH with a patient-centric perspective.[8] In this review, we aim to provide a more in-depth analysis of the characteristics of the NASH landscape and PT that might allow for the implementation of multi-stakeholder, adaptive clinical trials in the years to come. In doing so, we provide a comprehensive view on the design considerations, the developmental phase where PT might find better accommodation, the methodological aspects, as well as the operational and regulatory principles. This review will reflect part of the work conducted within a consortium of 36 private and public partners that have come together in a strategic partnership to deliver on the IMI (Innovative Medicines Initiative) proposal goals to advance the field of PT; the project is called EU Patient-cEntric clinicAl tRial pLatforms (EU-PEARL), which includes the preparation of a NASH integrated research platform (IRP) trial.[9]

2 | WHY PLATFORM TRIALS FOR NASH?

The current paradigm of 'one drug, one trial' is effective but slow and not very efficient compared to using a master protocol (MP). Among other limitations, drug development through stand-alone trials entail multiplication of placebo arms, screening for only one study at a time, and assembling and dismantling the trial infrastructure. A MP is a methodological approach that involves studying one or more treatments in one or more diseases (or disease subgroups) using the same overarching trial design.[10] PT are one of the potential ways to implement a MP, essentially an adaptive form of the umbrella study that can be conducted for an indefinite period of time, where interventions can be added or dropped using a decision-based algorithm. The MP contains key design and operational elements that allow each intervention to be examined without having to set up separate independent studies. This approach allows the use of a common screening platform to identify all the interventions for which participants may be eligible within the MP, creating more opportunities for participants and potentially fewer screen failures, while potentially reducing screening time overall. MP often include periodic interim analyses using Bayesian algorithms for declaring futility or success using estimated posterior probabilities.[11,12] These analyses can potentially be paired with response-adaptive randomisation, so as to assign more subjects to promising therapies and potentially allowing subjects in arms declared futile to be re-assigned to other arms

or treatments. MP are usually embedded in a trial network where each sponsor can share in the resources of the overall infrastructure[13]; the PT together with a supporting research infrastructure is known as an IRP, under which PT are conducted. There are several advantages to using a shared network including shared governance (e.g. steering committee, data review committee), central facilities (e.g. laboratory, reading centre, adjudication committee, data management systems), federated patient data networks and a cadre of experienced clinical sites/investigators; these advantages result in faster start-up, lower cost and more consistent data. All of these efficiencies in trial design could certainly help the NASH field where the science is complex (i.e. multiple therapeutic targets/pathways), there is a robust pipeline of early drug candidates, and there is challenging recruitment of participants (due to specific inclusion criteria).

A MP is not a 'one size fits all' proposal but with proper planning may be a 'one size fits many' solution for a specific disease or disease pathway. There is a significant amount of effort that needs to be put forward to reap the benefits of a MP and IRP. In addition to establishing a trial infrastructure, upfront planning with multiple parties including but not limited to investigators, institutional review boards/ethic committees (IRBs/ECs), pharmaceutical/biotech companies and health authorities (HA) is necessary to agree on the design, operations and governance. Importantly, since the design elements can lead to fewer participants required for the overall conduct with higher chances of being allocated to arms with active compounds due to a shared control arm and Bayesian decision rules, a MP in NASH might be an effective way to provide a more 'patient-centric' approach for drug development.

3 | OVERALL APPROACH FOR DRUG DEVELOPMENT IN NASH

The traditional drug development pipeline is founded on an expectation that a compound beneficially influences one or more of three key domains—how a patient 'feels, functions or survives' (Figure 1). The first of these, *feels*, is best captured using patient-reported outcome measures (PROs). Although PROs have been developed for use in non-cirrhotic NASH and/or cirrhotic NASH,[14] to date no PROs have received regulatory approval as trial endpoints in liver disease. Indeed, only one PRO for individuals with non-cirrhotic NASH has been developed and validated that meets current regulatory standards.[15]

The recognition of the unmet need for therapies in NASH and the length of time necessary to demonstrate clinical benefit have led the drug regulatory agencies to set up accelerated approval pathways. The FDA Accelerated Approval Pathway and the EMA Conditional Marketing Authorization rely on demonstrating an effect on a surrogate endpoint that is 'reasonably likely, based on epidemiological, therapeutic, pathophysiological, or other evidence to predict benefit' on morbidity or mortality.[16,17] Fibrosis stage, based on histological assessment from a liver biopsy,[18] is considered the strongest predictor of adverse clinical outcomes, including liver-related death.[19] Therefore, progression to (or regression from) cirrhosis is considered a *generally accepted surrogate* and, in the belief that worsening (i.e. increasing) grade of steatohepatitis or stage of fibrosis predicts likelihood of progression to cirrhosis, histological regression is considered a *likely surrogate*[20,21] (Figure 2). In this regard, endpoints for a NASH Phase 2b or Phase 3 PT would need to be consistent with HA guidance that requires demonstration of histological improvement for accelerated or conditional approval, while demonstration of benefit on clinical outcomes would be a post-marketing requirement.[20,21]

There is extensive summary data collected from Phase 2b and Phase 3 NASH clinical trials that allow for meta-analysis to be conducted to estimate the treatment effect that has been observed to date from these clinical trials for the co-primary endpoints of interest. This information is combined with the elicitation of information from clinical experts with respect to what is perceived to be the different levels of evidence required to show that an investigational NASH treatment has shown different levels of evidence of its effectiveness in improving fibrosis and/or achieving NASH resolution. This combined information can serve as the starting point for the initiation of the initial cohorts in a NASH PT for the cohort sizes required. It is expected that as data are gathered over time and knowledge in the disease area changes, as well as the standard of care, these assumptions and estimates will be updated as information becomes available. This concerns data from the primary analysis of the different cohorts over time based on the sharing of the concurrent control and also any shifts that occur in the patient population. Therefore, it is believed that there is adequate information at present to initiate cohorts in a NASH PT that are sufficiently sized to allow for determination of whether or not an effective treatment could be advanced to Phase 3 based on the information gathered in this Phase 2b PT.

The choice of biomarkers for an early Phase 1b or 2a NASH PT for multiple agents poses a conundrum, since the balance between the need for understanding how the drug works (e.g. target engagement, safety) relative to the need to develop reliable endpoints predictive of mid-term and long-term clinical efficacy lacks straightforward solutions. Generally speaking, not only in PT, demonstrating target engagement in early phase trials through pharmacodynamic markers is essential to establish a potentially clinically meaningful dose range. However, these pharmacodynamic markers are not always available for serum-based or non-invasive measurements and are sometimes complex to measure outside of a dedicated clinical research context (e.g. measurement of lipogenesis inhibition) or when available, are specific to a particular class of drugs. Therefore, depending on the mechanism of action of a specific compound, it may be extremely difficult to incorporate pharmacological endpoints meant for demonstrating target engagement in a PT where the specified endpoints are generally similar for all compounds. In addition, some target engagement biomarkers would not necessarily be directly related or predictive of histological benefit in NASH. While target engagement as well as pharmacodynamic markers could be

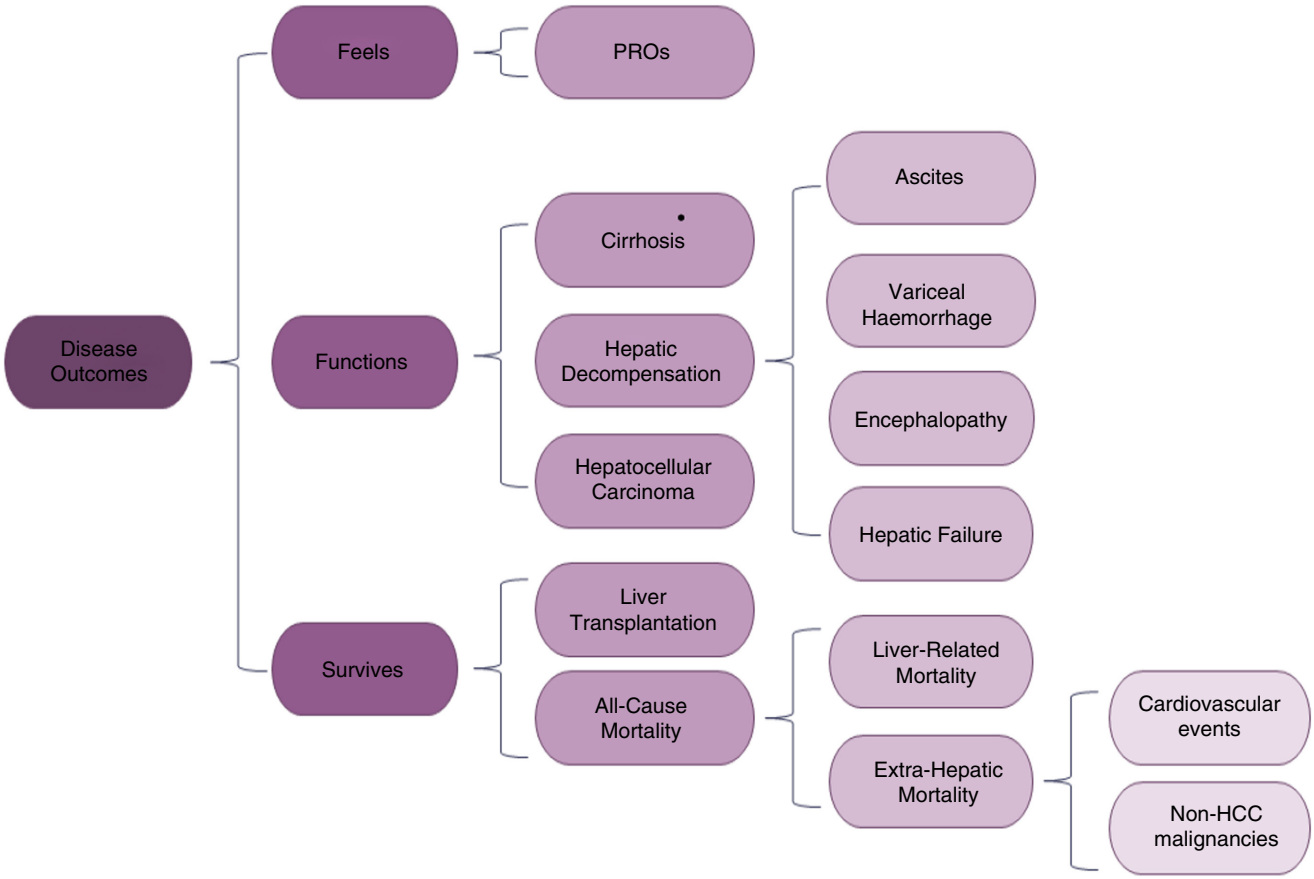

FIGURE 1 A conceptual framework for liver disease outcomes. *Function* relates to preservation of hepatic function (e.g. protein synthesis, detoxification) and avoidance of decompensation events, whereas *survival* encompasses both liver-related and non-liver related (e.g. cardiovascular, malignancy) death as well as liver transplantation that are attributable to NASH. HCC, hepatocellular carcinoma; PROs, patient-reported outcomes.

measured as part of an PT with the purpose to gain a better understanding of the effect of a compound, it would be advisable that these measures be kept simple (e.g. blood or urine based), so as to not make the trial overly complex (e.g. cost, patient burden, specialised assays/techniques with limited availability) and not part of the decision-making process for the trial. It is most appropriate to assess target engagement as part of independent Phase 1 single and/or multiple ascending dose studies where there is also pharmacokinetic data to help modelling drug responses and bring forward a limited number of doses with demonstrated activity into the PT. The choice of appropriate biomarkers predictive of clinical relevance is critical to the use of adaptive designs in trials especially in a PT. In the case of NASH PT where a Phase 2a/b design could be considered, this is particularly challenging given the current lack of fully validated non-invasive biomarkers that are predictive of histological or clinical improvement. However, initiatives such as IMI2-sponsored LITMUS programme[22,23] and the Foundation for the National Institutes of Health-sponsored Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE) programme,[24] as well as, data from ongoing phase 3 trials are driving towards identification and validation of biomarkers and are expected to reshape the NASH landscape and trial designs in the next few years.

4 | TRIAL DESIGN CONSIDERATIONS

4.1 | Cirrhotic versus non-cirrhotic population

The choice of patient population is the first question to address in designing a NASH MP. On one hand, cirrhotic patients represent the population with the highest unmet need because they have the highest near-term risk of morbidity and mortality. On the other hand, improving histology or function at the cirrhotic stage may be difficult to achieve and, thus far, most anti-fibrotic agents have failed.[6,25,26] In the cirrhotic population, the traditional histological surrogate endpoints are not appropriate, and clinical trial endpoints are defined by clinical outcomes. Therefore, it follows that the design of cirrhotic trials is different from that of non-cirrhotic trials and a PT population cannot consist of both cirrhotic and non-cirrhotic participants. An important aspect of designing a PT is the need for a steady or abundant supply of potential interventional agents to ensure optimal utilisation of the PT. The paucity of drugs designed for treatment of cirrhosis may not make such a PT viable, at least based on the current pharmacological landscape for NASH. Moreover, the heterogeneity in terms of disease prognosis based on baseline characteristics is very high in cirrhotic

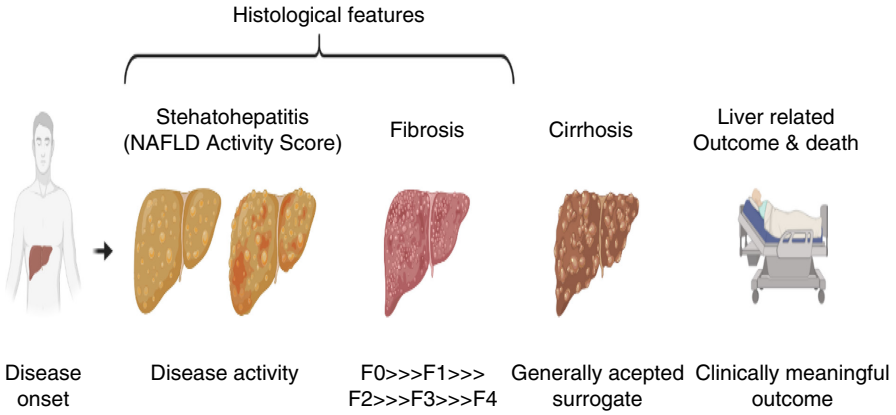

FIGURE 2 Surrogates & clinically meaningful outcomes as endpoints in NAFLD trials. Steatohepatitis is graded according to the NAFLD Activity Score (NAS) score based on the level of steatosis (scored from 0 to 3), inflammation (0 to 3) and ballooning (0–2) and staged based on the level of fibrosis according to the NASH Clinical Research Network (CRN) methodology with a range from no fibrosis (F0) to cirrhosis (F4).[17] NASH resolution is defined as absent fatty liver disease or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning and any value for steatosis with no worsening of liver fibrosis. Clinical benefit can be verified by demonstrating superiority to placebo in delaying disease progression measured by a composite endpoint that includes the following: progression to cirrhosis on histopathology, reduction in hepatic decompensation events (e.g. hepatic encephalopathy, variceal bleeding, ascites), change in MELD score from less than or equal to 12 to more than 15, liver transplant and all-cause mortality.[18,19]

TABLE 1 Advantages and disadvantages of a master protocol for a NASH cirrhotic population.

Advantages	Disadvantages
• Represents the highest unmet clinical need • Common control arm of sufficient size may provide additional natural history data	• Few drugs designed for improving cirrhosis • Patient heterogeneity at the cirrhotic stage results in widely different rates of decompensation which necessitates that each trial has its own full-size control arm • Safety and pharmacokinetic issues in a cirrhotic population would necessitate a highly customised approach for each tested drug • Long duration of the trial for clinical outcomes

patients with very different rates of progression to clinical events. A shared, common control arm, which is often a major benefit of a PT, would therefore be a challenge, as the control arm would need to be as close as possible to the particular population included in the active arm (Table 1).

4.2 | Screening process

One of the major shortcomings of traditional trial designs in NASH is the very high rate of screen failures and the limited ability to screen for several trials both simultaneously and sequentially because of temporal and material constraints related to liver biopsy or an imaging procedure (e.g. MRI). A NASH PT with multiple investigational agents will have a major advantage of allowing for a more efficient screening procedure. As such, a patient will be screened for the platform and, depending on which selection criteria are fulfilled, the chances that he or she can be included in a interventional cohort will be greatly enhanced without having to repeat the screening process. The screening procedures will have to be optimised to ensure a central assessment of all the different biological, histological and imaging parameters. In addition to accelerating start-up for new interventions, establishing centralised assays for the IRP will also help ensure homogeneity and reproducibility in assessment of biological parameters throughout the PT. A single electronic data capture system will centralise all the relevant data to assess participant eligibility. Exclusion criteria may be somewhat different depending on the mode of action of the investigational agent (i.e., compound-specific restrictions). However, a functioning PT would require a common and rather homogenous set of inclusion criteria. Most inclusion and exclusion criteria are the same or somewhat similar for all NASH trials and can be readily defined (see Table 2). A few exclusion criteria may be specific to a particular compound and described in the intervention-specific appendix (ISA) for that treatment (e.g. disallowed medication(s) due to confounding or drug–drug interactions, specific medical conditions that may be contraindicated for certain compounds, or compound specific laboratory thresholds).

4.3 | Control arm

A major conceptual advantage of the master protocol is the possibility of a common, single placebo/standard of care control arm. The common control arm would reduce the number of patients assigned to placebo thereby allowing more patients to be assigned to active drugs. This advantage not only reduces the overall number

TABLE 2 Common selection criteria for a NASH master protocol.

Inclusion	Exclusion
Age 18 to 75 years, inclusive	Significant weight loss or weight gain, defined as an increase or decrease of ≥5% in body weight based on subject report (if prior clinic-based weights are not available) within 6 months before study start
BMI ≥ 25 kg/m^2 (23 if Asian ethnicity) and ≤45 kg/m^2	Current or recent history (i.e. <3 years) of liver disease of other aetiology at screening (e.g. drug-induced, autoimmune hepatitis, hemochromatosis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency)
Histological evidence of NASH with fibrosis stage 2 or 3 based upon a liver biopsy obtained no more than 6 months prior to study start and a nonalcoholic fatty liver disease activity score (NAS) of ≥4 with at least a score of 1 in each component of the NAS (if Phase 2b)	Current or past history of cirrhosis or evidence of decompensated liver disease (e.g. ascites, variceal bleeding)
Absolute hepatic fat ≥10% assessed by MRI-PDFF (if Phase 2a)	Current or past history of hepatocellular carcinoma, primary sclerosing cholangitis, biliary diversion, acute or chronic pancreatitis, or liver transplant
Woman of childbearing potential (i.e. those subjects who do not meet the post-menopausal definition regardless of age) must have a negative highly sensitive serum β-human chorionic gonadotropin pregnancy test at screening and a negative urine β-hCG at study start	ALT or AST ≥ 5× upper limit of normal, platelet level <150,000, serum albumin <3.2 g/dL, INR > 1.3 (except for those on warfarin therapy), or total bilirubin >1.5 mg/dL (unless consistent with history of Gilbert's disease)
Subjects must have signed an informed consent form indicating that they understand the purpose of and procedures required for the study and are willing to participate in this study	Use of drugs historically associated with nonalcoholic fatty liver disease (NAFLD) (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, valproic acid and other known hepatotoxins)
	History of significant alcohol consumption (significant alcohol consumption is defined as >20 g/day in females and >30 g/day in males, on average) within 5 years of screening or inability to reliably quantify alcohol consumption

of participants needed from a statistical perspective but is also more appealing to participants. There are, however, some aspects of a NASH PT that can impact the use and size of the control arm. Since one or more baseline characteristics (e.g. fibrosis stage, absolute amount of liver fat, presence of diabetes) can potentially impact the outcome of some endpoints/objectives, stratification will be required between treatment and control arms. Another issue is that the double-dummy concealing procedure cannot obviously be the same for oral and injectable drugs for ethical and practical reasons. Therefore, while the data could not be shared fully from a statistical point of view, if the population characteristics are relatively similar across different delivery systems (i.e., route and frequency) some of the control arm information could be shared dynamically within the Bayesian framework. Ultimately, there will be a minimum number of patients assigned to placebo for each intervention, but the number will vary based on the amount of accumulated placebo data due to differences in the relative times between when interventions have started in the PT, the characteristics of the population and the route/frequency of administration (Figure 3).

The fact that different interventions will join the PT at different time points may result in a lack of synchronicity between active and control arms, which in turn might create a historical segment of the control arm, with the theoretical concern that changes in management practices over time may influence the outcomes (i.e. non-concurrent controls). However, since all patients are managed within the platform, the risk of time-induced changes may be minimised and therefore not have a sizeable impact on variability in the comparator arm. Another potential issue might be derived from differences in the population (based on inclusion and exclusion criteria) that allow for randomisation to only certain interventions and the corresponding placebo arm and, therefore, it may only be appropriate to compare controls who would have been able to be randomised to specific interventions and not across all interventions. Despite the heterogeneity based on intervention design and the form and frequency of dosing of different placebos, there is specific statistical methodology that will be applied in the NASH IRP to allow the maximal use of a common control arm.

Sharing all control data across the whole platform study might not be generally be possible. For example, if time trends are expected like in dynamic diseases as for COVID-19, then using all control data could bias the results. Though model-based analysis methods[27] could eliminate or mitigate the problem, using only concurrent control data is recommended by regulatory authorities. Furthermore, sharing control data across all sub-studies would require that all ISAs have the same inclusion and exclusion criteria and that it has no negative impact on the blinding. For example, if ISAs have slightly different inclusion and exclusion criteria or patients can pre-select to which ISAs they want to be randomised to, then in the statistical analysis only the control data of patients should be utilised which had in principle the chance to be randomised to the treatment arm being analysed. Especially if there are different route of administrations, for example, i.v. and oral, then each route of administration should have its own control group. The patient cohort accepting

one route, but not the other, could differ and using the control data of both cohorts could bias the results.

4.4 | Enrolment

Many participants express preferences for certain trial characteristics: either short or long trials (where chances for individual benefit are higher), for trials without invasive procedures, for less demanding scheduling of visits, etc. Therefore, the MP should be designed to accommodate a largely uniform design, as far as, trial duration, requirements for invasive and non-invasive assessments, general risk/benefit, minimum number of visits, etc. Participants will initially be provided with informed consent regarding the risks and benefits of the procedures and the PT itself. The participant will then review the risk/benefit profile and mode of administration (i.e. oral vs. injectable) for each investigational agent in the trial and consent for each intervention he/she would be agreeable to receive if eligible so as to ensure participant choice and autonomy. It would be desirable to have a participant agree to as many interventions as possible to facilitate the greatest flexibility in treatment allocation across the PT. Once a participant undergoes screening for the PT and fulfils the selection criteria for one or more intervention cohorts, the participant will be randomised to an intervention and then to an arm (active or placebo) within that intervention (Figure 4).

4.5 | Procedure harmonisation

There are some logistical aspects that would be of particular importance in a NASH IRP and therefore will require specific consideration, specifically, standardised lifestyle counselling[27] and liver biopsy reading, with the latter being particularly relevant since several studies have demonstrated large intra- and inter-reader variability of histological features.[28,29] Consequently, it will be especially important to implement mechanisms that minimise variability and aid reproducibility of biopsy assessments during the development of the operational plan for the NASH PT.[30] A committee of central pathologists will be created which will be trained for consensual definition and recognition of the relevant lesions. Moreover, the centralised reading will incorporate digitising the slides and using automated machine-based reading of quantifiable parameters or artificial intelligence methods[31,32] to aid in reader assessments and provide additional quantitative data analysis (e.g. collagen fibre architecture and density).

5 | POTENTIAL PHASES OF A NASH PLATFORM TRIAL

5.1 | Phase 3/4 master protocol

Phase 3/4 NASH trials are fairly large trials (around 700 or more subjects per arm) with an interim analysis based on one or two histological surrogates after ≥12 months of treatment. Since these are registration trials, they follow highly stringent regulatory requirements for the Phase 3 interim analysis. In addition, these trials continue for an extended period of time of 4–6 years in an attempt to collect clinical outcomes data (i.e. Phase 4 post-marketing portion). If successful, this outcome part of the trial will lead to be submitted to the HAs so these trials will need to comply with all regulatory demands which may not be feasible and beyond the scope of a NASH PT. Challenges about maintaining patients in these long trials, particularly in the control arm, are a principal concern. While the advantages of a shared control arm along with standardised outcomes and procedures of an PT would be highly desirable given the size and complexity of these trials, it may be particularly difficult to gain alignment with the HAs (and biotechnology/pharmaceutical companies) on adaptive randomisation and the use of a Bayesian decision algorithm. In addition, there may not be a large enough pipeline to

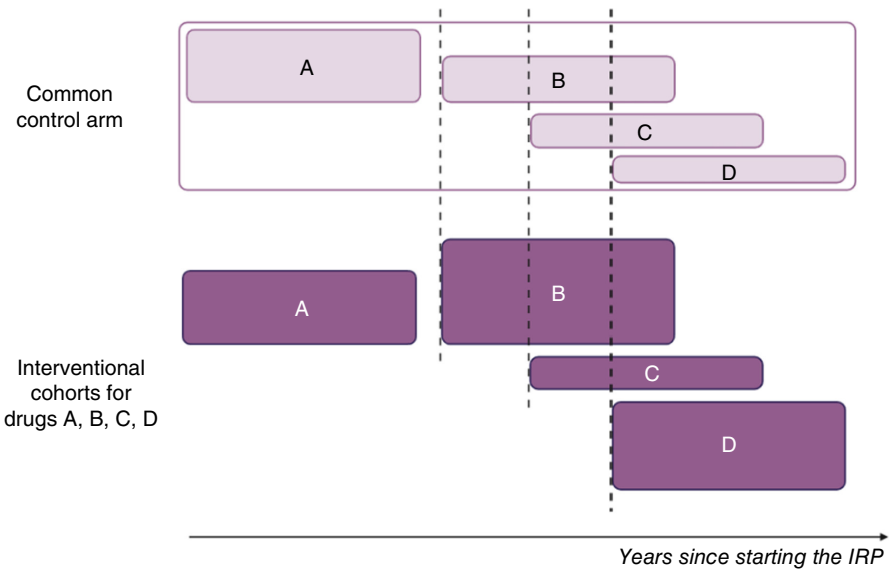

FIGURE 3 The impact of timing and intervention-specific differences on recruitment in the control arm. Length of boxes corresponds to trial duration; height of boxes corresponds to the number of patients for each intervention). In this example, all trials have the same duration.

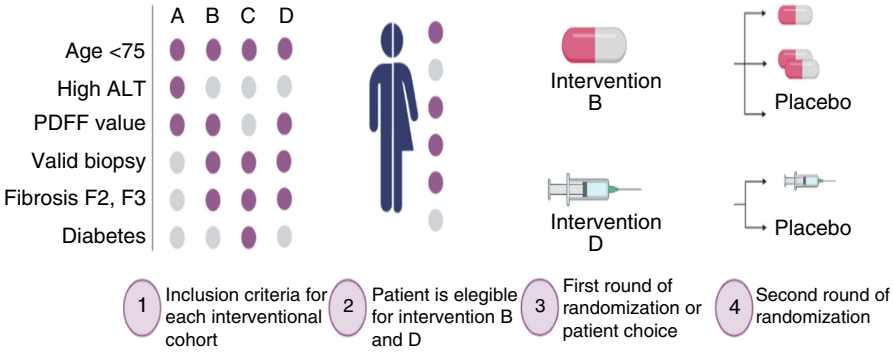

FIGURE 4 Profile pattern of each patient leads to appropriate trial eligibility and enrolment.

ensure enough parallel molecules in development to take full advantage of the NASH PT design.

5.2 | Phase 2b master protocol

Phase 2b NASH trials use the same histological endpoints as Phase 3 studies and typically have a ≥12-month treatment duration although some studies have been conducted in shorter timeframes (i.e. 6–9 months). Screen failure rates are high and the response rate in the control arm displays substantial heterogeneity due to the smaller sample sizes compared to Phase 3. Typically two or three active doses are utilised based on the safety and tolerability profile described in Phase 1 and Phase 2a studies. From a NASH PT perspective, a Phase 2b design seems well suited in that there is a robust pipeline and would help accelerate the most promising compounds to Phase 3. It is also agnostic to the mechanism of action of any given compound since histological change is a common endpoint for all compounds. The use of the Bayesian design helps reduce the overall sample size and gates to a Phase 3 based on the probability of future success. As is typical with Phase 2b studies, there are few HA concerns, but sufficient data must be generated to support meetings with HAs (e.g. an end-of-Phase 2 meeting and/or scientific advice meeting) and progression to Phase 3. Lastly, the shared standard of care/control arm can provide valuable longitudinal data and the opportunity to evaluate non-invasive biomarkers in the context of histological data (Table 3).

5.3 | Phase 2a master protocol

Phase 2a trials in NASH are less standardised in terms of design and outcomes compared with Phase 2b trials, but are of short duration. Typically they are conducted over a 3–4 months and utilise non-invasive endpoints. These studies often include patients who have NAFLD or 'likely NASH' based on non-invasive assessments making them faster and easier to recruit since a liver biopsy with a specific NASH histological profile is not required. The sample size is also relatively small based on the magnitude of the effect size and lower variance of the measurements compared to histological endpoints. They include several arms with different doses but have an overall lower cost than a Phase 2b trial. While the common control arm for a Phase 2a PT trial adds value to the study itself, it offers less advantage in terms of natural history and biomarker research since it lacks histological and long-term data. The outcomes and methods of assessment thereof are well accepted for Phase 2a trials which simplify the design of a MP.

5.4 | Phase 2a/b master protocol

A NASH 2a/b MP with a seamless design would function based on the combination of serum and imaging biomarkers for the Phase 2a portion followed by histological assessment as the primary endpoint for the Phase 2b portion of the trial. A particular challenge for this type of design would be to identify biomarkers to drive the Bayesian rules of the trial (i.e. the magnitude of effect for success and futility). For this design to work it is necessary that outcomes measured in the Phase 2a portion be reasonably predictive of success for histological improvement. It is currently unclear which biomarkers are highly predictive of histological improvement and whether those that predict the resolution of NASH also predict fibrosis regression. The two main biomarkers measured in Phase 2a trials are hepatic fat content and serum ALT as noted above since both have been shown to be partially associated with NASH resolution, however, there are no well-validated fibrosis biomarkers associated with fibrosis reduction. Consequently, the seamless Phase 2a/b design would be best suited to compounds with a mechanism of action that would impact liver fat and to some extent inflammation and less so for compounds that had direct anti-fibrotic effects. Any potentially newly validated biomarkers may be incorporated into the platform trial design from now until the completion of the project as information from LITMUS and NIMBLE are forthcoming in the near term.

This seamless design would allow the transition of an individual patient, without discontinuation, from a Phase 2a to a Phase 2b trial. This way patients taking part in the Phase 2a trial will not be lost for a Phase 2b trial offering an overall time savings (e.g. >6–12 months). However, in order to allow the patients to transition from Phase 2a to 2b, they must be biopsy-confirmed NASH patients meeting the Phase 2b inclusion criteria at the beginning of the Phase 2a portion. Since historically many compounds fail to

TABLE 3 Comparison of phase 2 designs for a potential NASH platform trial.

Phase 2a	Phase 2b	Phase 2a/b
Advantages		
• Faster recruitment (i.e. NAFLD population) • Expected high interest (e.g. strong pipeline) • Small sample size (i.e. smaller network of sites needed) • Lower cost	• More promising compounds (i.e. demonstrated activity in Ph2a) • Increased utility of control arm for natural history and validation of biomarkers in a NASH population • Useful for any mechanism of action (i.e. histological assessment) • Reduced sample size using Bayesian approach very impactful	Same as Ph2b including: • Potentially the largest pipeline (i.e. allow Ph2a portion to be optional if Ph2a data exists thereby allowing even more compounds) • Overall time savings when Ph2a compounds move directly to Ph2b and greater potential for Bayesian rules to reduce the overall sample size • Even greater utility because of more biomarker data linked to histology
Limitations		
• Less utility of shared control arm for natural history or biomarker validation (i.e. non-NASH population, no histological data) • Not useful for testing any mechanisms of action (i.e. most reliable endpoint is liver fat which is suitable mainly for metabolic compounds) • Bayesian analysis and shared placebo less valuable as sample size small using Frequentist approach (i.e. ~15–20 patients/arm)	• Slower recruitment (i.e. biopsy confirmed NASH) and larger network needed • Potentially fewer compounds in pipeline • Higher cost than Ph2a	• If a treatment arm fails (as often occurs in Ph2a), it will be difficult to re-assign a participant (i.e. wash-out required and new baseline biopsy) which could result in the loss of difficult to identify NASH patients • The Ph2a decision relies on liver fat, which is mainly suitable for metabolic compounds; other biomarkers can be used but have limited translatability to histology thus far. • Less safety data prior to treating NASH patients (i.e. no Ph2a safety data) • Higher overall cost than either Ph2a or Ph2b alone

progress from Phase 2a to Phase 2b, there is a possibility of patients in a failing Phase 2a arm (for efficacy or safety reasons) will not be able to be re-assigned thereby losing the more difficult to identify NASH patients (versus the more abundant NAFLD patients often used in Phase 2a). However, the shorter treatment duration for the Phase 2a portion of the PT may allow a more rapid decision using the Bayesian rules and, therefore, potentially smaller sample sizes and re-allocation from failing arms to more successful ones (i.e. response adaptive randomisation).

It should be noted that the re-allocation of patients who failed one treatment in an ISA to another treatment arm of a different ISA within the same PT might be problematic, for example, for the interpretability of trial results. Moreover, such re-allocation might be also not reasonable depending on the trial objective and the corresponding trial population. For example, if treatment naïve patients should be investigated in the platform, then a re-allocating patient does not make sense per se. Furthermore, the non-responding of subjects might be related to specific genetic profile. If the mechanism of action is the same for different drug in the different sub-studies, patients with a certain genetic profile might have a higher likelihood to be a non-responder. Then by re-allocating patients repeatedly, the trial population of the later studies would be artificially enriched by patients likely to fail. Therefore, there might be more reluctance in broad indications with a large pool of patients compared to rare diseases with small patient populations only.

6 | REGULATORY CONSIDERATIONS

HA have noted that the growth of precision medicine, especially in oncology, has expanded enormously in the last decade. Some of this growth has been accompanied and facilitated by the use of MP. However, the use of MP poses some unique challenges to the HA and oversight by IRBs and ECs. Hence, specific guidance has been issued very recently on the topic by the FDA,[33] the EU Heads of Medicine Agencies[34] and the National Institute for Health Research in the United Kingdom.[35] The main themes that underlie all these recommendations are focused on design, safety and statistical methodology.

It will be necessary to provide a detailed rationale and discuss the benefits of a MP design versus similar stand-alone studies to gain support from the HA. This is particularly important since some regulators have expressed concern that MP are used as a means to simplify authorisation and reduce review times rather than creating an innovative and efficient trial environment.[36] The design of the MP would adhere to the HA guidance on NASH drug development[16,17] and specifically define the utility of a PT design including a more efficient evaluation of potential compounds. It would also maintain a high degree of endpoint assessment including adjudication of histology and adverse events, and development of a data-rich control arm that would allow for evaluation of clinical endpoints (including evaluation of novel biomarkers) to advance understanding of the

history of the disease in the context of a randomised, controlled trial. Another general consideration is that the study design will follow the requirements to be scientifically sound with sufficient preclinical and clinical data to support evaluation of the study hypothesis while ensuring patient safety.

From a safety standpoint, a NASH PT would need to establish a comprehensive plan and independent committee to monitor for liver safety so as to recognise a liver signal in the background of chronic liver disease. Establishing other committees to ensure adjudication and unblinded review of clinical events of interest (especially liver and cardiovascular related) for each treatment would also be warranted in order to interpret any relevant or unexpected adverse events and to provide necessary safety updates. While not specific to a NASH PT, a major challenge is timely dissemination of new safety information to investigators, IRB/EC and HAs in the context of a PT design with multiple interventional agents ongoing concurrently. A well-structured plan and a clear communication pathway for reporting events to both compound owners and governing bodies (i.e. HA, IRB/EC) must be established before the trial starts. In addition, new safety information must also be used to re-assess the risk–benefit analysis to decide whether updating of informed consent is necessary or even the closure of an arm or treatment. Some of these concerns may be overcome by limiting the number of treatments and arms that can be conducted at any given time.

The use of Bayesian decision rules presents some challenges and requires alignment with the HA on the use of concurrent and non-concurrent controls. In addition, the minimum amount of safety data (i.e. the number of patients and time exposed to treatment) would need to be aligned with the HA and pre-specified in the design to align with the decision rules ensuring that a treatment arm was not progressed without sufficient safety data. Additionally, the MP needs to be specifically designed to maintain data integrity and avoid multiplicity issues and type I errors in the context of a design that seeks to analyse data frequently during the study with a shared control arm. A carefully designed statistical analysis plan (SAP) will need to describe in detail how the statistical issues previously described will be addressed. Prior alignment with the HA on the SAP will help to ensure acceptance of the data and alignment on the magnitude and probability of efficacy to progress to the next phase of development. In addition to the SAP, there needs to be alignment with the HA on the timing and development of clinical study reports and public disclosure of data (since different treatments will complete the study in the context of the ongoing NASH PT). Since the NASH IRP is registered as a single trial (i.e. as a master protocol) in the European Union (EU), data from each arm would not need to be disclosed until the end of the trial which may not be practical as the IRP PT is potentially perpetual. To avoid this issue, the NASH IRP PT will need to propose a dissemination policy for each treatment consistent with HA guidelines and acceptable to interventional compound owners.

The results of a Phase 2b NASH platform study are for decision-making purposes of the sponsor and not subject to regulatory review for product approval per se but may be part of a regulatory submission (mainly for compound safety). In that regard, the regulatory authorities offer advice on the conduct of the study to ensure that the results, if positive, would be likely predictive of success in Phase 3, specifically in terms of endpoints and the statistical control of type 1 error and data sharing. This is stressed by the regulatory agencies[33-35] and re-iterated in our interactions with FDA during a Critical Path Initiative Meeting and with the EMA in an Innovative Task Force meeting in the context of the EU-PEARL project. The regulatory agencies offer accelerated/conditional approval based on histological improvement from a liver biopsy after at least 1 year of treatment, however, as discussed in the prior section *Potential Phases of a NASH Platform Trial*, there are several shortcomings associated with liver biopsy as primary endpoint. In this regard, the issue is not a regulatory one but rather a scientific one where endpoints that have stronger associations to outcomes, which have higher precision/lower variability, and that can be conducted non-invasively are needed to accelerate drug development in NASH. Each regulatory agency offers a biomarker qualification programme and as new data emerges from other initiatives in the area of biomarker development, it is possible that such new biomarkers may be available and accepted by the regulatory agencies.

7 | CONCLUDING REMARKS

Before considering a design for the NASH IRP master protocol within EU-PEARL, it is reasonable to examine the master protocol landscape to see what the predominant designs are and what has made them successful. A recent systematic review reported that the majority of master protocols were designed as Phase 2 trials in oncology using a binary endpoint and frequentist decision rules. Although in that

TABLE 4 Endpoints and biomarkers used for measuring therapeutic efficacy in Phase 2a trials.

Endpoint	Biomarker	Relevance for improved histology	
Liver fat	MRI-PDFF	Yes[a]	NASH resolution
Biochemical	ALT	Yes[a]	NASH resolution
Metabolic	HbA1c, HOMA, serum insulin, lipids	No	
NIT fibrosis	ELF, FIB4, ProC3, NFS	Likely[a]	Fibrosis improvement

[a]Depending on mechanism of action and study duration although the optimal threshold may require further validation.

same review, platform studies included several other diseases and were equally designed as Phase 2 or Phase 2/3 with both binary and time-to-event endpoints employing mainly Bayesian decision rules and half of the studies using response-adaptive randomisation.[37–39] Phase 2 is likely the preferred design as it offers a robust pipeline for most indications and the ability to make decisions more rapidly before committing to longer, more costly development. This is particularly true for NASH where there is an abundance of compounds in early development and refinements of preclinical models and population genetics are revealing potential therapeutic targets.[40,41] There are less regulatory requirements for a Phase 2 study as the data generated is more for decision-making purposes rather than regulatory approval. Moreover, most pharmaceutical companies may be concerned by not having complete control over the design and oversight of pivotal trials. Therefore, focusing on Phase 2 designs for a NASH PT is deemed more appropriate.

For the aforementioned reasons, the team within EU-PEARL has focused on three types of Phase 2 trials with each using a Bayesian statistical approach with and without response adaptive randomisation: a Phase 2a, a Phase 2b, and a seamless Phase 2a/b. Each design has relative advantages and limitations compared to one another (Table 4). After considering the characteristics of each design and in discussion with both academic and industry representatives, the team within EU-PEARL has decided to design a Phase 2b MP with a broad and well-accepted set of objectives and endpoints (Table 5). However, there are many details that have yet to be worked through

TABLE 5 Phase 2b NASH master protocol objectives and endpoints.

Objectives	Endpoints
Primary	
To evaluate the efficacy of study intervention(s) compared to placebo on NASH histology after 48 weeks of treatment relative to baseline	• Experiencing (No/Yes) at least 1-stage fibrosis improvement without worsening of NASH, or • Experiencing (No/Yes) resolution of NASH without worsening of fibrosis
Secondary	
To evaluate the efficacy of study intervention(s) compared to placebo on other histological parameters after 48 weeks of treatment relative to baseline	• Experiencing (No/Yes) both NASH resolution and 1-stage improvement in fibrosis • Experiencing (No/Yes) at least 2-stage improvement in fibrosis without worsening of NASH • Change in steatosis score • Change in inflammation score • Change in ballooning score • Change in NAFLD activity (NAS) score • Change in steatosis-activity-fibrosis (SAF) score • Change in NASH activity (inflammation and ballooning)
To evaluate the efficacy of study intervention(s) compared to placebo on biomarkers over time and after 48 weeks of treatment relative to baseline	• Absolute and percentage change from baseline in liver function tests (i.e. ALT, aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], total bilirubin, direct bilirubin and alkaline phosphatase [ALP]) • Absolute and percentage change from baseline in fibrosis biomarkers: pro-C3, pro-C6, ELF score and its individual components (i.e. type III procollagen peptide (PIIINP), hyaluronic acid (HA) and tissue inhibitor of metalloproteinase-1 (TIMP1)) • Absolute and percentage change from baseline in liver stiffness as measured by ultrasound elastography • Absolute change in simple scores (i.e. FIB-4, APRI and NFS)
To evaluate safety and tolerability of the study intervention(s) throughout the study based on the incidence, change from baseline in continuous measures or clinically significant findings relative to baseline	• Adverse events (AEs) • Clinical laboratory tests (including haematology, blood chemistry, blood coagulation, lipids, metabolic parameters [fasting plasma glucose, fasting insulin, HOMA-IR and HbA1c)] and urinalysis) • 12-lead electrocardiograms (ECGs) • Vital signs (including body weight) • Physical examinations
Exploratory	
To evaluate the change from baseline in Patient Reported Outcomes (PROs) following treatment with study intervention(s) relative to placebo over time and at week 48	• NASH-CHECK score • CLDQ NASH score • EQ-5D score
To evaluate the change from baseline in exploratory biomarkers following treatment with study intervention(s) relative to placebo over time and at week 48	• RNA biomarkers • Proteomics • Genomics • Metabolomics

such as how much flexibility can or needs to be in the master protocol, what exactly are the criteria to declare 'graduates' or 'futility' for a treatment arm (i.e. the magnitude of histological change that change would be sufficient to progress a compound), what are the optimal Bayesian probability thresholds given the variance in the measurements, would a frequentist design be more appropriate, does type I error rate and multiplicity need to be controlled and, if so, how. Answering these questions and others will require extensive statistical simulations, refinement and discussions among all stakeholders to eventually achieve a workable NASH MP.

Overall, EU-PEARL seeks to provide tools for future IRP development and simultaneously implement those tools into PT that are ready to be used at the end of the grant period in 2023. A hallmark of these IRPs is that they are patient centric. The PT for NASH seeks to fulfil this mission not only through patient engagement, which is embedded in the process of developing the IRP (e.g. patient input into the design, communication materials, informed consent wording), but also through the innovative features of the MP itself. The shared control arm and Bayesian analysis with adaptive randomisation translates into fewer patients using placebo and a greater chance of being assigned to successful therapies. In addition, the IRP trial will enable compounds to start more rapidly because of the established MP and research network, which may ultimately translate to more rapid development of therapeutics for patients. These innovations also benefit IMP owners by reducing the costs and time to start and conduct the trial. Communicating the potential benefits of a NASH PT will require clear and specifically tailored messaging to patients, investigators and pharmaceutical companies.

Ultimately, the success of the NASH IRP will be based on its utilisation and so, the question remains 'if we build it, will they come'? In order to be able to set up the NASH PT as a Phase 2b from its inception, it would require an extensive clinical network, with dozens if not hundreds of actively enrolling sites. Therefore, potentially a global clinical network, which implies at least three conditions. First, highly motivated clinical investigators that are able to recruit participants in spite of colliding interests with other traditional clinical trials in NASH underway in their centres; second, the remarkable logistical complexity demands a well-oiled governance structure and the support of a global clinical research organisation; and last and foremost, the prior points ineluctably imply a large initial investment, thus being mandatory that large pharmaceutical companies join the IRP. Given the current landscape of drug development in NASH, where the drug pipeline is characterised by an aggressive race between companies to be the first to achieve regulatory approval for their compounds, in addition to the lack of difficulty to screen and enrol participants in standalone trials as compared to other diseases (e.g. rare diseases), it might be necessary to provide 'proof-of-platform' in NASH before the concept of IRP is widely embraced by all stakeholders. For instance, academically driven small IRPs focused on repurposing or in collaboration with small biotechs and non-profit organisation may become a preliminary step before larger interest and investment comes in and the IRP can be escalated to a global scope.

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