JHEP|Reports

Patient-reported outcomes in NAFLD/NASH clinical trials: A blind spot that needs addressing

To the Editor:

We read with interest the article by Younossi *et al.*,[1] which explored patient-reported outcomes (PROs) in non-alcoholic steatohepatitis (NASH) populations. Although the authors comprehensively assessed the current knowledge and evidence about the impact of NASH on PROs and highlighted the importance of developing and implementing NASH-specific PRO instruments in research endeavors in clinical practice, little is known about the inclusion of PROs in non-alcoholic fatty liver disease (NAFLD)/NASH clinical trial protocols. Trial protocols serve as the foundation for planning and implementing clinical trials; thus, providing a glimpse of future trial results. Therefore, including PRO measures in trial protocols can provide essential data to inform shared decision-making and improve clinical guidelines and health policy recommendations. Furthermore, it could aid in addressing and mending what the authors call "a significant and often unrecognized health-related quality of life (HRQoL) burden among individuals with NASH".

To complement the authors' work and learn about PROs in NAFLD/NASH clinical trial protocols, we aimed to assess the proportion of NAFLD/NASH interventional trial protocols reporting the inclusion of PROs as predefined outcomes of interest among protocol trials registered on clinicaltrials.gov. We reviewed the clinicaltrials.gov registry to explore whether PROs are routinely included in NAFLD/NASH clinical trial protocols. Using the keyword "non-alcoholic fatty liver disease," we queried clinicaltrials.gov for NAFLD/NASH protocol trials. The search was restricted to interventional, phase II-III trials. Relevant protocol trial data was extracted and descriptively summarized to chart the available protocols registered on clinicaltrials.gov.

By July 29, 2022, 334 interventional phase II and III NAFLD/NASH protocols were registered on clinicaltrials.gov. Of these, 284 (85%), 28 (8.4%), 12 (3.6%), and 6 (1.8%) investigated pharmacological compounds, dietary supplements, biological components, and behavioral interventions, respectively. In addition, two studies researched devices, and one investigated a blood donation procedure. As shown in Fig. 1A, most protocols (86%) were phase II trials, and roughly half were reported as completed. Less than 10% included children, and eight (2.4%) trials were designed to include only males. The industry was the predominant source of funding for the protocols registered (61.3%). Remarkably, only 5% of all registered protocols reported PROs as outcomes of interest. The most common instrument for collecting PRO data was the SF-36, which was planned to be used in 8 trials. The NASH-CHECK was reported in 2 (0.6%) protocols.

No significant differences were observed in the inclusion of PROs according to trial phase (phase II = 13, 4.5% *vs.* phase III = 4, 8.5%; $p = 0.2$) and funding source (industry-funded = 11, 5.3% *vs.* academic = 6, 4.6%; $p = 0.7$). Trial protocols including children were more likely to include PROs than those that did not include children (5/29, 17.2% *vs.* 12/305, 3.9%; $p = 0.001$).

The fact that only 5% of the NAFLD/NASH protocols registered on clinicaltrials.gov reported the systematic collection of PROs is worrying and reveals an overall lack of patient-centric appraisals in the quest for treatments against the most common chronic liver disease and one of the most prevalent chronic conditions worldwide. The trend shown in Fig. 1B is discouraging as it suggests that the number of clinical trials including PROs has barely increased in recent years. This is a matter of concern because NAFLD and NASH have a remarkable impact on patients' quality of life. Even if this is not being studied systematically in clinical trials, there is evidence that some PROs are related to the degree of fibrosis of NASH and therefore are valuable tools to gather information about patients' HRQoL.[2] Moreover, their derivatives (focused on patients' experiences) are self-reporting instruments that measure the patients' perception while receiving care or participating in clinical trials.[3]

The NASH-CHECK is the only specific PRO measure in the NAFLD/NASH field. This PRO measure was recently created and validated in patients without cirrhosis.[4] Some aspects included in the NASH-CHECK relate to symptoms such as pain, fatigue, itch, cognition, and sleep impact. These traits may impact daily activities, social interactions, and the mental well-being of patients with NASH. Overall, these symptoms and their effects can impact work productivity, ability to work, cost of medication, and cost of lifestyle management, thus having a negative economic impact. In the trials reported in this letter, only 2 out of 334 studies reported using NASH-CHECK. Although the latter finding is not surprising because the NASH-CHECK is a relatively young PRO measure, we expect future clinical trials to routinely include it as a pre-specified outcome measure in their trial protocols. Due to the increasing number of clinical trials specifically for patients with cirrhosis, it is necessary to elucidate if a derivative of NASH-CHECK or another NASH-specific PRO measure for the population with cirrhosis should be developed.

We urge NAFLD/NASH stakeholders to include patient perspectives in clinical research to gain information beyond NAFLD-focused metrics and to improve our understanding of what matters to patients while participating in clinical trials. This will help improve published trials' quality and provide clinician-scientists with data to further implement patient-centered care for NAFLD.

Keywords: Non-alcoholic fatty liver disease; Patient-reported outcomes; Health-related quality of life; Non-alcoholic steatohepatitis.

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A

	Protocols in clinicaltrials.gov (n = 334)
Trial phase	
Phase 2, n (%)	287 (86)
Phase 3, n (%)	47 (14)
Status	
Completed, n (%)	169 (50.6)
Recruiting, n (%)	59 (17.6)
Active not recruiting, n (%)	19 (5.7)
Suspended/terminated/withdrawn, n (%)	53 (15.8)
Unknown, n (%)	17 (5.1%)
Age groups included in RCTs	
Included children, n (%)	29 (8.6)
Included individuals >60 yr, n (%)	201 (60.1)
Included only males, n (%)	8 (2.4)
Funding source	
Industry, n (%)	205 (61.3)
Academic, n (%)	129 (38.7)
Reported PROs as an outcome of interest, n (%)	17 (5)
SF-36, n (%)	8 (2.4)
Health-related quality of life (not specified), n (%)	5 (1.5)
NASH-check, n (%)	2 (0.6)
PEDQOL, n (%)	2 (0.6)
PROMIS fatigue questionnaire score, n (%)	2 (0.6)
PGI-S, n (%)	1 (0.3)
Food frequency questionnaire (FFQ), n (%)	1 (0.3)

B

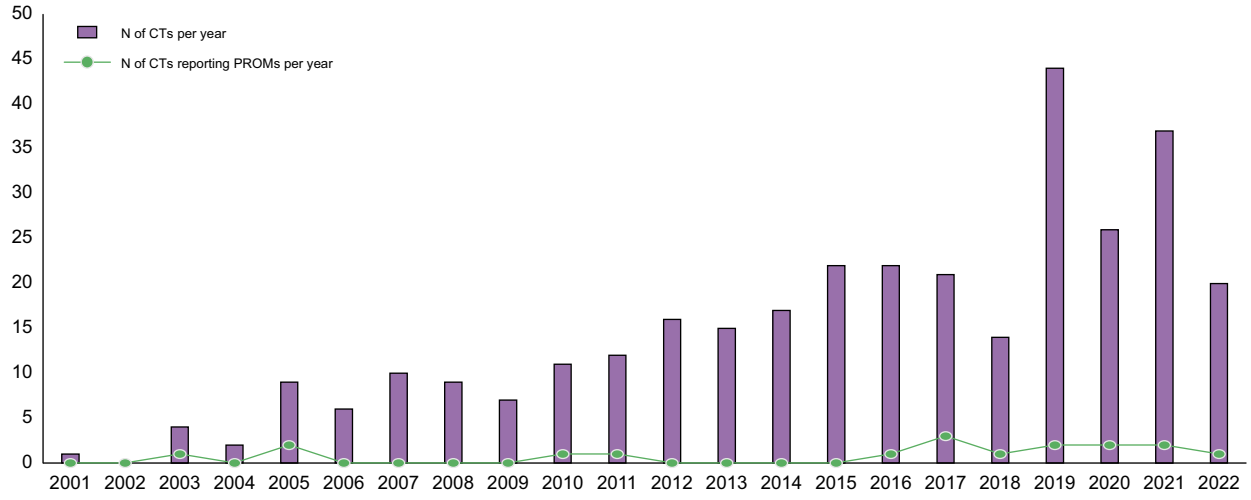

Fig. 1. Characteristics of the NASH clinical trial protocols and representation of PROs. (A) Overview of trial protocol characteristics and PROs, (B) Number of NASH trial protocols and those including PROs per year (2001-2022). CT, clinical trials; NASH, non-alcoholic steatohepatitis; PROs, patient-reported outcomes.

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Conflict of interest
JMP reports receiving consulting fees from Boehringer Ingelheim and Novo Nordisk. He has received speaking fees from Gilead and Intercept, as well as travel expenses from Gilead, Rubió, Pfizer, Astellas, MSD, CUBICIN, and Novo Nordisk. He has received educational and research support from Gilead, Pfizer, Astellas, Accelerate, Novartis, Abbvie, ViiV, and MSD. He also received funds from the European Commission/EFPIA IMI2 853966-2, IMI2 777377, H2020 847989, and PI19/01898. All other authors: no conflicts. None of the authors have any personal conflict concerning the present manuscript.

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Authors' contributions
Conceived and designed the analysis: JMP, RMN, EdS; Collected the data: EdS, RMN, JRE; Contributed data or analysis tools: RMN, EdS; Performed the analysis: EdS, RMN; Wrote the paper: all authors; Supervision of the work: JMP; All authors provided significant intellectual contributions to the final draft of the paper and approved it for journal submission.

Data availability statement
The data used to perform this research letter can be shared upon reasonable request.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2022.100597.

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Author names in bold designate shared co-first authorship

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