How to Design a Multicenter Clinical Trial in Hepatic Encephalopathy

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The design of clinical trials on Hepatic Encephalopathy (HE) is not an easy task, in fact there are several issues related to the performance of clinical trials in HE that have impeded progress in the field, mainly because most of the studies on HE therapy were performed before the era of rigorous Randomized Controlled Trials (RCTs). In this review we discuss the major problems affecting previously published trials on HE treatments aiming to provide evidences, suggestions and indications to prepare well designed RCTs in three different settings: (1) management of hospitalized patients with episodic HE; (2) secondary prophylaxis in patients following an episode of HE; and (3) management of minimal/covert HE. (J Clin Exp Hepatol 2019;9:137–145)

The design of clinical trials on Hepatic Encephalopathy (HE) is not an easy task, in fact there are several issues related to the performance of clinical trials in HE that have impeded progress in the field. The conclusions of published metanalysis about HE treatment strategies have often emphasized this topic. For example, "we need additional randomized clinical trials to determine the effect of Branched Chain Amino Acids (BCAA) compared with interventions such as non-absorbable disaccharides, rifaximin, or other antibiotics"[1]; "most of Randomized Controlled Trials (RCTs) conducted with probiotic as treatment suffered from a high risk of systematic error ('bias') and a high risk of random error ('play of chance') and therefore providing evidences of low quality".[2] For how concerns non-absorbable disaccharides, Gluud and coll. in 2004 conclude that "there is insufficient evidence to determine whether non-absorbable disaccharides are of benefit to patients with hepatic encephalopathy",[3] whereas, in a update published in 2016, the same authors conclude that non-absorbable disaccharides have beneficial effects in the treatment and prevention of HE; their use, in this context, confers additional benefits including a reduction in serious liver-related morbidities and all-cause mortality.[4] These latter conclusion is due to the addition of further studies conducted by means of different designs in which a "preventive approach" has been added to the traditional therapeutic approach used to establish the efficacy of a given treatment in HE. This review will deal with the main problems in designing RCTs in this field.

Most of the studies on HE therapy have evaluated interventions that are no longer relevant, many of the drugs that were proposed for HE treatment several years ago, at present, are obsolete and studies of treatment for HE should be reassessed or repeated using the current standard of care. However, these studies could be considered the cornerstone of the therapeutic approach of HE, providing important information, e.g., staging modalities of HE, because they introduce a placebo/no intervention controls or were performed with a cross-over or double-blind design. Moreover, there are recent randomized controlled trials (RCTs) which are designed and conducted without a rigorous assessment. Future well-designed studies should include homogeneous patients and be focused on the choice of appropriate and specific end points. The inclusion of both patient groups with minimal and overt HE in the same study, for example, is still part of the current literature, although it is now clear that these two types of patients are not comparable, and that the methodology used to stage their symptoms is completely different. The appropriateness of the study end points is extremely important also.

Major problems of previously published trials on HE treatments can, therefore, be summarized as follows: (1) very few studies compared active treatments with placebo, (2) uncertain inclusion criteria due to unclear definitions of HE (acute, chronic, episodic, recurrent HE), (3) unsolved problems about objective HE staging, in fact, a standardized and objective staging of its severity is also urgently needed. The development of a simple and clinically applicable standardized grading scale useful for both diagnosing and staging is essential to obtain a diagnostic tool easy

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Abbreviations: BCAA: Branched Chain Amino Acids; HE: Hepatic Encephalopathy; RCTs: Randomized Controlled Trials

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to be applied in practice and sufficiently accurate to offer precise end points for controlled therapeutic trials, (4) different type of HE (precipitant-induced and spontaneous) mixed in the same study, (5) debating role about the need to treat Minimal and Covert HE (MHE/CHE).

Therefore, three types of therapeutic trials could be considered and discussed in this review: (1) management of hospitalized patients with episodic HE; (2) secondary prophylaxis in patients following an episode of HE; and (3) management of minimal/covert HE.

MANAGEMENT OF EPISODIC HEPATIC ENCEPHALOPATHY

The benefit of recently assessed drugs is concentrated in the prevention of HE recurrence, but there is a large need also for trials on episodic HE. It was generally acknowledged that trials on management of episodic HE are extremely difficult to undertake primarily because that the only management of the factor(s) that precipitated the event may be sufficient to resolve the HE. Generally, the large majority of the "therapeutic" studies were conducted on episodic precipitated HE and the study design is based on a "therapeutic approach" i.e. on the resolution/amelioration of HE symptoms, as reported in Table 1. However, in patients with episodic, precipitant-induced HE the effect of the active treatment and that of stopping the precipitant and of general care can be hardly distinguished. To avoid the confounding role following the resolution of precipitating factors, maintaining a standard treatment in both groups and to add the treatment under evaluation in the study group only and the placebo in the control group could be useful. In fact, if the optimal standard of care is initiated and maintained, the treatment trial can be initiated earlier if they include a placebo comparator; this would allow an evaluation of the trial treatment as an adjuvant to standard therapy. On the contrary, in case of a positive result, what is working could be considered the combination of the treatments and there is no possibility to suggest the use the new one alone instead of the old one. In consequence, it was agreed that the optimal standard of care was instituted, treatment trial could be initiated earlier if they include a placebo comparator. This would allow evaluation of the new treatment as an adjuvant to standard treatment. In this setting, the amelioration/disappearance of neuropsychological symptoms represents the main end-point, therefore the double blindness is strongly recommended. Patients who are not expected to survive the hospitalization, who are terminally ill or have acute on chronic liver failure should be excluded. Many possible endpoints could be considered and would need to be tailored specifically to address the trial objectives; clearly different endpoint might be appropriate in large-scale clinical investigations and small-scale proof-of-concept trials. Therefore, robust clinical outcomes such as in-hospital and remote survival, liver-related and total deaths, completeness and speed of recovery from HE, number of days in intensive care, total length of hospital stay, quality-of-life measures, and associated costs should be considered. Markers for HE, such as psychometric testing, can be employed if standardized and validated tools are available in all centers. Individual centers can utilize additional, accessible, validated markers if they choose. Following this direction, Cordoba and coll. aimed to assess the efficacy of albumin on the management of episodic hepatic encephalopathy in a multicenter, prospective, double-blind, controlled trial. Both groups of patients received before the randomization, a standard treatment based on identification and treatment of precipitating factors, of fecal retention or constipation, standardization of e.v. calories and hydration, as well as oral intake and vitamin supplementation. Moreover rifaximin 1200 mg was administered orally or through a nasogastric tube at a dose of 1200 mg/day.[5] Unfortunately, the results were negative because albumin does not improve the resolution of HE during hospitalization, but differences in survival after hospitalization suggest that the development of encephalopathy may identify a subgroup of patients with advanced cirrhosis that may benefit from the administration of albumin. Therefore, suggestions for design clinical trials for episodic HE can be summarized as follows: (a) a detailed standard-of-care algorithm must be agreed upon a priori and must be instituted and monitored diligently throughout the trial, (b) patients should not be enrolled into trials until after the institution of optimal standard-of-care therapy and only if their mental state abnormalities persist, (c) the optimal standard of care should be instituted and maintained, the treatment trial can be initiated earlier if they include a placebo comparator; this would allow an evaluation of the trial treatment as an adjuvant to standard therapy, (d) large-scale, multicenter treatment trials should be evaluated using robust clinical outcomes to define end point(s).

SECONDARY PROPHYLAXIS OF HEPATIC ENCEPHALOPATHY

Therapeutic strategies aimed to prevent the development of HE in cirrhotic patients are considered of strong clinical and social importance. In fact, an effective prophylactic approach is considered able to: (a) avoid a frequent cause of decompensation, (b) avoid the persistent cognitive impairment, as well as a possible brain damage even reducing mortality, (c) reduce the rate of hospitalization/re-hospitalization and (d) consequently reduce the social economic burden, both for the community and for patient and caregiver. Recently, to test the efficacy of a given treatment in the setting of the secondary

Table 1 Published Studies on Episodic Hepatic Encephalopathy Treatment.

First author	Year	Study type	Active treatment (s)	Patients treated	Period of treatment	Objectives	Main results
Simon Talero[5]	2013	Randomized controlled trial	Albumin ev	26 (30)	4 days	Amelioration/ resolution of HE	The percentage of patients without hepatic encephalopathy at day 4 did not differ between both groups (albumin: 57.7% vs. saline: 53.3%; $P > 0.05$). However, significant differences in survival were found at day 90 (albumin: 69.2% vs. saline: 40.0%; $P = 0.02$).
Sharma[6]	2017	Randomized controlled trial	Lactulose + albumin	60 (60)	10 days	Amelioration/ resolution of HE	**Resolution** within 10 days: 75% with lactulose plus albumin 53% in control group ($P = 0.03$).
Sharma[7]	2013	Randomized controlled trial	Lactulose + rifaximin	63 (57)		Amelioration/ resolution of HE	76% of patients compared with 50.8% had complete reversal of HE ($P < 0.004$). There was a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose and placebo (23.8% vs. 49.1%, $P < 0.05$).
Rahimi[8]	2014	Randomized controlled trial	Polyethylene glycol 3350-electrolyte solution (PEG)	25 (25)	Hospitalization	Amelioration of HE	21 vs 13 patients had an improvement of 1 or more in HESA score ($P < .01$).
Sidhu[9]	2017	Randomized controlled trial	L-Ornithine L-aspartate (LOLA)	98 (95)	5	Amelioration/ resolution of HE	The grade of OHE was significantly lower in the LOLA group (compared to placebo) on days 1–4 but not on day 5. The mean time taken for recovery was lower in the LOLA group compared to the placebo group (1.92 ± 0.93 versus 2.50 ± 1.03 days, $P = 0.002$; 95% confidence interval -0.852 to -0.202).
Bajaj[10]	2017	Randomized controlled trial	Fecal Microbiota Transplantation (FMT)	10 (10)	30 days	Safety, cognitive improvement	Eight (80%) standard of care participants had a total of 11 SAEs compared to 2 (20%) FMT participants with SAEs (both FMT unrelated; $P = 0.02$). Five SOC and no FMT participants developed further HE ($P = 0.03$). Cognition improved in the FMT, but not the SOC, group.

BCAA, branched chain amino acids; HE, hepatic encephalopathy.

Table 2 Published Studies on Secondary Prophylaxis of Hepatic Encephalopathy.

First author	Year	Study type	Active treatment (s)	Patients treated	Period of treatment	Objectives	Main results
Riggio[11]	2005	Randomized controlled trial	Lactitol/rifaximin	50 (25)	30 days	Efficacy of a pharmacological prophylaxis on the incidence of post TIPS HE	25 pts developed hepatic encephalopathy (33%, CI 95% = 22–45%). One-month incidence was similar in the three groups ($P = 0.97$). Previous hepatic encephalopathy (relative hazard = 3.79; 1.27–11.31) and basal-TMT-A Z-score > 1.5 (RH = 3.55; 1.24–10.2) were predictors of post-TIPS encephalopathy at multivariate analysis.
Sharma[12]	2009	Randomized controlled trial	Lactulose	61 (64)	Minimum of 6 months after enrollment	Recurrence of HE	Twelve (19.6%) of 61 patients in the HE-L group and 30 (46.8%) of 64 in the HE-NL group ($P = .001$) developed HE.
Les[13]	2011	Randomized controlled trial	BCAA/ maltodextrin	58/58	56 weeks	Recurrence of HE	The actuarial risk of remaining free of HE did not differ between groups (BCAA = 26/47%, MDX = 20/34%, $P = 0.274$).
Agrawal[14]	2012	Randomized controlled trial	Lactulose/ probiotics	80/77 (78)	12 months	Recurrence of HE	77 patients developed HE (L, $n = 18$; P, $n = 22$; and N, $n = 37$). There was a significant difference between L and N ($P = 0.001$) and between P and N ($P = 0.02$) but no difference between the L and P groups ($P = 0.349$).
Dhiman[15]	2014	Randomized controlled trial	Probiotics	66 (64)	24 weeks	Recurrence of HE	23 of 66 patients (34.8%) in the probiotic group and 33 of 64 patients (51.6%) in the placebo group had breakthrough episodes of overt HE.
Bass[16]	2010	Randomized controlled trial	Rifaximin	140 (159)	6 months	Recurrence of HE	A breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group.
Rockey[17]	2014	Randomized controlled trial	Glycerol phenylbutyrate	90 (88)	16 weeks	Recurrence of HE	Glycerol phenylbutyrate significantly reduced the proportion of patients who experienced an HE event (21% versus 36%; $P = 0.02$).

BCAA, branched chain amino acids; HE, hepatic encephalopathy; MDX, maltodextrin.

prophylaxis of HE, an alternative paradigm to the above discussed "therapeutic approach" has emerged: the use of a "preventive approach". Most of papers published on secondary prophylaxis of HE considered the "preventive approach", both in patients who recovered from HE, and for patients with recurrent HE. A large series of studies have been published following this aim and the main results have been reported in Table 2.

It was unanimously agreed that trials for secondary prophylaxis for HE should be randomized and placebo-controlled, moreover, the ideal trial on secondary prophylaxis of HE should have the following characteristics: (a) *eligibility:* out-patients stabilized after one or more episodes of HE and absence of HE at inclusion. Transjugular Intrahepatic Portosystemic Shunt (TIPS) carriers should be excluded or enrolled in different RCTs aimed at this specific setting.[11] Moreover, it could be discussed if these patients may or may not be receiving maintenance treatment with, for example, a non-absorbable disaccharide and/or rifaximin. In fact, although there is evidence for the prophylactic efficacy of combinate therapy with non-absorbable disaccharides and rifaximin, patients who have experienced at least one previous episode of overt HE are not necessarily prescribed medication nor are they necessarily compliant with its use. Therefore, it is important to establish whether patients are assuming a stable prophylactic treatment regimen or not. In this setting, if patients are receiving prophylactic treatment already, then any new agent will be evaluated as adjuvant therapy. If these patients are not receiving prophylactic treatment, then the new medication will be evaluated as a stand-alone treatment. Once a precipitating event has occurred, specific treatments for the prevention of precipitant-induced HE might be hypothesized and treated with a standardized protocol. The sample size could be estimated from the incidence of HE in the population at risk (for example, from the incidence of HE occurring in patients submitted to a TIPS). The inclusion of a "no-treatment" or a "placebo" group is mandatory. (b) *End-points:* the development of one or more episodes of overt HE (Grade II or more) represent the most robust primary end-point, whereas, hospitalization, survival, socio-economic burden analysis and Health Related Quality of Life evaluation should be chosen as secondary end-points. Finally, the preventive approach can also be considered for hospitalized patients, evaluating the possibility of preventing HE induced by a specific precipitating factor, i.e. bleeding, infections. In this setting patients should be free of HE at enrollment and submitted to a standardized treatment for the precipitating factor. Cost/benefit ratio, as well as data on the tolerability and safety, should be considered. Because a prophylactic treatment should be prolonged lifelong, the ideal therapy should be extremely safe and well tolerated.

MANAGEMENT OF MINIMAL/COVERT HEPATIC ENCEPHALOPATHY

Up to 80% of patients with liver cirrhosis can show neuropsychological and neurophysiological abnormalities that are not detectable by the clinical evaluation usually used to identify the presence of HE. Despite its subtle nature, MHE and CHE can have a significant effect on a patient's daily life, being also related to the development of HE, and in special circumstances (e.g., impairment in driving skills or in work performance, association with falls, quality of life, cognitive complaints and socio-economic status of patient and caregiver) the indication to treat the patient may prevail. However, because of the multiple methods used to define MHE and CHE (even based on normative data for studied population), the varying and multiple endpoints, short-term treatment trials, as reported in Table 3, and differing agents used in trials to date, recently published guidelines state that treatment of MHE and CHE is not routinely recommended apart from on a case-by-case basis.[34]

Therefore, the ideal trial should have the following characteristics: (a) *"robust" end points*. A trial on minimal HE for which the modification of psychometric tests or the ammonia levels lowering are considered as its main end-point is meaningless, being clinically irrelevant. An abnormal psychometric test and its possible improvement are both clinically irrelevant findings for the patients for whom the quality of life and the prevention of future overt HE manifestations could be considered important features. In the treatment of minimal HE, then, appropriate end points should be the improvement of quality of life, as well as the driving capacity or the prevention of future overt HE development. The modification of psychometric tests should not be chosen as the main end-point of the study; the tests should instead be used merely as a criterion to include comparable patients. (b) *Patient population*. Patients receiving any treatment for HE or those with previous episodes of HE should be excluded. It was agreed that patients with a history of overt HE or treatment exposure should be excluded from these trials as treatment status has a significant confounding effect on the classification of neuropsychiatric performance. The patients' inclusion should be based on the objective definition of the presence of minimal or covert HE. In single-center or proof-of-concept studies, investigators may use tests for assessing the severity of HE with which they are familiar, provided that normative reference data are available, and the tests have been validated for use in this patient population. Further information is needed on the interchangeability and standardization of tests to assess the severity of HE for use in multicenter trials. As an interim, two or more of the current validated tests should be used and applied

Table 3 Published Studies on Treatment of Minimal Hepatic Encephalopathy.

First author	Year	Study type	MHE/CHE diagnosis	Active treatment (s)	Patients treated	Weeks of treatment	Objectives	Main results
Watanabe[18]	1997	Original, randomized	NCT A, symbol digit test, BDT	Lactulose	22 out of 36	8	Psychometry	MHE had disappeared in 10 (50%) of the 20 treated patients at week 8, but it persisted in 11 (85%) of the untreated 13 patients.
Horsmans[19]	1997	Original, randomized	NCT, RTT, sinusoid test, psychomotor performance tests	Lactulose	7 out of 14	2	Psychometry, ammonia	NCT improved respectively in 5/7 vs. 1/7; RRT in 6/7 vs. 4/7 and ammonia levels in 5/7 vs. 1/7.
Dhiman[20]	2000	Original, randomized	NCT A, NCT B, FCT A, FCT B, PC, BDT	Lactulose	10 out of 18	12	Psychometry	Psychometry improvement in 8/10 vs. 0/8.
Prasad[21]	2007	Original, randomized	NCT A, NCT B, FCT A, FCT B, PC, BDT	Lactulose	45 (25)	12	Psychometry, QoL	Significant improvement in psychometry: $P < 0001$; and QoL: $P < 0.002$. Improvement in HRQoL was related to the improvement in psychometry.
Sharma[22]	2008	Original, randomized controlled trial	NCT A, NCT B or FCT A and FCT B, CEP	Lactulose or probiotic or lactulose + probiotic	92 (31/31)	4	Psychometry, CEP, ammonia	Normalization of all parameters in half of treated patients (17/31, 16/31 and 17/30 respectively).
Mittal[23]	2011	Original, randomized	NCT A, NCT B, FCT A, FCT B, PC, BDT	Lactulose or probiotics or LOLA	160 (40/40/40)	12	Psychometry, ammonia, QoL	MHE reversal in 19/40 vs. 14/40 vs. 14/40 vs. 4/40. Improvement in QoL.
Sharma[24]	2012	Original, randomized	NCT A, NCT B, FCT A, FCT B, digit symbol test, serial dotting test, LTT, CFF	Lactulose	105 (55)	12	Psychometry; OHE development	Improvement of MHE in 21/32 (66%) vs. 9/36 (25%).
Sidhu[25]	2016	Original, randomized	NCT A, FCT A, digit symbol test, BDT, PC	Lactulose vs. rifaximin	112 (55/57)	12	MHE reversal, QoL	MHE reversal in 38/55 and in 42/57; HRQoL was significantly improved in both groups.
Pratap[26]	2015	Original, randomized	NCT A, FCT B (or FCT A, FCT B), CEP	Lactulose or probiotic	73 (40/33)	8	MHE measures, ammonia	Psychometric improvement in 23/33 and in 25/40. Improvement in MHE correlated with reduction of ammonia levels.

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Table 3 (*Continued*)

First author	Year	Study type	MHE/CHE diagnosis	Active treatment (s)	Patients treated	Weeks of treatment	Objectives	Main results
Sidhu[27]	2011	Original, randomized	NCT A, FCT A, digit symbol test, BDT, PC	Rifaximin	94 (49)	8	MHE reversal, QoL	MHE reversal in 37/49 vs. 9/45. Improvement in QoL. Improvement in HRQoL correlated with improvement in psychometry.
Bajaj[28]	2011	Original, randomized	NCT A, NCT B, digit symbol test, BDT, ICT	Rifaximin	42 (21)	8	Psychometry, QoL, driving ability, anti-inflammatory interleukins	Improvement in psychometry, driving performance and QoL.
Liu[29]	2004	Original, randomized	NCT, brainstem evoked potentials	Synbiotics or fiber	55 (20/20)	4	Psychometry, ammonia psychometry	Modulation of the gut flora was associated with a significant reduction in blood ammonia levels and reversal of MHE in 50% of patients. Synbiotic treatment was also associated with a significant reduction in endotoxemia. The Child–Turcotte–Pugh functional class improved in nearly 50% of cases.
Malaguarnera[30]	2007	Original, randomized	TMT A, TMT B, symbol digit test, BD, MMSE, EEG	Probiotic + prebiotic	60 (30)	12	Psychometry, ammonia, EEG	Improvement in psychometry and ammonia; no EEG modifications.
Bajaj[31]	2008	Original, randomized	NCT A, digit symbol test, BDT	Probiotic yogurt	25 (17)	8	MHE reversal, OHE development, QoL, ammonia, cytokines	MHE reversal in 71% vs. 0%; OHE development in 0% vs. 25%; no differences in QoL and cytokine. Levels. Excellent adherence in cirrhotics after probiotic yogurt supplementation with potential for long-term adherence.
Bajaj[32]	2014	Original, randomized	NCT A NCT B, digit symbol test, BDT	Probiotics	30 (14)	8	Psychometry, ammonia, inflammatory markers, QoL	Reduction in endotoxin and TNF-α but not in cytokines. No effects on psychometric performance.

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uniformly across centers. The sample size should be calculated according to one of the clinically relevant end points, such as the quality of life or the incidence of overt HE. The assessment of the efficacy of a given treatment to prevent overt HE in patients with minimal HE requires the need of large multi-center studies, randomized and placebo-controlled, as in general these patients are not routinely treated. A parallel design

Table 3 (*Continued*)

First author	Year	Study type	MHE/CHE diagnosis	Active treatment (s)	Patients treated	Weeks of treatment	Objectives	Main results
Burkard[33]	2013	Original, randomized	PHES battery	Potassium–iron–phosphate–citrate	51 (25)	4	Psychometry	Normalization of psychometry in 72% vs. 26.9%. QoL improvement.

MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; HRQoL, health related quality of life; NCT-A, number connection test-A; NCT-B, number connection test-B; BDT, block design test; SDT, serial dotting test; DST, digit symbol test; LTT, line tracing test; PHES, psychometric hepatic encephalopathy score; ICT, inhibitory control test; CFF, critical flicker frequency; EEG, electroencephalogram, ICT, inhibitory control test; BCAA, branched chain amino acids; SIBO, small intestine bacterial overgrowth; CEP, cognitive evoked potentials.

with a placebo or a no-treatment arm is mandatory. Because minimal HE is a chronic condition, the choice of the drug to be tested should be limited to those that can be administered for a very long period without significant side effects.

CONCLUSIONS

The existing literature on HE medical management still suffers from a lack of standardization, and this heterogeneity makes pooling of data difficult or meaningless. There is still unmet need for "robust" controlled clinical trials on treatment effects on HE, because decisive clinical studies are few, although the number of patients and their resource utilization remains high. Therefore, to date, there is a lack of strong evidences for allocating resources and establishing priority policies regarding management of HE. In conclusion, we must consider that, until now, we have learned more from the "preventive" than from the "therapeutic" approach in the management of HE. In our opinion the "preventive" approach should be strongly considered when a clinical trial in HE is designed. In fact, it appears an appropriate methodology not only, as previously discussed, in the setting of secondary prophylaxis of outpatients free from HE, but also in hospitalized patients to study the possibility of preventing HE induced by a specific precipitating event: i.e. variceal bleeding or infection without HE as well as in the promising setting of the primary prophylaxis of patients with high risk to develop HE.

CONFLICTS OF INTEREST

The authors have none to declare.

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