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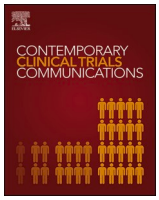

MUC-FIRE: Study protocol for a randomized multicenter open-label controlled trial to show that MUCous FIstula REfeeding reduces the time from enterostomy closure to full enteral feeds

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ABSTRACT

Background: After enterostomy creation, the distal bowel to the ostomy is excluded from the physiologic passage of stool, nutrient uptake, and growth of this intestinal section. Those infants frequently require long-term parenteral nutrition, continued after enterostomy reversal due to the notable diameter discrepancy of the proximal and distal bowel. Previous studies have shown that mucous fistula refeeding (MFR) results in faster weight gain in infants. The aim of the randomized multicenter open-label controlled **MUC**ous **FI**stula **RE**feeding ("**MUC-FIRE**") trial is to demonstrate that MFR between enterostomy creation and reversal reduces the time to full enteral feeds after enterostomy closure compared to controls, resulting in shorter hospital stay and less adverse effects of parenteral nutrition.

Methods/Design: A total of 120 infants will be included in the MUC-FIRE trial. Following enterostomy creation, infants will be randomized to either an intervention or a non-intervention group.

In the intervention group, perioperative MFR between enterostomy creation and reversal will be performed. The control group receives standard care without MFR.

The primary efficacy endpoint of the study is the time to full enteral feeds. Secondary endpoints include first postoperative bowel movement after stoma reversal, postoperative weight gain, and days of postoperative parenteral nutrition. In addition adverse events will be analyzed.

Discussion: The MUC-FIRE trial will be the first prospective randomized trial to investigate the benefits and disadvantages of MFR in infants. The results of the trial are expected to provide an evidence-based foundation for guidelines in pediatric surgical centers worldwide.

Trial registration: The trial has been registered at clinicaltrials.gov (number: NCT03469609, date of registration: March 19, 2018; last update: January 20, 2023, https://clinicaltrials.gov/ct2/show/NCT03469609?term=NCT03469609&draw=2&rank=1).

1. Background

Enterostomies in infants may be created for different reasons, for instance necrotizing enterocolitis or focal intestinal perforation. During the presence of an enterostomy, regular stool passage is interrupted since the distal loop of the bowel (the part following the enterostomy) does not participate in the processing of stool. Therefore, it does not contribute to the absorption of enteral nutrients. As a consequence, these infants need additional parenteral nutrition. Due to the potential negative side effects of parenteral nutrition, all patients should return to enteral nutrition as soon as possible. Consequently, numerous pediatric surgical centers worldwide routinely perform mucous fistula refeeding (MFR) into the bowel distal due to the enterostomy creation. Case reports and retrospective analyses of the benefits of MFR have presented low complication rates and faster postoperative weight gain. However, several centers shy away from this approach due to the lack of high-quality evidence of the benefits of this treatment. The aim of this study is to assess the benefits and disadvantages of MFR in a prospective randomized trial. We hypothesize that MFR between enterostomy creation and reversal reduces the time to full enteral feeds after enterostomy closure compared to a control group without MFR. In addition, the side effects of parenteral nutrition may be reduced and the postoperative hospital stay following ostomy closure shortened.

The current literature on MFR includes a multitude of low-level evidence studies. In a recent retrospective analysis of 28 patients (13 in the MFR group and 15 in the control group), Gause et al. reported a shorter duration of parenteral nutrition and a faster time to full enteral feeds in the MFR group [1]. Moreover, Yabe et al. have shown that MFR has a beneficial effect on low-birth-weight infants, leading to better weight gain and, again, a shorter duration of parenteral nutrition compared to a historical control group [2]. Regarding the safety of MFR, a systematic review of case reports and small case series undertaken by Richardson et al. did not identify a single complication directly associated with the practice [3].

Taken together, studies published so far have shown a faster weight gain in MFR than non-MFR groups [1, [3–6]. These promising results, however, need to be confirmed by a randomized, controlled study, which is the intention of this trial.

2. Methods

SPIRIT reporting guidelines were applied as recommended by Chan et al. [7].

2.1. Design

The primary objective of the MUC-FIRE study is to investigate whether MFR between enterostomy creation and reversal reduces the time to full enteral feeds after enterostomy closure compared to standard care. The primary endpoint of the study is time to full feeds (in hours), defined as time to actual enteral intake of the age-dependent caloric requirements per day (defined as 90 or 120 kcal/kg/24 h) for at least 24 h and a concomitant reduction of parenteral fluids to <20 ml/kg/24 h [8,9].

Based on the infant's birth weight and mother's gestation week at birth, the treating physician decides when full enteral caloric intake is achieved before randomization. Full enteral feeds are defined as follows.

- In premature infants with a birth weight <1000 g or premature infants with a birth weight ≥1000 g and mother's gestation week at birth before 37 + 0, the nutritional aim is 120 kcal/kg/24 h.
- In contrast, in mature neonates and infants (e.g., mother's gestation week at birth at least 37 + 0), the nutritional aim is 90 kcal/kg/24 h.

Concerning the secondary endpoints, any reoperation will be documented. Infants' diapers will be cleaned and changed according to a fixed schedule in order to uniformly document the time to first bowel movement following enterostomy closure (mucous stool is considered a bowel movement). For the assessment of postoperative weight gain (g/d) and calculation of the Z-Score (standard deviation score) [WHO — weight-for-age], all infants will be weighed according to a fixed schedule, namely during morning rounds prior to feeding in an unclothed status. The calculation of days of postoperative total parenteral nutrition (>20 ml/kg/24 h) will start on the day of enterostomy closure and end on the day of full enteral nutrition. The parenteral nutrition will be prepared by the hospital pharmacy on a daily basis in consideration of the simultaneous enteral caloric intake. Laboratory parameters indicating cholestasis (conjugated bilirubin, gamma-glutamyl-transferase, alanine-aminotransferase, aspartate-aminotransferase, hemoglobin) and sodium absorption (sodium in urine) will be measured during

routine blood withdrawal time points at baseline, every two weeks until enterostomy takedown, at three-month follow-up, and in cases of pathological clinical signs (jaundice, acholic stools). Weight gain during the five days after the primary endpoint has been reached will also be documented, as will the duration of central venous lines (days) and number of central line infections, the estimated ratio of the diameter of the two bowel loops which are anastomosed, and the length of the hospital stay (days). To measure the time taken to achieve a predefined volume of oral intake (defined as 150 ml/kg/24 h for premature infants and 120 ml/kg/24 h for born-mature as well as corrected-mature infants) for at least 24 h, feeds will be advanced according to the predefined nutritional protocol.

2.2. Inclusion/exclusion criteria

A total of 120 infants younger than 366 days of age will be included. After enterostomy creation, infants will be randomized to two different postoperative protocols while awaiting enterostomy closure. They will only be enrolled if they meet the inclusion/exclusion criteria outlined in Table 1. The application of prokinetic drugs will not be allowed at any point during the study. Reoperation (e.g., relaparotomy) prior to randomization is not an exclusion criterion.

3. Methods against bias

Patients will be randomized to the intervention and non-intervention groups in a 1:1 ratio. The randomization will be stratified by study center, height of stomata (jejunostomy/proximal ileostomy or terminal ileostomy) [3,10], weight (<1000 g or ≥ 1000 g), and mother's gestation week at birth (before 37 + 0 or at least 37 + 0) [11,12], as these are important prognostic factors for the primary endpoint.

Due to the nature of the intervention blinding of the study is not possible. To ensure admission before allocation, the randomization is performed centrally by the Department of Biostatistics of the Hannover Medical School. Randomization will take place after enterostomy creation. This should reduce the number of missing values due to patient exclusion after surgery (e.g., due to any unforeseen need for resection of the ileocecal valve). Furthermore, the treating physician can then determine the full feed kcal goal on the basis of the stratification.

3.1. Study interventions and assessments

The study design is depicted in Fig. 1. All patients will receive standard care with standardized enterostomy creation and closure and will be treated according to a predefined feeding protocol. In the intervention group, perioperative MFR between enterostomy creation and enterostomy closure will be performed. In the control group, no perioperative MFR between enterostomy creation and enterostomy closure will be executed. The interventional period (MFR vs control) will last at least 21 days and until the patient's weight exceeds 2000 g. Patients will be followed up at three and six months postoperatively, following enterostomy closure, and at 12 months, if recruited early enough for such follow-up to take place within the overall study duration.

Specifically, patients will be seen and evaluated according to the study calendar given in Table 2.

Death, bowel perforation due to catheterization of the distal bowel loop during refeeding or withdrawal of written consent may lead to discontinuation. Patients in whom the treatment is discontinued for any reasons will remain in the study for the evaluation of efficacy and safety endpoints.

Current data suggest a low complication rate in mucous fistula refeeding. Lau et al. [13], with the up to date largest study population (n = 77), documented no major complications. However, a retrospective analysis by Haddock et al. [14] with an inhomogeneous population reported on the risk of bowel perforation, bleeding and death associated with mucous fistula refeeding. Therefore, these criteria are adverse events during the study period. Postoperative complications are classified according to the Clavien-Dindo classification and based on the assessment of complications on a daily basis.

All study data is collected by the investigator and/or other study personnel. A validated clinical trial data base (electronic case report form) is provided in which the data are entered. Data will be collected, handled, stored and analyzed in accordance with national regulations.

3.2. Statistical methods

The primary analysis will be performed on the intention-to-treat population; that is, all randomized patients will be analyzed in the treatment group to which they are initially allocated. The treatment effect will be assessed by the hazard ratio for reaching full enteral feeds estimated with a Cox regression adjusted for center, weight and mother's gestation week at birth (<1000 g and before 37 + 0 vs. ≥ 1000 g and before 37 + 0 vs. ≥ 1000 g and at least 37 + 0), height of stomata (jejunostomy/proximal ileostomy vs. terminal ileostomy), and treatment, and the respective 95% confidence interval. It will be concluded that the refeeding procedure is superior if the lower bound of the two-sided 95% confidence interval for the hazard ratio (refeeding vs no refeeding) is greater than 1. If information is missing concerning time to full feeds, patients will be censored at the last known status before full feeds. A per protocol analysis will be conducted as a sensitivity analysis in all patients who have no substantial protocol deviations. Consistency

Table 1
Selection criteria.

Inclusion criteria	
1	Only infants younger than 366 days of age with status post-ileostomy or jejunostomy creation (double-loop enterostomies and split enterostomies (with mucous fistula)) will be included in the study to create a homogenous cohort of patients with similar diseases (e.g., necrotizing enterocolitis [NEC], focal intestinal perforation [FIP]). Also, infants of this age group are unique in several respects, such as the response to parenteral nutrition and its hepatic toxicity, resulting in neonatal cholestasis. The ostomy localization is restricted to the jejunum and ileum. Therefore, the cohort of patients shows a similar bowel length for fluid, vitamin, and electrolyte absorption.
2	All patients with meconium ileus are included in the study. If later (required) diagnostics verify cystic fibrosis, the diagnostics as well as the diagnosis need to be documented in the eCRF, and subgroups will be established in further analysis.
3	Signed written informed consent will be obtained from parents/legal guardians indicating their willingness to comply with the treatment and follow-up procedures for their child.
Exclusion criteria	
1	The resection of the ileocecal valve is an exclusion criterion because of its association with extensive bowel resection and therefore prolonged parenteral nutrition [15].
2	Colostomy.
3	Patients with small bowel atresia are excluded because of prenatally underdeveloped bowel distal to the atresia.
4	Multiple ostomies (more than just an enterostomy and a mucous fistula).
5	Patients with chromosomal abnormalities (if known at the time of randomization) are excluded because of potential malabsorption and malnutrition due to an underlying syndrome.
6	Hirschsprung disease secondary exclusion.
7	Participation in another drug-intervention study.
8	Intestinal perforation due to congenital heart defects with impairing hemodynamic.

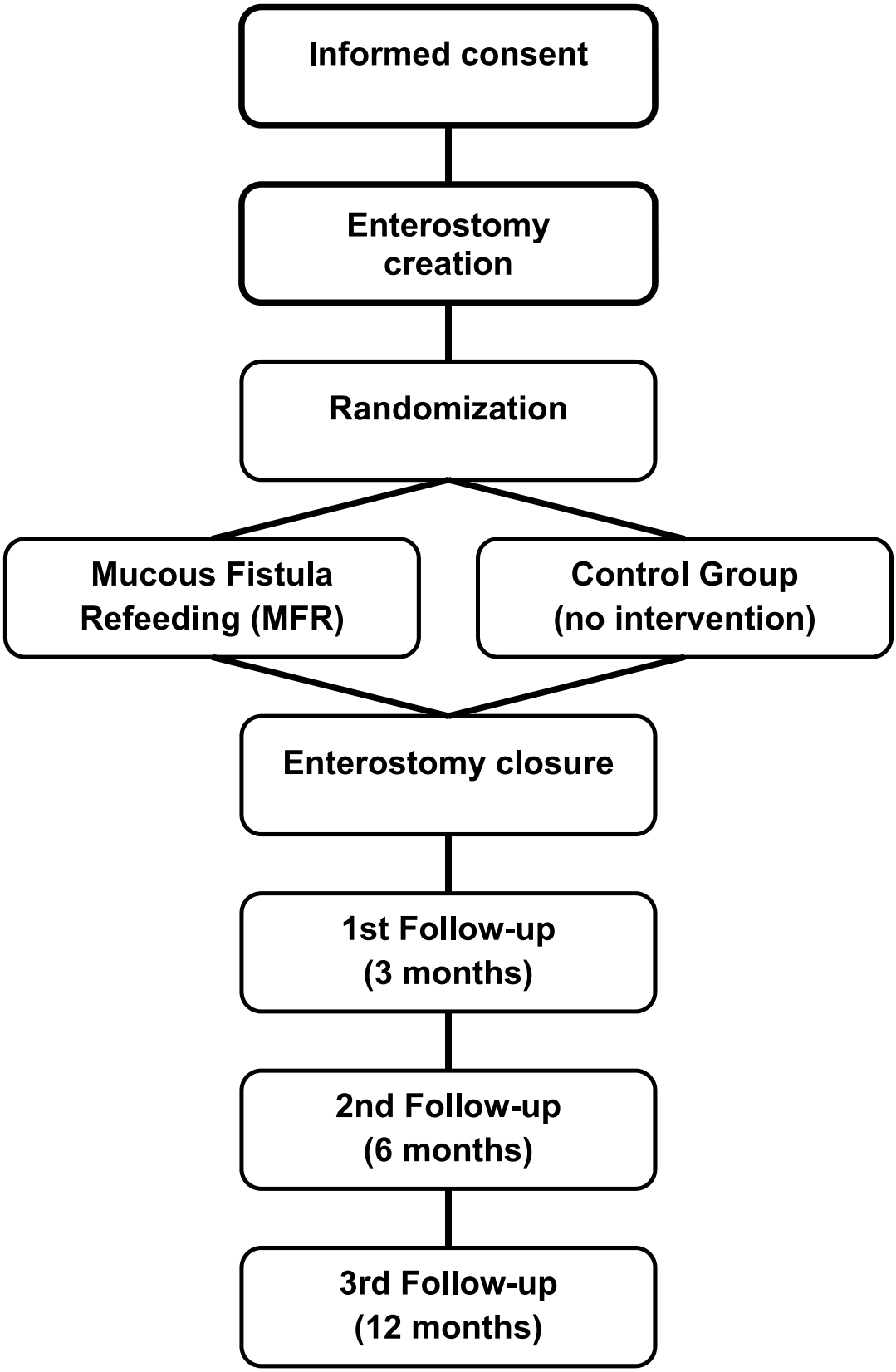

Fig. 1. Flowchart of the MUC-FIRE study.

Table 2
Study calendar.

	Enterostomy Creation	Screening	Pre-Treatment Phase	Treatment Phase (Refeeding or Control)	End of Treatment[d] (Enterostomy Closure)	Post-Treatment Phase	FU 1 3 months 3 months after entero-stomy closure	FU 2 6 months 6 months after entero-stomy closure	(FU 3 12 months)[a] 12 months after entero-stomy closure
			at least 1 week up to 6 weeks	at least 3 weeks up to 8 weeks	approx. 6 weeks after enterostomy creation	at least 2 weeks up to 8 weeks			
Data Assessment			daily	daily		daily	Outpatient clinic	Outpatient clinic	Outpatient clinic
Randomization			x						
Demographic data		x							
Informed consent		x							
In-/Exclusion criteria		x							
Operation protocol	x				x				
Body weight		x	x	x		x[b]	x	x	x
Laboratory			x[c]	x[c]		x[c]			
Refeeding protocol				x					
Nutrition protocol				x		x			
Medical history		x							
Adverse events			x	x	x	x	x	x	x
Time to first bowel movement after enterostomy closure [hours]						x			

[a] Only applicable for patients recruited early enough to complete the 12-month follow-up within the 48 months of overall study duration.
[b] Weight is measured during the five days after the primary endpoint is reached.
[c] Every two weeks starting at randomization and in cases of pathologic clinical signs (jaundice, acholic stools); laboratory analysis: During routine blood withdrawal, laboratory analysis for the blood parameters of gamma-glutamyl-transferase, alanine-aminotransferase, aspartate-aminotransferase, hemoglobin, and conjugated bilirubin will be performed every two weeks starting from randomization until enterostomy closure. Additionally, in urine, sodium concentration is determined in the same time interval. No additional sample volume is necessary for this study.
[d] The day of enterostomy closure (day of operation) is the last day within the treatment phase; the day after operation is set as the first day of the post-treatment phase.

between the findings in the intention-to-treat population and the per protocol population will be examined, as this is an important prerequisite for a successful interpretation of the study.

Furthermore, time to full feeds after randomization (in days) will be analyzed in line with the Cox regression model for the primary endpoint.

All secondary analyses will be exploratory and will be conducted on the intention-to-treat population.

3.3. Sample size and power consideration

The literature on MFR is scarce, and information on the primary endpoint "time to full enteral feeds" is limited [3]. In a retrospective analysis of 24 patients published in 2016 [1], 13 children underwent MFR while the remaining 11 did not. The median time from enterostomy takedown to enteral feeds was seven days in the control group and four days in the refeeding group. The data presented for the control group are in line with the retrospective data of 42 patients treated at the Hannover Medical School between 2005 and 2015 who meet the inclusion criteria. The latter did not receive refeeding of stool and had a median time to full enteral feeds of seven days. According to Gause et al. [1], a survival analysis is appropriate. Their publication reported median times corresponding to a hazard ratio of 1.751 for time to enteral feeds (4 days vs 7 days), 2.331 for parenteral nutrition discontinuation (6 days vs 14 days), and 2.667 for goal feeds (7.5 days vs 20 days). Because time to enteral feeds in their publication is in line with our retrospective data of time to full feeds, a hazard ratio of 1.751 is assumed for the treatment effect. In order to show a treatment effect with a power of 80% and a two-sided type I error probability of 5% with a log rank test, a total of 100 events (full enteral feeds) is required, if the hazard ratio for the treatment effect is 1.751. Since patients will be in neonatal intensive care, every patient is expected to reach full enteral feeds. Nonetheless, to account for possible deaths and patients that are not able to reach full enteral feeds or abide by the study protocol, the sample size was increased by 20 patients, resulting in a total of 120 patients. Sample size was estimated in nQuery Advisor 7.

4. Discussion

As suggested by Gause et al. [1], a multicenter study of MFR is warranted in order to address the limitations of the retrospective studies carried out to date. The results of this randomized controlled study may strongly influence the perioperative care of neonates within the pediatric surgical community worldwide. If our hypothesis is confirmed, the postoperative hospital stays of infants undergoing small bowel ostomy closure will be shortened. Additional benefits of MFR could include a shorter duration and, therefore, fewer side effects of parenteral nutrition. Moreover, an economic benefit through a reduction in costs for parenteral nutrition and shorter hospital stays may be achieved.

The MUC-FIRE trial will be the first prospective randomized trial to clarify the benefits and disadvantages of MFR between enterostomy creation and reversal. Therefore, the results of the trial are expected to lay an evidence-based foundation for guidelines in numerous pediatric surgical centers worldwide.

5. Trial status

To date, three protocol amendments have been submitted during the recruitment period of the study, all of which were approved by the local ethics committees. In the first amendment, dated November 2018, we adapted the postoperative nutrition protocol following enterostomy closure. The exclusion criteria were updated in the second amendment (June 2019). In this context, we also modified the patient's informed consent form for easier data collection in the event that patients were transferred to other hospitals. In the third amendment (November

2020), the nutritional aim was specified with respect to birth weight as well as gestation week at birth, and the sample size was adapted. The current version of the study protocol is V3.0, which came into force on November 19, 2020. Currently the approval of the fourth amendment by all local ethics committees is pending. Within this, the documentation of AESIs (Adverse Events of Special Interest) and the evaluation of the stool transfer protocol and the respective statistical analyses are specified, several local ethics committees already approved the study protocol version 4.0.

Recruitment started on June 15th, 2018, and the first patient was randomized on June 19th, 2018. A total of 60 patients have been recruited (status as of December 31, 2022) in 16 German and Austrian study sites.

Currently 36 patients have finished the study, from which 9 patients terminate the study prematurely (status as of December 31, 2022). The duration of the study was extended to safely reach the desired recruitment rate. At present, one third of the anticipated patient numbers has been reached. Therefore, additional centers have been enrolled to reach the goal of 120 patients. Therefore, additional sites in the Netherlands have been enrolled to reach the goal of 120 patients. We estimate that recruitment will we completed by early 2025.

Current information on study sites and protocol amendments is presented at the website of the study: www.muc-fire.de.

Ethics approval and consent to participate

The study is conducted in accordance with the principles of ICH-GCP (as far as possible for this kind of study) and the Declaration of Helsinki.

The study protocol and patient consent form were approved by all local ethics committees before initiation at the study sites. Likewise, all amendments to the protocol were approved by the local ethics committee.

Written, informed consent is obtained from parents and legal guardians. Parents will be informed that monitors and potential auditors will be granted direct access to the study patient's source medical records without violating patient confidentiality.

The trial is covered by a participant insurance in case the trial site (clinic) does not cover the study by its liability insurance.

An independent Data Safety Monitoring Committee has been established to detect possible harm and assure a continuous risk/benefit assessment. The Data Safety Monitoring Committee consists of three independent pediatric surgical experts who assess the progress of the study, safety data, and, if needed, critical efficacy endpoints. The Data Safety Monitoring Committee meets on a yearly basis and, to date, has consistently recommended that the trial be continued.

Consent for publication

Results of the study will be published by the study group.

Availability of data and materials

After completion of the trial, data analyses will be performed by the Institute of Biostatistics at Hannover Medical School. The results and study protocol will be published, including all data concerning how to perform MFR.

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Authors' contributions

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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