Mucositis reduction with probiotics in children with cancer: a randomised-controlled feasibility study

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ABSTRACT

Background A recent systematic review and meta-analysis identified a paucity of randomised-controlled trials (RCTs) investigating the use of probiotics to reduce or prevent mucositis and infection in children with cancer.

Objective This study evaluated the feasibility of undertaking an RCT and investigated the efficacy of probiotics for reducing or preventing mucositis and infection in children with cancers.

Setting The Paediatric Oncology and Haematology department at Leeds Teaching Hospital, UK.

Patients Children aged 1 year or older, receiving chemotherapies likely to cause mucositis.

Interventions Participants were randomised to receive the probiotic or placebo on day 1–14 of a chemotherapy cycle. Participants were also required to complete a patient diary for 21 days.

Main outcome measures To assess whether it is feasible to recruit children diagnosed with cancer who are at risk of developing mucositis to an adequately powered RCT.

Results Between May and November 2019, 34 out of 39 eligible participants were approached. Ten patients were recruited (4 probiotic and 6 placebo) of which 2 participants withdrew. Seven participants partially completed the diary but only two participants completed 80% or more. Eligible participants appeared to prefer giving informal verbal feedback when in direct contact with research and healthcare professionals.

Conclusion This study demonstrated that recruitment needs to be improved prior to undertaking an adequately powered RCT.

Trial registration number NCT03785938.

What is already known on this topic?

- Currently, there are no widely used preventative interventions for mucositis.
- Studies have suggested probiotics may reduce symptoms of mucositis and infection in people with cancer.
- A systematic review demonstrated that there is insufficient evidence to conclude probiotics could reduce symptoms of mucositis and infection in children with cancer

What this study adds?

- The proposed approach was not feasible to undertake an adequately powered randomised-controlled trial to investigate the efficacy of probiotics.
- Barriers identified which could impact a future study include recruitment and adherence to the data capture.
- Further research is required to identify and develop evidence-based targeted interventions to improve recruitment in paediatric oncology supportive care studies.

INTRODUCTION

Chemotherapy and radiotherapy-induced diarrhoea is a common adverse event and associated with mucositis.[1] Changes to the gut flora may impact the gut defence barrier, immune function and absorption of vital nutrients.[2] It is estimated that 20%–45% of all chemotherapy patients experience severe diarrhoea. Radiotherapy or chemotherapy-induced diarrhoea may interrupt or even stop treatment, impair the quality of life and prolong hospital stay of patients with cancer, also potentially increasing health economic burdens.[3]

A systematic review[4] has identified a number of trials (N=2982 participants) examining the efficacy of probiotics to prevent mucositis in people with cancer. Data suggests probiotics may reduce the incidence of diarrhoea, but there were insufficient studies to assess the true effect of probiotics, particularly in children.

Symprove (Symprove, Farnham, Surrey, UK) is a liquid probiotic food supplement that contains four strains of bacteria with a total of 109 colony forming units: (*Lactobacillus rhamnosus* NCIMB 30174, *Lactobacillus plantarum* NCIMB 30173, *Lactobacillus acidophilus* NCIMB 30175 and *Enterococcus faecium* NCIMB 30176) in a water-based suspension of barley extract.[5]

The use of Symprove in randomised-controlled trials (RCTs) has been investigated in conditions affecting the gastrointestinal system.[6 7] The use of Symprove has been approved for use in children, but there have been no paediatric clinical trials investigating the use of Symprove. Liquid probiotic has been reported as safe in previous studies undertaken, and there have been no reports of serious adverse events attributed to Symprove.[5 8]

We undertook a feasibility study (the MaCROS study) to investigate whether it is possible to undertake an RCT investigating the use of probiotics compared with placebo for preventing and reducing mucositis and infection in children diagnosed with cancer. Data from this study will be used to inform

and assess the feasibility of a pragmatic randomised-controlled trial.

AIM

The aim of the study was to evaluate the feasibility of an RCT to investigate the efficacy of liquid probiotics to prevent or reduce mucositis and infection in children diagnosed with cancer who are undergoing treatment with regimes likely to cause mucositis.

METHODS

This protocol is guided by the CONSORT 2010 statement for feasibility and pilot studies.[9] It was registered on the Clinical-Trials.gov registry and approved by national and local research governance systems.

OBJECTIVE

The primary objective of this study was to determine: whether it is feasible to recruit children diagnosed with cancer who are at risk of developing mucositis. This will be summarised using an evaluation traffic light system (online supplemental file 1).

Outcomes

Primary outcome measures included the following:

1. The completion rates of participants taking the liquid probiotic/placebo for 2 weeks
2. The completion rate of the symptom diary (paper/web-app) by participants/parental to record the symptoms of mucositis from the start of chemotherapy for 21 days
3. Evaluation of the research protocol
4. Barriers to compliance with the protocol

Secondary outcome measures included:

5. Evaluation of intended outcomes to be assessed of an RCT including the incidence of diarrhoea, nausea and vomiting and evaluation of inpatient admissions.

Trial design

Single-centre double-blind randomised-controlled feasibility study.

Study setting

The paediatric haematology and oncology department at Leeds Teaching Hospital Trust, Leeds, UK (LTHT) between the 23 May 2019 and 21 November 2019.

Eligibility criteria for participants

Eligible patients were children aged 1–18 years receiving chemotherapy on paediatric cancer protocols that reported mucositis as an expected adverse event. Participants receiving myeloablative therapy were also eligible.

Exclusion criteria

- Patients who have already started the course of chemotherapy
- Patients receiving radiotherapy or surgery alone
- Patients who have taken probiotics supplements the month prior to starting their next course of chemotherapy
- Patients with confirmed immunodeficiency prior to their diagnosis of cancer.

Consent

Consent on behalf of children participating under the age of 16 was taken from their parents/responsible persons and those 16–18 years old supplied their own consent.

Interventions

Participants were required to commence the blinded liquid probiotic or placebo enterally. The intervention was taken from the first day of their chemotherapy/pre-stem cell transplant chemotherapy conditioning and continued daily for 14 days.

The dose prescribed varied according to age groups:

- Under the age of 4: 20 mL once a day.
- 4–8 years of age: 0.5 mL/kg once a day
- Above the age of 8: 1 mL/kg once a day

Randomisation, allocation concealment and blinding

Simple randomisation was undertaken. Healthcare professionals (apart from the trials pharmacist) and participants were blinded to the randomisation, allocation and intervention delivered.

Patient diary

The diary included questions about mucositis using a modified Children's International Mucositis Evaluation Scale (ChIMES).[10] This included questions about gastrointestinal symptoms (eg, stool frequency) as ChIMES is designed to be used for oral mucositis and there is no validated evaluation scale to assess gastrointestinal mucositis. There was the option to complete a paper diary or a web-based app.

Investigation of in-patient episodes

Clinical records were reviewed to investigate in-patient admissions. This included recording any febrile episodes, infections and any supportive care interventions that were required (eg, need for total parental nutrition).

Statistical analysis

Statistical power was not calculated for this feasibility study. We targeted recruiting between 20 and 40 participants as the initial objective. Secondary outcome data on 'full RCT outcomes' are presented using descriptive statistics.

Evaluation of the feasibility for undertaking an RCT

The feasibility of undertaking an RCT was evaluated using both quantitative and qualitative methods relating to timing of the return of patient diaries, department referral rate, recruitment rate and numbers lost to follow-up. Acceptability and tolerability of the treatment intervention were assessed through completion rate of the probiotic/placebo course, use of the patient diaries and planned to be explored through interview with the patients/parents. The feasibility criteria are summarised in online supplemental file 1.

Evaluation of participant/parent experience

Participants and parents were invited to discuss their experiences of participation in the trials. It was intended to ask questions regarding recruitment, the process of gaining consent and randomisation, and experiences of adherence of the probiotic/placebo and patient diary.

RESULTS

Primary outcomes

Between May and November 2019, there were 39 patients who met the eligibility criteria, of whom 37 were screened, 34 participants were approached and 10 were randomised (figure 1).

Five patients were eligible to participate, but were not approached because:

- We were unable to communicate with the parents without an interpreter.

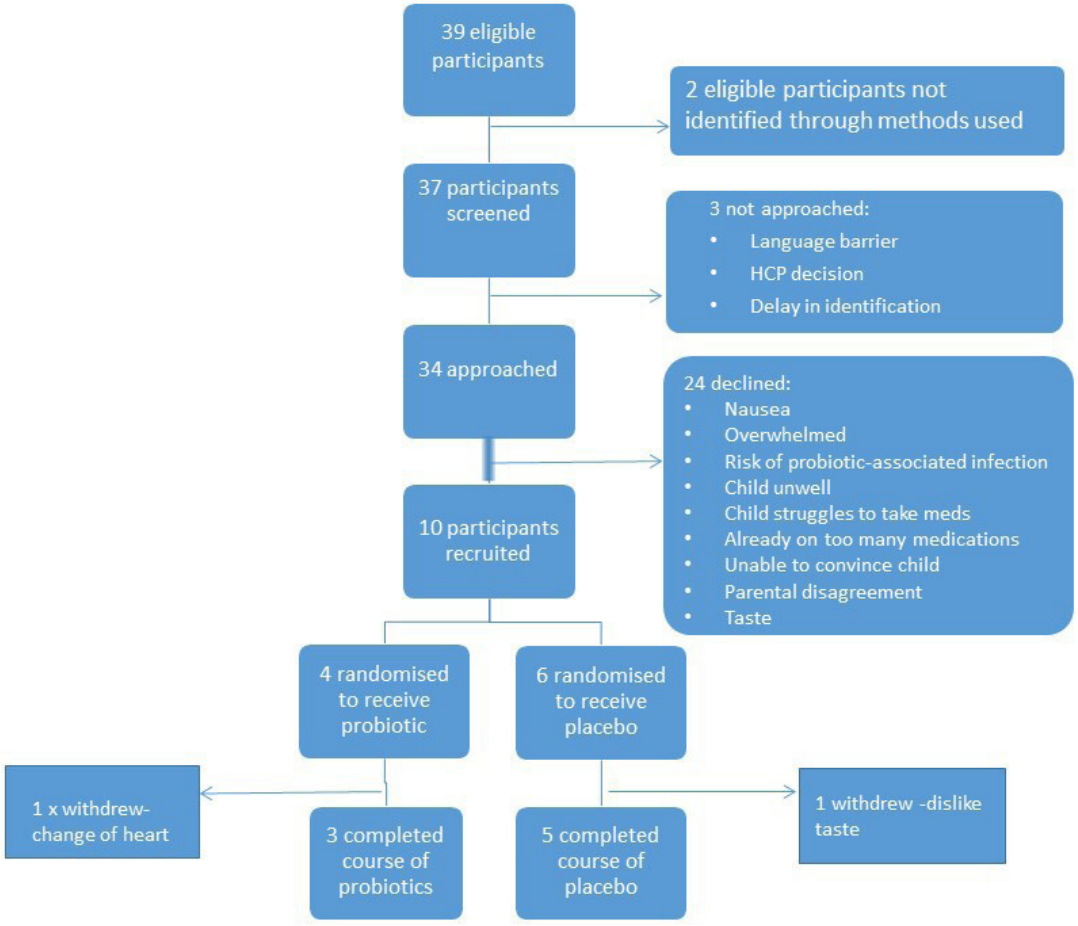

Figure 1 Consort diagram for the MaCROS study. HCP, health care professional.

► Eligibility discovered late and commenced chemotherapy before they could be approached.

Twenty-four out of 34 approached participants declined to participate. Reasons for deciding to decline, captured by verbal feedback, are summarised in table 1.

Ten eligible patients agreed to participate in the MaCROS study. Of these, 9 were diagnosed with solid tumours, and 1 was diagnosed with a malignant haematological condition. Two patients diagnosed with neuroblastoma were undergoing high-dose chemotherapy with autologous stem cell rescue. Details of the anonymised demographic information are summarised in table 2.

Two participants aged 12 (placebo) and 15 years (probiotic), respectively, withdrew participation after 1 day. Both reported a dislike for the taste of probiotic/placebo and stated they were unable to continue with the full 14-day course.

Of the 10 participants who were recruited to the MaCROS study, 8 adhered to the full course of probiotic/placebo. A further teenage participant disliked the taste and stated it made them feel nauseous but that they chose to complete the course because they understood the importance of participating in research trials to help future children diagnosed with cancer.

The volume of probiotic was mentioned by several parents who completed participation in the feedback given in the diaries. Some parents stated they struggled to deliver the volume required and that they felt using smaller volume and higher concentration would be easier to manage. One parent felt that distributing the volume throughout the day (eg, two times a day instead of one time a day) would be easier.

Seven participants opted to use the paper diary, and three opted to use the web-app (table 2). Three parents who chose to use the paper diary stated they would prefer to use the app but found the WiFi connection in the inpatient area unreliable.

Seven participants submitted diaries. Four submitted partially completed data paper diaries and three submitted partially completed data on the web-app. Three out of the seven

Table 1 Verbal reasons why participation in the study was declined

Reasons for declining after being approached once	Reasons for declining after being approached two or more times
'Worried about experiencing nausea'	Parents were unable to convince child to participate.
'Too much to deal with right now'	Parent felt that their child already had too many medications.
Worried about risk of probiotic-associated infection.	Initially overwhelmed with the new diagnosis. Asked researcher to return later and then declined.
Struggling to persuade the child to take any oral medicines.	Child too unwell.
Child dislikes the taste of milk/yoghurts.	Mother wanting to participate, father not happy to.
Does not want to take 'gamble' of potentially receiving the placebo.	Heard from another parent that the probiotic/placebo does not taste nice.

Table 2 Summary of demographics of patients included in the MaCROS study

Patient number	Sex (male=M/female=F)	Diagnosis	Cycle/day	Consent	Paper/diary	Stopped further participation in MaCROS study
1	F	Ewing's sarcoma	Last cycle	10/06/2019	Paper	Stopped participation
2	F	Osteosarcoma	Cycle 6	02/07/2019	Web app	
3	F	Undifferentiated sarcoma	Cycle 2	02/07/2019	Not completed	
4	F	HR NBL HD chemotherapy and stem cell rescue	Day 0	04/07/2019	Not completed	
5	M	HR NBL	Day 20	04/07/2019	Paper	
6	F	HR NBL- HD chemotherapy and stem cell rescue	Day 0	04/07/2019	Web app	
7	M	AML	Cycle 1	04/09/2019	Web app	
8	M	NHL	Cycle 2	05/09/2019	Paper	
9	M	Metastatic-relapsed osteosarcoma	Cycle 1	09/07/2019	Paper	Stopped participation
10	M	Osteosarcoma	Cycle 3	19/11/2019	Paper	

AML, acute myeloid leukaemia; HD, high dose; HR NBL, high-risk neuroblastoma; NHL, non-Hodgkins lymphoma.

participants who submitted data completed at least 80% of data for 14 days (duration of the course of probiotic/placebo). Only two participants completed 80% of the data required for the 21 days. No participant completed 100% of the information requested.

In summary, it was felt that this study may be feasible, with modifications (see online supplemental file 1)

Identified barriers

Incomplete data was a significant issue in analysis of outcomes. Specific questions were left blank by patients even when responses were given for that day. Because of this, a complete-case analysis was undertaken with no attempts to impute missing data, and results should be interpreted cautiously.

Table 3 summarises results from data captured from the patient diaries. Seven out of 10 patients submitted partially completed diaries. The percentage of days filled (excluding those who did not return diaries) for the duration of the 21 days ranged from 4.8% to 90.5%. The median percentage of total diary completed was 46.9% (approximately 10 days of data). The participants were more likely to fill in the diary when taking the probiotic/placebo; the mean percentage of diary completed for the first 14 days was 64.2% (range 7.14%–100%), and 5/7 (71%) participants who returned diaries completed more than 75% of data during the 14-day course.

Secondary outcomes

Nine out of 10 participants were admitted to the ward for chemotherapy. Two of the three participants who were febrile but not neutropenic did not receive antibiotics. The participant who did was undergoing a high-risk procedure (autologous transplant). All three participants who developed febrile neutropenia received antibiotics. One participant who was not febrile received antibiotics following the recommendation from the microbiology team. Findings are summarised in table 4.

No participants were admitted to intensive care. Expected serious adverse events which occurred included a participant developing neutropenic enterocolitis, vaso-occlusive disease, post-transplant ileus and a *Clostridium difficile* infection. All 10 participants' supportive care interventions are summarised in table 4.

Four participants recorded feedback in the diaries, which were submitted. Some feedback related to adherence with the probiotic/placebo and use of the patients diary (see table 5).

DISCUSSION

The MaCROS study demonstrated that modifications to recruitment and data collection using patient diaries are required prior to undertake an adequately powered RCT.

Table 3 Findings from patient diary

Patient number	Probiotic/ placebo	Percentage of diary completed (21 days in total)	Percentage of diary completed during the 14-day course probiotic/placebo	Median loose stool (range) per day	Median stool type per day (range)	Median score for nausea per day (range)	Median frequency of vomiting per day (range)	Median pain per day (range)	Median difficulty drinking (range)	Median difficulty swallowing (range)
1*	Probiotic	4.8	7.14	0	1	3	0	3	1	1
2	Placebo	52.3	78.5	1 (0–5)	3 (1–5)	3 (1–5)	0 (0–0)	4 (0–5)	2 (1–4)	2 (1–4)
3	Probiotic	0	0	NA	NA	NA	NA	NA	NA	NA
4	Placebo	0	0	NA	NA	NA	NA	NA	NA	NA
5	Probiotic	61.9	92.9	1 (0–3)	6 (4–7)	Not documented	1 (0–2)	1 (1–2)	1 (0–3)	1 (0–3)
6	Probiotic	90.5	100	3 (0–10)	5 (4–7)	2 (1–3)	1 (0–3)	1 (0–3)	0 (0–2)	0 (0–2)
7	Placebo	4.8	7.14	7	4	1	Not documented	1	1	1
8	Placebo	61.9	92.9	3 (0–7)	6 (6–7)	2 (1–3)	1 (0–3)	1 (1–3)	2 (1–4)	3 (0–4)
9*	Placebo	0	0	NA	NA	NA	NA	NA	NA	NA
10	Placebo	52.3	78.5	1 (0–3)	4 (3–7)	2 (2–4)	1 (0–3)	1 (1–3)	NA	2 (1–4)

* Withdrawn

Table 4 Data taken from clinical and electronic records of those recruited to the MaCROS study

Patient no	Age	Probiotic/ placebo	Diagnosis	Inpatient (routine chemotherapy)	Was routine admission for chemotherapy extended?	Febrile	Febrile neutropenic?	Positive blood culture?	Organism
1*	12 years	Probiotic	Ewing's sarcoma	Yes	No	No	No	N/A	
2	13 years	Placebo	Osteosarcoma	Yes	Yes	Yes	No	No	
3	7 years	Probiotic	Undifferentiated sarcoma	Yes	No	No	No	NA	
4	12 years	Placebo	HR NBL- HD chemo and stem cell rescue	Yes	NA†	Yes	Yes	No	
5	1 year, 7 months	Probiotic	HR NBL	Yes	No	No	No	Yes	*Streptococcus mitis/oralis*, *Streptococcus vestibularis*, *Streptococcus parasangui*
6	1 year, 7 months	Probiotic	HR NBL HD chemo and stem cell rescue	Yes	NA†	Yes	No	Yes	Gram negative bacilli
7	14 years	Placebo	AML	Yes	NA†	Yes	Yes	No	
8	3 years	Placebo	NHL	Yes	Yes	Yes	Yes	No	
9*	15 years	Placebo	Metastatic-relapsed osteosarcoma	No	No	No	No	NA	
10	8 years	Placebo	Osteosarcoma	Yes	Yes	Yes	No	No	

*Withdrawn.
†Inpatient until count recovered.
AML, acute myeloid leukaemia; HD, high dose; HR NBL, high-risk neuroblastoma; NHL, non-Hodgkins lymphoma.

To improve the recruitment rate to the study (10/35), a pragmatic trial could have a larger group of potential recruiters; only two clinicians were available for this task. Further understanding of the perception of supportive care studies by families may improve rates as well. In the MaCROS study, some healthcare professionals felt there were too many competing demands to consider when contacting a parent/guardian of individual eligible patients and chose not to approach them. It was noted at times that healthcare professionals felt it was not appropriate to approach a family because the family were still coming to terms with a relapse or new diagnosis, but conversely, relapsed and new patients were recruited into the study.

'Research fatigue' was also noted. A number of families expressed a desire not to be approached about the participation of the MaCROS study because they had already been contacted about other research trials and felt 'saturated' from the requests.

Recruitment may have also been impacted by established relationships between patients, families and healthcare professionals. Studies have previously reported how families may be more likely to participate in a trial when approached by a professional with whom they have already established rapport and confidence.[11–13] A strategy to overcome this in a future study include having the patients' named consultant approach the family about participation.[11]

As large-scale recruitment appears to be a significant barrier in many paediatric RCTs, it is clear further research is needed to develop and validate interventions that address this issue.[14]

Diary completion was the second area requiring modification. The burden of daily symptom recording is recognised to be high, and it was noted better information was received in the first 14 days when the placebo was still being taken compared with the last 7 days. Web-apps were, in this small study, better completed than paper diaries and always returned, but less commonly selected (3/10). Some parents who expressed an interest in using the web-app stated the poor WiFi connection in hospital dissuaded them from using it. Solutions to these barriers and

Table 5 Feedback delivered in diaries (both paper and web-app)

Probiotic/placebo	Feedback
Probiotic	'X found it difficult to drink the sample as the smell is quite off-putting, we did get it down but I'm sure if it had a better smell the task would be easier' 'From an adults' point of view, all the chemo and extra meds the kids have to then take another product that has such a bad smell and taste is hard for them'
Probiotic	'Y stopped eating-not sure if its due to feeling sick or not eating because of mucositis' 'I don't think she had the trial medicine today as she had to stop any oral intake (bowels slowing down)' 'Trial med not given as no oral/NG tube allowed'
Placebo	'Dose taken an hour later as Z had yoghurt with food at the time dose was due' 'Being a baby, it is difficult to say how sickly Z feels so it's all a best guess' 'Would be helpful to have reminders'
Placebo	'20 mL is too much to put down an nasgastric tube in a small child' 'Not eaten for a while' 'Again 20 mL is too much volume, it makes him retch as you put it down'

NG, nasogastric.

how families can be further supported need to be considered for a future RCT.

Although officially a 'successful' feasibility goal, ingestion of the intervention was challenging. Two participants dropped out of the study after the first dose because they did not like the taste of the liquid (one from each arm), and the volume of medicine was commented on by others. Modifications to the frequency, dose and taste of the probiotic/ placebo may, therefore, improve compliance. Increasing the frequency of dosing would reduce the volume required for each dose. On the contrary, the increased burden of delivery could be an issue for some participants and their parents. Dosing could be explored further with Symprove, the company who supplied the probiotic.

In an attempt to minimise the poor taste barrier to participant adherence and retention, methods to mask taste were explored. A healthy family were asked to drink the Symprove probiotic in different combinations. The Symprove probiotic was added to a variety of drinks, including Lucozade, lemonade, sugar-free cordial (Robinsons), orange juice and milkshake. The family stated the probiotic tasted best in the sugar-free cordial. Therefore, for the remainder of the study participants were advised to mix the probiotic/placebo with sugar-free cordial juice if they could not tolerate the taste. In undertaking a larger study, the palatability of probiotics must be thoroughly explored using patient public involvement.

Alternative strategies to undertaking a feasibility study may also be considered. Undertaking a different approach could improve the limitations of incomplete data and recruitment that were identified in the feasibility study, which could still occur in an RCT. After altering recruitment and data collection approaches, it may be prudent to undertake a further feasibility study prior to undertaking an adequately powered RCT or consider a pilot study embedded into a large RCT. However, there are strengths and limitations to all study designs, and this should be considered in further detail prior to undertaking any future study.

CONCLUSION

The MaCROS study has demonstrated that undertaking an RCT may only be feasible if recruitment is improved. Modifications to the protocol will need to focus on recruitment strategies and adherence to data capture. More support for participants and their families to complete diaries is essential.

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Contributors HH designed and undertook the research described in this and also wrote the first and repeated drafts of this manuscript. BP and SK both supervised HH while undertaking this study and also gave feedback for the initial and subsequent manuscript drafts.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This protocol was approved by the UK National Health Service (NHS) Ethics Committee process (REC ref: 19/YH/0005) and approved by the Leeds Teaching Hospital Trust (LTHT) Research and Innovation team.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The protocol for this study is accessible online.

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