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ARTICLE

Study protocol of a double-blind randomised placebo-controlled trial on the effect of a multispecies probiotic on the incidence of antibiotic-associated diarrhoea in persons with spinal cord injury

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Abstract

Study design Multi-centre, double-blind randomised placebo-controlled study.

Objective To investigate whether the use of a multispecies probiotic can prevent antibiotic-associated diarrhoea in people with spinal cord injury (SCI).

Setting Three Dutch SCI rehabilitation centres.

Methods Fifty-six people aged 18–75 years with SCI during inpatient rehabilitation, who require antibiotics, will be given probiotics or placebo randomly assigned (T0). After cessation of the antibiotics (T1), the participants will use probiotics/placebo for 3 more weeks (T2). Defaecation, assessed by the Bristol Stool Scale, and bowel management will be monitored daily until 2 weeks after cessation of probiotics/placebo intake (T3). Also, the degree of nausea and information on quality of life will be collected at T0, T1, T2 and T3.

Main outcome measures The difference between the incidence of antibiotic-associated diarrhoea between people with SCI using probiotics compared to those using a placebo at the moment the antibiotics stops, the probiotics stops and two weeks thereafter.

Secondary outcome measures The time to reach effective bowel management, degree of nausea and quality of life.

Registration The Dutch Trial Register- NTR 5831.

Introduction

Neurogenic bowel dysfunction is one of the most disabling impairments caused by spinal cord injury (SCI). It is defined as a colonic dysfunction resulting from a lack of central nervous control [1]. In a survey among 1334 people with SCI, 39% reported constipation, 36% haemorrhoids and 31% abdominal distension [2]. Other possible consequences are diarrhoea and incontinence [3].

Bowel dysfunction following SCI has a huge impact on quality of life (QoL) [2, 3]. In people with faecal incontinence, 62% reported a negative effect on QoL, compared with 8% in controls [1, 4]. Bowel management can reduce the impact on QoL and prevent faecal incontinence and constipation [2]. Bowel management is influenced by many factors such as the use of digital anal stimulation, diet or pharmacological treatment [1]. In acute SCI, achieving effective bowel management is a multifaceted and time-consuming process [2]. It is an important component of the rehabilitation period and remains a lifelong challenge.

Other frequently observed secondary conditions in SCI are neurogenic bladder dysfunction, respiratory and skin problems [5]. People with SCI are therefore at risk of developing infections [6, 7] that often require antibiotic

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treatment. One of the side effects of antibiotic use is dysbiosis of intestinal microbiota, which can result in antibiotic-associated diarrhoea (AAD) [8]. AAD is defined as three or more liquid stools (Bristol Stool Scale (BSS) 5, 6 or 7) per day for 3 or more days [9–11]. In 2017 a paper was published on the use of antibiotics and the prevalence of AAD in people with SCI [12]. In this study 22% of 215 people with SCI suffered from AAD.

AAD might have a negative influence on the rehabilitation process. For example, frequent periods of diarrhoea often result in a delay in achieving effective bowel management. Furthermore, it leads to feelings of general discomfort, other complications such as pressure ulcers, and people might be less active [13]. All this can result in even more complications [7, 14].

Several systematic reviews and meta-analyses have shown probiotics to be beneficial in preventing AAD in people with various diagnoses, such as irritable bowel syndrome and paediatric AAD [15, 16]. In 2014 a randomised controlled trial was published on the effect of probiotics on AAD in people with SCI. This study indicated that probiotics could reduce the incidence of AAD in hospitalised people with SCI. The authors advised a randomised placebo-controlled trial to confirm this success [9]. In 2015 Wong et al. published a protocol for a systematic review on the effectiveness of probiotics in preventing and treating AAD in people with SCI [17]. They concluded that the effectiveness of the current use of probiotics to prevent and treat AAD remains inconclusive.

In conclusion, there is much to gain for people with SCI who need antibiotic treatment and are therefore at risk of AAD and trials on the effect of probiotics in this population are scarce. Therefore, in this study, we will investigate the effect of a specifically designed multispecies probiotic on preventing AAD in people with SCI who are treated with antibiotics in a placebo-controlled trial. We will also examine whether the use of probiotics in this population, shortens the time needed to achieve effective bowel management, prevents nausea and improves QoL.

Objectives

The primary objective is to test the hypothesis that people with SCI, using antibiotics supplemented with a multispecies probiotic have less AAD compared with people with SCI, using antibiotics supplemented with placebo. The secondary objectives are to investigate whether intake of a multispecies probiotic in persons with SCI who use antibiotics: 1. ensures that effective bowel management is achieved faster compared with placebo 2. decreases nausea and 3. increases QoL compared with placebo.

Methods

Trial design and study setting

This double-blind randomised placebo-controlled study will investigate the effect of a multispecies probiotic on the development of AAD. The design of the study is shown in Fig. 1. The study will be performed at three rehabilitation centres in the Netherlands: Heliomare at Wijk aan Zee, Reade at Amsterdam and De Hoogstraat at Utrecht.

Eligibility criteria

All people (aged 18–75 years) with an SCI who are admitted to one of the three inpatient rehabilitation centres will be informed on the study and invited to participate. They are asked shortly after their admission, before they might develop an infection and will need antibiotics, so they will have time to think about their possible participation. If they decide to participate, their informed consent will be registered in the electronic patient record. People with informed consent, who develop an infection and still meet the inclusion criteria, will be enroled in the study when starting antibiotic treatment. People meeting one or more of the following conditions are excluded from participation:

Known gastro-intestinal diseases;
Abdominal surgery within a year prior to enrolment to the study;
Previous or ongoing radiotherapy or chemotherapy;
Severe autoimmune diseases such as systemic lupus erythematosus;
Severe acute pancreatitis, multiple organ failure or sepsis;
Enteral feeding, except for nasogastric feeding;
Excessive alcohol intake (>15 units per week);
Planned or actual pregnancy or lactation;
Use of probiotics during or in the month prior to the study;
Use of antibiotics in the 2 weeks prior to the study;
More than one antibiotic treatment in the 6 months prior to the study;
Previous participation in this study;
Use of antibiotics for longer than 10 days;
Use of flucloxacillin or nitrofurantoin (as these antibiotics are not associated with ADD).

Sample size

Data on the prevalence of AAD in persons with SCI are limited. The study of Wong et al. among people with SCI showed an incidence of AAD of 55% in the control group, while an incidence of 17% was observed in the probiotics

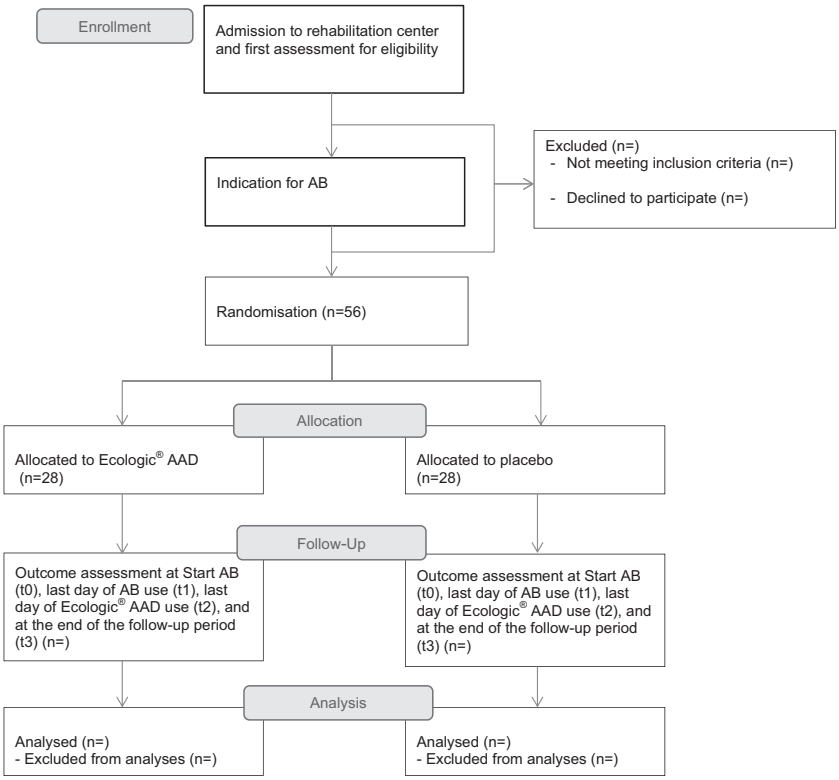

Fig. 1 Flow chart of the study design

group [9]. Based on these results, we estimate that a sample size of 28 per arm is needed to show a 35% difference in the proportion of participants developing AAD (60% in the control group and 25% in the multispecies probiotic group) with a statistical power of 80% and at a significance level of 5%.

Allocation and blinding

The trial will be performed double-blinded in three rehabilitation centres. The randomisation will be performed centrally by an independent department and stratified by rehabilitation centre. Blocked randomisation will be used to ensure a good balance of participant characteristics in each group and all study products will be sequentially numbered. Coded study products will be given to the researchers. Everyone involved in the study is blinded to the intervention until the study is completed. At the end of the study, the independent department will divide the participants into two blinded groups. Hence, the researchers performing the statistical analyses will not know, which group the intervention group is. After performing the analyses, code numbers will be opened by the coordinating and principal investigators. The principal investigator receives sealed envelopes with the allocation of each number, ensuring that if a medical problem occurs for which treatment allocation is needed, the code can always be broken. No participant information will be shared with the company performing the randomisation.

Intervention

When put on a course of antibiotics, the participant will be enroled in the study and be randomly assigned to receive either a multispecies probiotic or a placebo. The multispecies probiotic or placebo is orally taken, twice daily and 2 h before or after intake of antibiotics. After cessation of antibiotic treatment, the participant will continue to use the probiotics/placebo for a further 3 weeks (Fig. 2). To improve adherence to the intervention, the multispecies probiotic or placebo is administered by the nursing staff. Possible reasons for discontinuing the intervention will be participant withdrawal or worsening disease. The reason for drop-out will be registered. Participants who receive less than 75% of the recommended dose of multispecies probiotic or placebo will be considered as non-compliant.

In this study we will use Ecologic®AAD. This multispecies probiotic has been specifically developed to prevent antibiotic-associated disturbances of the intestinal microbiota. The product has shown to reduce the incidence of diarrhoea [18, 19]. This multispecies probiotic has a recommended dosage of 5 g twice daily, with a total viable cell count of 1×10^{10} colony forming unit/day. This dosage is based on prior human studies in healthy volunteers and general surgery patients showing a health benefit without adverse reactions [18–22]. The multispecies probiotic has been used in several clinical studies in different

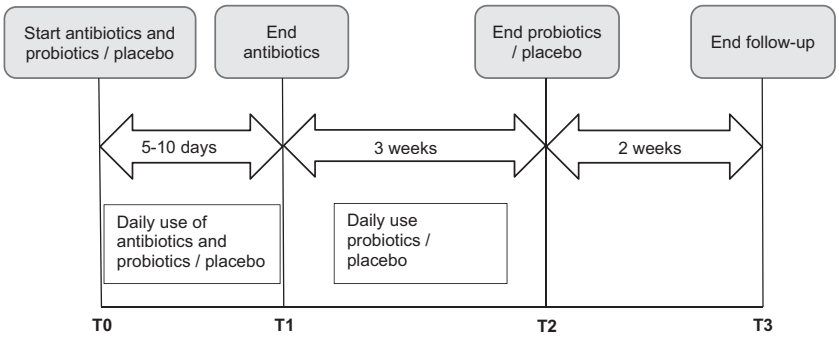

Fig. 2 Schedule of data collection

populations, without any adverse effects. It is commercially available in several countries and no serious adverse effects have been reported [18, 21, 23]. This probiotic food supplement consists of the following nine probiotic bacterial strains: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Enterococcus faecium* W54, *Lactobacillus acidophilus* W37, *Lactobacillus acidophilus* W55, *Lactobacillus paracasei* W20, *Lactobacillus plantarum* W62, *Lactobacillus rhamnosus* W71 and *Lactobacillus salivarius* W24. The product also contains maize starch, maltodextrin, fructo-oligosaccharides P6, maize dextrin P9, potassium chloride, hydrolysed rice protein, magnesium sulphate, amylase and manganese sulphate. A placebo will be used as a comparator. The placebo product is indistinguishable in colour, smell and taste from the active formulation, and will have the same composition but without the live bacteria, fructo-oligosaccharides and maize dextrin P9.

Data collection and management

Data will be collected when the treatment with antibiotics starts (T0), when the use of antibiotics stops (T1), when the use of probiotic/placebo stops (T2) and 2 weeks after the probiotic/placebo is stopped (T3) (Fig. 2). In each centre, data will be collected by a research assistant. To promote data quality, the assessors are instructed how to collect the data. All participants will receive a study identification number. The study identification number and baseline data will be stored at a central database and printed. Outcome data will be both added to the electronic database and on paper. The database is password protected; paper copies are stored in a locked locker. Both versions will be accessible to the involved researchers only. Data entry and validity will be double checked randomly by two investigators. A data monitoring committee is not required, as the risk of harm is classified as negligible. The study is approved by the Medical Ethics Committee of Amsterdam UMC. We have started collecting data in 2018 and data collecting is expected to be completed in 2021.

Adverse events and serious adverse events (SAE)

Any adverse event that occurs within the study will be registered by the principle investigators of the three centres and notified to the coordinating researcher. In case of an SAE the ethics committee will be notified as well. When unexpected circumstances require changes of the protocol, modifications will be reported at the Dutch trial register site and if relevant, reported to the ethical committee, study personnel and manufacturer of the product. In case of a SAE for which treatment allocation is needed, the code can be broken at all time.

Outcomes, characteristics and descriptive variables

An overview of the primary and secondary outcomes, descriptive variables and timing of the data collection is shown in Table 1.

Primary outcome

The primary outcome will be the difference between the incidence of AAD between people with SCI using a multispecies probiotic compared with those using a placebo, which will be determined using the BSS at T1, T2 and T3 [24]. The BSS has been shown to be valid and reliable in persons with SCI [9]. The consistency of stool is scored on a scale of 1 to 7, where 5, 6 and 7 indicate a liquid stool. In addition, the frequency of defaecation will be recorded to monitor the defaecation pattern. AAD is defined as three or more liquid stools (BSS score 5, 6 or 7) per day for 3 or more days. The BSS is filled out daily. At T1 (end of antibiotic intake) the incidence (yes/no) of AAD in the period from T0 to T1 is determined. At T2 (end of probiotic/placebo) the incidence since T1 and at T3 (follow-up) since T2.

Secondary outcomes

The secondary outcomes will be time to reach effective bowel management, degree of nausea and QoL. Effective

Table 1 List of outcome measures & answer categories

Construct	Timing					Measure	Definition
	Daily	T0	T1	T2	T3		
Primary outcome							
Incidence of AAD	X		X			BSS and frequency of defaecation	Yes/no AAD: ≥3 or more liquid stools (BSS chart 5, 6, or 7) per day, for 3 or more days
Secondary outcomes							
Effective bowel management		X	X	X	X		Yes/no Effective bowel management: stable bowel medication scheme without incontinence or obstipation
Faecal incontinence		X	X	X	X	ISCoS dataset bowel management	Yes/no Faecal incontinence Frequency of faecal incontinence during the past 4 weeks (T0) or since the preceding measurement moment (T1–T3). Answer categories are (a) ≥2 times a day (b) once a day (c) 1-6 times a week (d) never
Obstipation		X	X	X	X	ISCoS dataset bowel management	Yes/no Obstipation: defaecation frequency of twice a week or less Frequency of defaecation during the past 4 weeks (T0) or since the preceding measurement moment (T1–T3). Answer categories are (a) ≥3 times per day (b) twice daily (c) once daily (d) not daily but more than twice every week (e) twice every week (f) once every week (g) less than once every week but at least once within the last 4 weeks (h) no defaecation within the last 4 weeks (i) never
Defaecation method		X	X	X	X	ISCoS dataset bowel management	Within the last 4 weeks (T0) or since the preceding measurement moment (T1–T3) (a) normal defaecation (b)straining/bearing down (c) digital anorectal stimulation (d) suppositories (e) digital evacuation (f) mini enema (g) enema (h) colostomy (i) SARS (j) other
Stable bowel medication scheme		X	X	X	X	Electronic patient record	Yes/no Changes in bowel medication. Medication scheme is considered stable when there are no chances in prescription during the past week (T0) or since the preceding measurement moment (T1–T3)
Nausea		X	X	X	X	VAS	Nausea during the past 4 weeks (T0) or since the preceding measurement moment (T1–T3). Ranges from 'no nausea' to 'worst possible nausea'. Scored as distance in mm from 'no nausea' to patient mark
Quality of life							
General quality of life		X	X	X	X	ISCoS dataset QoL	How satisfied are you with your life as a whole? Scores ranges from 0 (completely dissatisfied) to 10 (completely satisfied), or any number in between
Physical health		X	X	X	X	ISCoS dataset QoL	How satisfied are you with your physical health? Scores ranges from 0 (completely dissatisfied) to 10 (completely satisfied), or any number in between
Psychological health		X	X	X	X	ISCoS dataset QoL	How satisfied are you with your psychological health? Scores ranges from 0 (completely dissatisfied) to 10 (completely satisfied), or any number in between
QoL compared with before SCI		X	X	X	X	ISCoS dataset QoL	How satisfied are you with your quality of life now, compared with your quality of life before the SCI
Participant and disease characteristics							
Age		X					In years
Gender		X					Male/female
Neurological level of injury		X	X	X	X	AIS	ASIA impairment Scale
Time since injury		X					
Descriptive variables							
Walking ability		X	X	X	X	Hoffer	Classification of walking ability (a) nonambulatory (b) therapeutic walker (c) household walker (d) community walker
Bowel problems (not related to SCI)		X				ISCoS dataset bowel management	Gastro-intestinal or sphincter dysfunction, peri-anal problems, previous gastro-intestinal surgical procedures
Time needed to defecate		X	X	X	X		Average time required for defaecation (a) 0–30 min (b) 31–60 min (c) ≥60 min (d) unknown
Use of incontinence material		X	X	X	X		Need to wear pad or plug (within the last four weeks) (a) no (b) yes (c) unknown
Defaecation method		X	X	X	X		Within the last 4 weeks (T0) or since the preceding measurement moment (T1–T3) (a) normal defaecation (b) straining/bearing down (c) digital anorectal stimulation (d) suppositories (e) digital evacuation; (f) mini enema (g) enema (h) colostomy (i) SARS (j) other (k) unknown
Antibiotic use		X	X			Electronic patient record	Type and duration of antibiotic use
Medication use		X	X	X	X	Electronic patient record	Medication affecting bowel function

bowel management is defined as a stable bowel management including a stable bowel medication scheme and evacuation method, without incontinence or obstipation. Bowel function and evacuation methods will be determined using the Dutch Dataset on Spinal Cord Injury Rehabilitation (DDSCIR) [25]. This is a standardised dataset for collecting information on persons with SCI and is used in all Dutch SCI rehabilitation centres. The DDSCIR includes the translated international SCI datasets on bowel function and QoL [26, 27]. Defaecation frequency will be registered in the DDSCIR. Defaecation frequency is defined as the number of defaecations during the past four weeks (T0), or since the last measurement (T1, T2 and T3). Ten categories are distinguished, varying from more than 3 times a day, to no defaecation during the past 4 weeks. At T0 we will score whether the participant has an effective bowel management

during the past 4 weeks. At T1, T2 and T3 we will score whether the participant has an effective bowel management since the last measurement.

Degree of nausea will be measured with the Nausea Visual Analogue Scale. Participants will be asked to make a mark on a 10-cm-long line to score their feeling of nausea, ranging from 'No nausea' (0) to 'Worst possible nausea' [10]. The scale is scored by measuring the distance from 'No nausea' (0) to the participant's mark. This VAS method proved to be reliable and sensitive for assessing post-operative quantitative nausea intensity [28].

QoL in the DDSCIR is measured with the ISCoS QoL basic dataset [26], and is defined by four questions. General QoL (how satisfied are you with your life as a whole), physical health (how satisfied are you with your physical health), and psychological health (how satisfied are you with your psychological health), are rated on a scale from 0 to 10. Zero corresponds to completely dissatisfied and 10 corresponds to completely satisfied. The last question determines how satisfied the person is with his QoL today, compared with his QoL before the SCI. Seven categories are defined: (1) much worse, (2) worse, (3) a little worse, (4) about the same, (5) a little better, (6) better and (7) much better. The four questions are analysed separately.

Participant and disease characteristics

The participant characteristics that will be registered are age, gender and time since injury.

The disease characteristics will be the SCI classification according to the American Spinal Injury Association (ASIA) [29].

Descriptive variables

Descriptive variables are bowel problems not related to the SCI, the method of defaecation, time needed to defaecate and use of incontinence material. All are determined using the DDSCIR (Table 1). Bowel problems (not related to the SCI) which are distinguished are any gastro-intestinal or sphincter dysfunction, peri-anal problems and previous gastro-intestinal surgical procedures. Furthermore, type and duration of antibiotic prescribed and use of medication affecting bowel function will be registered. Ambulatory status will be categorised by the Hoffer classification as nonambulatory, therapeutic, household and community [30]. Walking ability will be measured because of its potential influence on bowel function.

Statistical methods

Descriptive statistics will be used to describe the participant and disease characteristics of both groups. Analyses will be performed according the per protocol principle. Participants who received at least 75% of the recommended dose of multispecies probiotic or placebo will be included in the analyses. In addition, analyses according the intention-to-treat principle will be performed. IBM SPSS Statistics version 23 will be used to analyse the data.

Primary research question

To answer the primary research question, differences in the presence of AAD between the probiotics group and the placebo group will be tested at T1, T2 and T3 using logistic regression analyses. To estimate differences between groups over time, longitudinal regression analyses will be used. Odds ratios, 95% confidence intervals (95% CI), and p values will be presented.

Secondary research questions

Differences in effective bowel management between both groups will be analysed at T1, T2 and T3, using logistic regression analyses. To establish whether there are differences in time to reach effective bowel management between the groups, longitudinal regression techniques will be performed. In addition to the analyses of the composite measure of effective bowel management, regression analyses will be performed for the separate variables of faecal incontinence and obstipation.

Whether people with SCI who take antibiotics supplemented with multispecies probiotics have less nausea and a higher QoL compared with people with SCI who take antibiotics supplemented with a placebo will be examined using linear regression analyses. The four aspects of QoL, general QoL, physical health and psychological health are analysed separately. Results of the regression analyses will be presented as Odds ratios or regression coefficients, respectively, 95% CI, and p values.

Ethics and dissemination

Ethics

The study design is described according to the Consolidated Standards of Reporting Trials (CONSORT statement) and SPIRIT 2013 checklist. Approval of the study has been obtained from the Medical Ethics Committee of Amsterdam UMC, location VUmc, Amsterdam, the Netherlands (approval number: 2016.229, A2018.217). The trial is registered in the Dutch Trial Register (NTR 5831; http://www.trialregister.nl/trialreg/index.asp). We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers will be followed during this research.

Dissemination

The results of the study will be spread via presentations at congresses and publication of peer reviewed articles.

Summary

Neurogenic bowel dysfunction is one of the most disabling impairments caused by SCI and achieving effective bowel management is a lifelong challenge. Also, people with SCI are at risk of developing infections that require antibiotic treatment and therefore at risk of developing AAD. AAD might negatively influence the rehabilitation process and might also decrease QoL. Multispecies probiotics have proven to be beneficial in preventing AAD in people with various diagnoses. However, trials on the effect of multispecies probiotics in people with SCI are scarce. When completed, this study will be the first randomised placebo-controlled trial on preventing AAD in people with SCI. As such, our study is of great importance. There is much to gain and our results might contribute to the care of people with SCI.

Funding Funding for this study will be provided by the research department of Heliomare. Winclove Probiotics B.V. supplied the probiotics and placebo products. Winclove Probiotics B.V. will not have any say in the analyses, interpretation or how the final paper is written. The results will be written up regardless of the findings.

Author contributions WF, JN and CvB designed the protocol, drafted and/or revised the paper, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. They will play an important role in acquiring data and/or interpreting the results. CK and IBvdV, did play a supportive role in the conceptualisation and methodology of the study or the review of the paper. They will not have a role in data collection, data analysis or decision to publish. CK and IBvdV approved the final version of the paper and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. WAW and JSS drafted and revised the paper, approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. WAW and JSS will play an important role in acquiring data and/or interpreting the results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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