Test-guided dietary management of eczema in children: A randomized controlled feasibility trial (TEST)

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Abstract
Background: Parents commonly ask about food allergy tests, to find a cause for their child's eczema, yet the value of routine testing is uncertain.

Objective: To determine whether a clinical trial comparing test-guided dietary advice versus usual care, for the management of eczema, is feasible.

Methods: Children (>3 months and <5 years) with mild-to-severe eczema, recruited via primary care, were individually randomized (1:1) to intervention or usual care. Intervention participants underwent structured allergy history and skin prick tests (SPT) with dietary advice for cow's milk, hen's egg, wheat, peanut, cashew and codfish. All participants were followed up for 24 weeks. A sample of doctors and parents was interviewed. Registration ISRCTN15397185.

Results: From 1059 invitation letters sent to carers of potentially eligible children, 84 were randomized (42 per group) with mean age of 32.4 months (SD 13.9) and POEM of 8.7 (4.8). Of the 42, 6 (14%) intervention participants were advised to exclude one or more foods, most commonly egg, peanut or milk. By participant, 1/6 had an oral food challenge (negative); 3/6 were told to exclude until review in allergy clinic; and 6/6 advised a home dietary trial (exclusion and reintroduction of food over 4–6 weeks) – with 1/6 partially completing it. Participant retention (four withdrawals) and data completeness (74%–100%) were acceptable and contamination low (two usual care participants had allergy tests). There were three minor SPT-related adverse events. During follow-up, 12 intervention and 8 usual care participants had minor, unrelated adverse events plus one unrelated hospital admission.

Conclusions: It is possible to recruit, randomize and retain children with eczema from primary care into a trial of food allergy screening and to collect the outcomes of interest. Changes to recruitment and inclusion criteria are needed in a definitive trial, to ensure inclusion of younger children from more diverse backgrounds.
INTRODUCTION

One in five preschool children in the United Kingdom have eczema, the clinical phenotype of atopic eczema/dermatitis. More than half develop symptoms by 1 year of age and almost all by 5 years of age. Eczema is associated with food allergy, and allergic reactions to different foods may cause eczema symptoms, either as part of an IgE or non-IgE-mediated reaction.

A common perception among parents and carers (hereafter parents) of children with eczema is that all symptoms are caused by food allergies. They often seek information online but unfortunately much of the advice is erroneous and some dangerous. Consequently, many parents restrict their child’s diets and request allergy testing to guide dietary decision-making.

Nwaru et al. reviewed the prevalence of the most common foods to cause IgE-mediated allergic reactions in children: cow’s milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish. They found an up to 15-fold difference between self-reported and challenge-verified prevalence of food allergy. Lifetime self-reported point prevalence is highest for cow’s milk allergy (2.3%) and lowest for fish allergy (0.6%). Based on objective food challenges, the prevalence is highest for cow’s milk allergy (0.6%) and lowest for wheat and shellfish allergy (both 0.1%). In general, the prevalence of cow’s milk allergy and egg allergy is higher in younger age groups than older age groups, while the prevalence of peanut allergy, tree nut allergy and fish allergy is higher in the older age groups. They found insufficient data to compare the estimates of soy and wheat allergy between the age groups. The discrepancy between self-reported and objective figures, particularly for milk, soy and wheat, may in part be due to non-IgE-mediated food allergy but also through over-reporting of symptoms. Food allergy is more common in children with eczema, however. Tsakok et al. report that up to 53%–66% of people with eczema are food sensitized, and 15%–81% have challenge-proven food allergy. Earlier onset, persistent and more severe disease is associated with increased risk of food allergy.

It remains unclear, however, whether test-guided dietary decisions improve eczema symptoms, or negatively affect children by unnecessarily reducing dietary choices and distract from the use of conventional treatments. Furthermore, there is evidence that children with eczema may benefit from early introduction of some allergenic foods. Introducing peanut and cooked hen’s egg into the infant diet, as part of complementary feeding, may reduce the risk of peanut or egg allergy. It is uncertain whether excluding these or other foods to which infants are sensitized but tolerant may increase the risk of food allergy developing, and if this is the case, how long after allergen exclusion this is likely to occur.

Ierodiakonou et al. found no consistent association between timing of allergenic food introduction and risk of eczema from either intervention or observational studies. One trial of infants with established eczema suggested dietary exclusion of eggs may be useful in children with positive allergy testing for egg. However, the trial was small (55 participants), in a specific population (paediatric dermatology clinic), with short follow-up (4 weeks) and no patient-reported outcomes. Better designed and conducted trials are needed to determine whether test-guided dietary management is worthwhile in the management of eczema. In the Trial of Eczema Allergy Screening Tests (TEST) study, we aimed to find out whether conducting a trial comparing food allergy testing and dietary advice versus usual care, for the management of childhood eczema in primary care, is feasible.

METHODS

2.1 Design

The protocol for this trial is published elsewhere, but in brief TEST was a single-centre, two-group, individually randomized, feasibility randomized controlled trial (RCT), with economic scoping and a nested qualitative study.

2.2 Participant recruitment and eligibility criteria

Between September 2018 and February 2019, participants were recruited from primary care centres located in, and surrounding, the city of Bristol, England. Eligible participants were children aged over 3 months and <5 years with mild or worse eczema, as defined by a Patient Oriented Eczema Measure (POEM) score of greater than two (scale 0–28, with a higher score equating worse eczema). We excluded children with medically diagnosed food allergy, awaiting referral/investigations for possible food allergy or who had previous investigations for food allergy.

Potentially eligible children were identified from a search of their primary care electronic medical records. Family Practitioners (FPs) were asked to exclude children who would be ineligible prior to sending their parent an invitation letter. Parents could also self-refer their child into the study opportunistically.

2.3 Procedure

Interested parents attended a baseline appointment at their primary care centre, where consent was received, data collected
Participants were randomized 1:1 to either the intervention or usual care, using a web-based system stratified by age and severity of eczema. The allocation sequence was concealed, and randomization was not done until all baseline measurements were completed. Participants, parents and their doctors were not masked to the allocation.

Participants in the intervention group underwent a structured allergy history, skin prick tests (SPTs) and were given dietary advice regarding six foods: cow's milk, hen's eggs, peanut, cashew, codfish and wheat. The structured allergy history was administered by the Clinical Studies Officer, which asked about relevant symptoms (skin, respiratory and gastrointestinal) and timing of onset in relation to ingestion of the study foods. The same researcher performed the SPTs using commercial extracts of the foods, along with positive (1.0% histamine) and negative (0.9% saline) controls, following standard procedure. The findings of the structured allergy history and SPTs were interpreted by following an algorithm to determine what advice or further action was recommended. All participants' results were reviewed by an allergy panel (MR, RB, DM and/or LW) and advice on food ingestion/avoidance relayed to the participant's parent by the Clinical Studies Officer. Children with possible IgE-mediated symptoms underwent an open food challenge which was supervised by DM at the Bristol Royal Children's Hospital, using a modified Practical Allergy (PRACTALL) dosing schedule and criteria for interpretation of challenge outcome. For children with possible delayed allergy symptoms, families were advised to exclude the possible allergen from their diet over a 2- to 4-week period and then reintroduce.

Participants allocated to usual care did not receive any additional assessments or tests as part of the study, but their treating clinicians could independently request these if deemed clinically indicated during the follow-up period.

Participants were followed up for 24 weeks. Parents were asked to complete questionnaires four-weekly and attend a face-to-face assessment of their child's skin at 24 weeks.

### Outcome measures

The main outcome of interest was the feasibility of conducting the trial and collecting the required data. As recommended by the core outcome group for eczema (HOME), the feasibility of collecting data on symptoms, signs and quality of life was assessed. The following instruments were used:

1. **Symptoms and long-term control** - Patient Oriented Eczema Measure (POEM)
2. **Clinical signs** - Eczema Area Severity Index (EASI)
3. **Quality of life** - Atopic Dermatitis Quality of Life (ADQoL), Infant Dermatitis Quality of Life (IDQoL) and Child Health Utility 9D (CHU9D)

We determined that a sample size of 80 participants was sufficient to inform the chosen outcomes.

### Analysis

Trial data were analysed descriptively, using Stata (version 15.1). Scale and quality of life scores were calculated following recommended conventions. Descriptive statistics were used to describe participant recruitment, retention, adherence and contamination.

### Health economics scoping

Healthcare (hospital visits and stays) and personal (over-the-counter medications, personal expenses, private/alternative treatments, travel, time off work/school) resource use were collected via the parent-completed diaries. All primary care consultations and prescribed medications were extracted from electronic medical records: eczema and/or food allergy-related consultations and prescribed medications were independently identified from the records by two clinicians (MJR and MS) and agreement compared.

### Nested qualitative study

We audio-recorded semi-structured interviews with 11 doctors and 21 parents, employing a flexible topic guide. Participants were purposively sampled: parents from both intervention and usual care groups, of children with a range of eczema severity, with varied socio-economic status, different lengths of time in the trial and test results; doctors from a range of practices, with differing lengths of time in the trial and attitudes to allergy testing. We stopped interviewing when we judged that we had achieved sufficient "information power". Interviews were transcribed, anonymized and analysed thematically using both inductive and deductive coding, aided by NVivo 10.

We present data relevant to the feasibility of the trial here, while more detailed findings on participants’ views on food allergy testing in eczema are published separately. We held three group meetings with parents of children with eczema over the course of the study, while feedback on the design,
delivery and findings of the trial were discussed. We also undertook three engagement events at the end of the trial with stakeholders and the general public.

Ethical approval

The study was reviewed by the Health Research Authority and given a favourable opinion by the NHS REC (West Midlands – South Birmingham Research Ethics Committee, Reference Number 18/WM/0124).

3 | RESULTS

3.1 | Participant recruitment and characteristics

Participants were recruited between September 2018 and February 2019 from 17 primary care centres. FPs were supportive of hosting the trial in their practice:

I think what attracted us to this trial was potentially having something else to be able to advise parents.

(FP 11)

The flow of the participants through the trial is shown in the CONSORT diagram (Figure 1). A total of 1276 potentially eligible children were identified on searches of electronic medical records but 217 were excluded by FPs, the most common reason (46%, 99/217) being diagnosed or suspected food allergy. Some doctors experienced difficulties applying some of the inclusion/exclusion criteria pre-invitation, for example:

It’s difficult [identifying when a child no longer has eczema] because all we’re going to get is an EMIS [electronic medical record] code saying eczema, we’re not going to get one saying ‘no longer has eczema’ and obviously because it sort of flares up and dies down doesn’t it so I don’t think - I certainly never coded ‘no longer has eczema’ for anything. So, I don’t think really we’d be able to pick that up.

(FP 11)

Replies were received from 203/1059 (19%) invitation letters with four additional opportunistic expressions of interest. Of these, 143 children were potentially eligible and 84 were randomized (42 into each group), 82 of these responding to the postal invitation and two self-referrals. The main reasons for non-randomization were (Figure 1) participant declined/uncontactable (31/143, 22%) and baseline visits not booked/conducted (24/143, 17%).

Scheduling and conducting baseline appointments were often challenging for multiple reasons: requirements relating to the primary care centre (availability of a suitable room and doctor on-site in case of an emergency), participant (availability of working parent and participant, “well child” including no recent antihistamine use) and availability of Clinical Studies Officer.

The baseline characteristics of the children and their consenting parent are shown in Table 1. Children’s mean age was 32.4 months (SD 13.9), with 48% female (40/84) and 77% white (65/84). 70% (59/84) of participants met the UK diagnostic criteria for atopic dermatitis with disease of mostly mild-moderate severity (POEM 8.7, SD 4.8; EASI 2.0, IQR 1.0, 4.8). The mother most commonly gave consent (78/84, 93%) and most consenting parents (48/84, 57%) were educated to degree level or equivalent.

Comparing what data were available on children who were invited with those who took part, there did not appear to be a difference in respect of age or gender, but self-reported disease severity was worse in potentially eligible/randomized children (Table S1).

3.2 | Intervention delivery, acceptability and advice given

All 42 participants randomized to the intervention group had complete allergy history and SPTs. However, the duration of baseline appointments for intervention participants (up to 90 min, compared with ~45 min for usual care, of which ~30 min for allergy history and skin prick testing) was sometimes trying for the young child.

By taking part in the trial, parents consented to randomization, yet some allocated to the usual care group expressed relief at not having to undergo skin prick testing:

I was quite glad … he didn’t have to do allergy testing … once I saw the fact that he wasn’t that happy about being probed and prodded. I thought yeah, probably better off not having to do it.

(Parent 7)

The majority (36/42, 85.7%) of intervention participants reported no allergy symptoms and had negative SPTs. In interviews, most accepted the results, finding them useful for ruling out the possibility of food allergy or reassuring them about their current practice with their children:

We had a negative result … but it definitely made a difference in terms of ok put your mind to rest … made us a bit more relaxed … And also, maybe more feeling of being in control.

(Parent 14)

However, some felt frustrated, still not knowing the cause of their child’s eczema or how best to manage it, or doubted the veracity or comprehensiveness of the tests:
FIGURE 1  CONSORT – participant recruitment and follow-up
I still don't know if he has an allergy to anything that wasn't tested, 'cos they only test for certain ones'. (Parent 16)

Six of the intervention participants had a history or SPTs result suggestive of possible food allergy. Three of these participants were advised regarding one food, one regarding two foods, one regarding three foods and one regarding four foods (Figure 2). The foods most commonly raising concern were egg (four participants), peanut (three participants) and milk (three participants). Dietary advice given to each of these participants: all six were asked to exclude one food at home; one had an oral food challenge to peanut, which was negative; and three were referred to the local allergy clinic for follow-up.

3.3 | Participant follow-up

Retention in the study was good with only four participants withdrawing (Figure 1 – three from usual care; one from intervention). Reasons for withdrawal (not mutually exclusive) were not having enough time (four participants); my child's eczema has improved (one participant); the study is not helpful for my child (one participant).

Completion of data items across the seven time-points (baseline through to week 24) was good (Table 2), varying from 74% (“Diet of child” most poorly completed question items) to 100%.

3.4 | Adherence to dietary advice and contamination

Except for peanut consumption in intervention participants (which was lower at 24 weeks), parent-reported consumption of the six foods were similar among both usual care participants and “test negative” intervention participants at baseline and week 24 (Table S2).

Adherence in the six “test positive” intervention participants was mixed. Regarding reported consumption of high-risk food(s) (that parents had been advised to exclude because of the need for assessment in allergy clinic or with an oral food challenge), adherence was 81% (29/36 person-weeks of available data). Regarding home dietary trial of low-risk foods, only 1/6 participant reported that they tried excluding (cow’s milk) but did not reintroduce it because of a perceived reduction in eczema symptoms.

There were no reports of participants in the intervention group whose tests were negative seeking allergy testing after the baseline appointment. In the usual care group, two participants saw an allergy specialist following the baseline appointment and had allergy testing: one due to a possible food reaction and one private referral at the request of the parent.

3.5 | Outcomes and adverse events

The main outcomes collected were similar between the two groups over the 24-week follow-up (Table 3). There were five minor adverse events in the intervention group at baseline after...
SPT (three related – localized redness, flushing or swelling of skin; and two unrelated – tiredness), which did not require any treatment. During follow-up, 12 children in the intervention and 8 in usual care groups had unrelated adverse events, mostly minor (Table S3) with one unrelated hospital admission for asthma by a child in the intervention group.

### 3.6 Health economics scoping

Diary resource use data were generally well-completed. For example, data completion for personal expenses ranged from 74% to 82%. While for some resources many parents reported usage, for example 45 parents reported buying over-the-counter medications, for other
resources, most parents did not report any use. Between 3% and 7% of parents reported travel costs, and 4% of parents reported private or alternative treatment use. Agreement between two clinicians on electronic medical record data about participant eczema/food allergy-related consultations and prescribed medications was high (between 78% and 85%).

Completion of the ADQoL and CHU9D was similar across measures and treatment groups (Table 3). Missing answers were mainly due to whole measure not having been completed.

### DISCUSSION

#### 4.1 Summary

We were able to recruit participants via, and deliver our intervention in, primary care centres, exceeding our target sample size within the planned 6-month recruitment period. Most participants were recruited via postal invitation, and while the logistics of the baseline visit were sometimes challenging (scheduling a time to conduct and appointment length), we found that the allergy testing component was acceptable to FPs and parents, with only minor adverse events. The lower than expected number of children in the intervention group (6/42, 14.3%) with “positive” tests reflects the population of children recruited to the study (mean age 32.4 months; with the most common reason for FPs excluding potentially eligible children being diagnosed or suspected food allergy). Participant retention, data completeness, reported adherence and contamination over the 24-week follow-up period were good overall. However, adherence to home dietary trials advice was poor, with only one of six participants partially excluding (but not reintroducing) one food. We have demonstrated that it is feasible to collect patient-level data on NHS and personal resource use and have identified areas where data collection can be optimized, which may reduce parent-burden (removal or refinement of question items) and improve data quality.

#### 4.2 Strengths and limitations

Our trial was well conducted and included a nested qualitative study, findings of which support the quantitative results. Specifically, FPs supported the need for the trial and parents were generally satisfied with their allocation and, in the intervention group, test results. However, FPs identified problems in “pre-screening” potentially eligible children against eligibility criteria at the mail-out stage and not all intervention parents were reassured by the SPT findings. In the design and delivery of the study, we built on learning from other eczema trials, benefitted from a multidisciplinary team (FPs, nurses, allergy specialists, dietitian, methodologists) and good patient and public involvement. We have been careful throughout to focus on the data that informs the feasibility of the proposed main trial, rather than clinical findings themselves.

The main limitation relates to the generalizability of our findings. The mean age of participants was higher than expected and consequently breastfeeding rates at time of enrolment were low (none fully and two partially breastfeeding at baseline). This means that we were unable to explore a prior concern that advice to exclude foods may discourage breastfeeding. Parents were also highly educated (57% degree or equivalent).

While the number of “test positive” intervention participants was lower than expected, half of these participants had issues with two or more foods. We have limited insight into why these children had not been identified before but may include factors such as limited access to formal assessment of food allergy; and difficulties attributing ingestion of foods to delayed symptoms (non-IgE-mediated allergies). In the nested qualitative study, the one “positive” intervention participant we spoke to had suspected a food allergy but despite seeking advice from their FP had not been investigated further and had experimented with dietary changes without professional guidance. Therefore, our understanding of how a positive test result affects parents and future management of the child’s condition is also limited.

Our data on adherence to dietary advice are limited in three respects. First, only 6/42 participants were asked to exclude one or more foods. Second, our follow-up questionnaires on food consumption did not distinguish between baked/cooked milk/egg. Lastly, we also do not have any qualitative data to help us understand the acceptability, or otherwise, of home dietary trials.

This was a feasibility study so was therefore not designed to detect difference between the two groups in terms of eczema severity or other outcomes.

### TABLE 3 Outcome measure scores at baseline and follow-up

|               | Intervention (n=29) | Usual care (n=31) |
|---------------|--------------------|------------------|
| Baseline (week 0) |                    |                  |
| Mean POEM (SD) | 9.0 (5.2)          | 8.4 (4.5)        |
| Median EASI (IQR) | 1.7 (0.7, 4.8)    | 2.1 (1.1, 4.0)   |
| Mean GAD–7 (IQR) | 3.5 (0, 10)       | 3 (1, 7)         |
| Mean ADQoL (IQR) | 0.841 (0.744, 0.841) | 0.841 (0.744, 0.841) |
| Median IDQoL (IQR) | 3 (2, 6)          | 4 (2, 5)         |
| Median CHU9D (IQR) | 0.951 (0.915, 0.979) | 0.960 (0.908, 1.000) |

Follow-up (week 24)
4.3 | Literature

As far as we are aware, this is the first study of its kind to be conducted in primary care. We drew on learning from the BEEP study,\textsuperscript{39} which also successfully delivered SPTs to young children in a community setting. The response rates observed from the mail-out invitation (203/1059, 19.2%) is similar to\textsuperscript{38,40} and the proportion meeting the UK diagnostic criteria for atopic dermatitis (70.0%) is higher than\textsuperscript{41} other trials of children with eczema in primary care.

Prior research has established that many parents are interested in dietary changes and allergy testing as a potential “cure” for their child’s eczema and are frustrated when this is not discussed or is dismissed by their doctor.\textsuperscript{4,5} Lay understanding of the limitations of blood and skin prick food allergy tests and non-specialist’s confidence in interpreting results are further barriers to the appropriate care of these children.\textsuperscript{42}

Parental belief that eczema is due to a food allergy can be a barrier to effective treatment, lead to unnecessary and potentially harmful dietary restrictions and is a source of parental frustration with healthcare professionals.\textsuperscript{4,5,8} Previous research has also highlighted parental concern about environmental as well as food allergens\textsuperscript{43} although these are usually more of an issue in older children with atopy.\textsuperscript{44}

Of 1276 potentially eligible children, 99 (7.8%) were excluded because of diagnosed or suspected food allergy; and 6/42 (14.3%) of intervention participants had possible/probable allergy to one or more foods. This compares with published estimates of 15%–36% of children with eczema and 6% of the general population.\textsuperscript{45} These disparities probably reflect differences in the populations studied and how allergy is defined. We assessed for possible allergies to six of the most common food allergens.\textsuperscript{46} As expected, egg, peanut and milk were most frequently associated with positive findings.\textsuperscript{47,48}

Adherence to dietary advice among intervention groups has previously been reported to be low, with around a third of participants in the EAT study adherent as per protocol.\textsuperscript{49} The tension between efficacy (does the intervention work under ideal circumstances) and effectiveness (does the intervention work in real life) needs to be carefully considered in the design of any follow-on trial.

4.4 | Research and practice

In the absence of any symptom constellations suggestive of food allergy, clinicians should continue to focus on positively promoting a “control, not cure” message when communicating with parents about childhood eczema. For the majority, this means supporting parents to moisturize their child’s skin regularly and use topical corticosteroids of an appropriate strength and duration according to the site and severity of their child’s eczema.

The importance of this topic, lack of research in this area and our study’s findings support the need for, and feasibility of, a definitive trial of food allergy screening in children with eczema. Because of the uncertainty around the diagnosis in primary care, we favour not asking FPs in any future trial to pre-screen potential invitees for suspected food allergy. We also think the emphasis should be on recruiting infants when complementary feeding starts and new foods are eaten for the first time; and on foods which are regularly consumed and may therefore be more likely to cause eczema symptoms, such as cow’s milk, egg or wheat. It is important to recruit from as diverse socio-economic and ethnic backgrounds as possible. Ways to achieve this may be through recruiting incident (rather than prevalent) cases of eczema and to concentrate recruitment in more deprived and ethnically diverse areas. Intervention design and delivery should probably sit on the pragmatic side of the efficacy/effectiveness divide, but investigators must be mindful of possible effects of delayed introduction or exclusion of foods on immune tolerance. Similarly, careful consideration must be made to any potential trade-off between dietary restrictions that might improve eczema symptoms but may impair other aspects of quality of life because of restricted dietary choices for the child and family.

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CONFLICT OF INTEREST

MJR: No financial interests; convenes the NIHR SPCR Allergy working group; and was a member of the NICE Quality Standard 44 for Atopic eczema in under 12 s and RCPCH “Care pathway for children with eczema” groups. LW: Direct – financial: writes articles, participates in infant formula advisory board meetings and presents at sponsored lectures relating to food allergy; has received infant formula company sponsorship to attend national/international allergy-related conferences/ meetings. Runs a private practice (Food Allergy Nottingham Service Ltd, 2013-) in addition to NHS role (Feb 2012-). BDA cow’s milk allergy course facilitator (2018-), Dietetic telephone service advisor for Allergy UK (2020-). Direct – non-financial: member of RCPCH faculty for tier 3 paediatric allergy course (2018-); member of Allergy UK health advisory board (2015-); member of iMAP implementation team (2017-); produces food allergy-related dietary information for BDA food allergy group (2014-); NICE Expert adviser relating to paediatric food allergy and gastro-oesophageal reflux (2017-2020); previous member of NICE food allergy guidelines GDG and RCPCH food allergy care pathway (2010-2011). RJB has received honoraria for participating in advisory boards for ALK-Abello, DBV technologies and Prota therapeutics, who research or manufacture treatments for people with food allergy.
AUTHOR CONTRIBUTIONS
MJR conceived the study in collaboration with RJB, MS, JRC and IM. MJR, RJB, MS, JRC, IM, ARGS, DM, KR, KG, PSB and JK developed the initial study design, with later input from JC, LS, LW, EA and JT. Specific advice was given by PSB and NLT on trial design and medical statistics; ARGS, LS and CC on the nested qualitative study; and KG and JC on the economic scoping. All the authors contributed to the drafting of the study protocol, led by MJR and approved the final manuscript.

DATA AVAILABILITY STATEMENT
No later than 3 years after the completion of the study, we will make available a completely de-identified data set to an appropriate data archive for sharing purposes.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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