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Reasons for unsuccessful recruitment of children with atopic dermatitis in primary care in the Netherlands to a cohort study with an embedded pragmatic, randomised controlled open-label trial: a survey

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ABSTRACT

Background The Rotterdam Eczema Study was an observational cohort study with an embedded pragmatic randomised controlled open-label trial. It was conducted in children with atopic dermatitis (AD) in the Dutch primary care system. The objective of the trial was to determine whether a potent topical corticosteroid (TCS) is more effective than a low-potency TCS.

Objective We are aiming to communicate transparently about the poor recruitment for the trial part and to explore the reasons why recruitment was weak.

Design We used a survey to find out what patients in the cohort did when they experienced a flare-up.

Methods Descriptive statistics were used to present the baseline characteristics of participants in the trial and the results of the survey.

Results In total, 367 patients were included in the cohort. Of these, 32 were randomly assigned to a trial treatment; they had a median age of 4.0 years (IQR 2.0–9.8). A total of 69 of the 86 children (80.2%) who could participate in the survey responded. 39 (56.5%) suffered a flare-up during the follow-up (making them potentially eligible for inclusion in the trial). 26 out of 39 (66.7%) increased their use of an emollient and/or TCS themselves. Only 12 of the 39 (30.7%) contacted their general practitioner (GP) as instructed in the study protocol, but 8 out of these 12 did not meet the inclusion criteria for the trial.

Conclusion The main reason why cohort participants did not take part in the trial was that they did not contact their GPs when they experienced an AD flare-up. Furthermore, the majority of patients who contacted their GPs did not match the inclusion criteria of the trial. We expect that the lessons learnt from this study will be useful when developing future studies of children with AD in primary care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ When it transpired that inclusion for the cohort was running behind schedule, we started recruiting patients through social media.
⇒ A limitation of the trial was an excessively narrow set of inclusion criteria.
⇒ A limitation of the survey is that we did not explore in depth why participants did not contact their general practitioners.

INTRODUCTION

Eczema, also known as atopic dermatitis (AD), is a persistent, intensely itchy, inflammatory skin condition that affects many children. In general practice, AD is among the top 10 most prevalent conditions in children aged under 18.[1] As there is no curative treatment for AD, suppressive treatment aims to control the condition. The majority of patients in general practice use emollients along with topical corticosteroids (TCS) as symptomatic, suppressive medication for managing their symptoms.[2 3] The recommended treatment strategy for TCS use when AD flares up differs between guidelines.[4] The Cochrane review of TCS treatment strategies concludes that potent and moderate TCS are probably more effective than mild ones, primarily in cases of moderate or severe eczema.[5] However, most of the included studies were small-scale and had a moderate to severe risk of bias. We, therefore, conducted a trial (the Rotterdam Eczema Study) aiming to test the hypothesis that a treatment strategy starting with a potent TCS during a flare-up of AD leads to faster and more efficacious results than starting with a low-potency TCS.

The Rotterdam Eczema Study was an observational cohort study with an embedded pragmatic, randomised controlled open-label trial. It was conducted in children being

treated by Dutch general practices.[6] A cohort study with an embedded trial design was chosen as it can be challenging to recruit and randomise the selection of children in primary care. This lets us follow-up and monitor the AD-affected children participating in the cohort and include them quickly in the trial in the event of a flare-up. The aim of the cohort was to determine the frequency and determinants of flare-ups of AD during a 1-year follow-up.

Recruiting patients for randomised controlled trials (RCTs) in primary care is challenging in many ways.[7 8] Two interventions where the evidence gave a high degree of certainty that they could improve recruitment were identified by the Cochrane review about strategies for improving recruitment to randomised trials.[8] These strategies are an open-trial design and telephone reminders for people who do not respond to a postal invitation. We incorporated the first of these strategies and participants received a reminder in the weekly digital questionnaire to contact their general practitioner (GP) if their AD worsened.

Nevertheless, we failed to enrol a sufficient number of patients in the trial part of the study . This article aims to communicate transparently about the failure to enrol a sufficient number of patients in our trial and to present descriptive data about the patients whom we did include in the trial. In addition, we want to determine why recruitment for the trial was unsuccessful and thereby provide information for researchers who may be considering cohort studies with an embedded RCT in future research.

METHODS

Study setting

Data were used from the Rotterdam Eczema Study. A detailed description of the study design for the Rotterdam Eczema Study has already been given.[6] Eligible children were recruited using two strategies. In the 'General Practitioner (GP) strategy', children were eligible for inclusion if they were aged between 3 months and 18 years, had AD diagnosed by a GP, and had received an AD-related consultation or prescription within the previous 12 months. All parents of children aged ≤16 and patients aged ≥12 gave informed consent. Follow-up of the cohort was for 12 months, during which patients received weekly questionnaires. Patients were also visited at baseline, after 6 months and after 12 months for objective assessment of the severity of AD using the Eczema Area and Severity Index (EASI). Inclusion for the cohort using this strategy turned out to be slower than expected, so in January 2020, we additionally started a strategy of 'open recruitment' through social media and newspapers. The same inclusion criteria were applied here as in the 'GP strategy'. However, children being treated by a specialist at the time of inclusion (eg, a dermatologist, paediatrician or allergist) were also included. The children recruited by open recruitment received the same weekly questionnaires. However, they were only visited at baseline, after 6 months and after 12 months if they lived near Rotterdam. Because of the inherent logistical challenges, patients recruited through social media were not able to participate in the trial part.

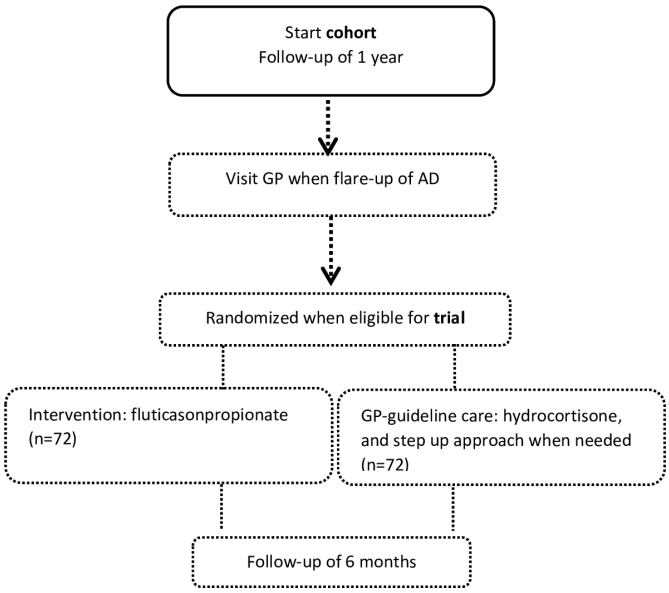

Figure 1 Flowchart of intended inclusion in the Rotterdam Eczema Study. AD, atopic dermatitis; GP, general practitioner.

If a patient in the cohort recruited via their GP experienced a flare-up during the follow-up period, they were instructed to visit their GP to check their eligibility for the trial. The GP examined the AD severity and checked the other inclusion and exclusion criteria (see online supplemental table 1). In brief, inclusion criteria for the trial were participation in the cohort, flare-up (ie, the need to intensify topical treatment) from the child's and/or parents' point of view, and a Three-Item Severity (TIS) score between 3 and 5. Patients were excluded from the trial if they had used a TCS in the 2 weeks before inclusion in the trial, had AD on their eyelids, had >50% of the body affected by AD, had other skin disorders hampering proper assessment of AD, were pregnant or breast feeding or had untreated skin infections based on clinical signs and symptoms (bacterial, viral, fungal or parasitic). If the patient was eligible for the trial, they were assigned randomly to either the intervention group (potent TCS, fluticasone propionate, once daily)) or the control group (moderately potent TCS, hydrocortisone, once daily). After 1 week, 4 weeks and 24 weeks, the children received a home visit from a researcher for inter alia an objective assessment of the AD severity using the EASI. They received a weekly online questionnaire for 24 weeks. See figure 1 for a flowchart of the study.

The weekly online questionnaire was the same for cohort and trial participants; the only difference was home visits at 1, 4 and 24 weeks during the trial follow-up whereas cohort participants visited the practice at 6 and 12 months.

To prevent patients from using any TCS they had at home if their AD worsened, they had to hand in any TCS if they were not using it at the time of the baseline visit,

and repeat prescriptions were stopped in the patient file. Throughout the follow-up period of the cohort, participants received a weekly questionnaire, with a reminder to contact their GP if their AD worsened. The above measures were taken to ensure that cohort participants would contact their GPs in the event of a flare-up so that suitability for the trial could be assessed. The inclusion and exclusion criteria for the trial can be found in online supplemental table 1. To determine the severity of AD for the inclusion criteria, the TIS score was used as recommended in the Dutch GP guideline.[9 10] The primary trial outcome was determined as the change in disease severity over 24 weeks of follow-up in the trial, as measured by the average score of the Patient-Oriented Eczema Measure (POEM; range of score: 0–28). POEM is a patient-reported outcome based on symptoms over the previous week that can be self-completed by the child's parent, the child or both together and it is part of the core outcomes for trials as determined by the Harmonising Outcome Measure for Eczema (HOME) initiative.[11]

During the study period, we noticed that inclusion rates for the trial were low. We wanted to identify the reasons for this inclusion problem. We designed a survey to find out what patients did when they had a flare-up (online supplemental file survey). The survey was designed and administered 1.5 years after the start of inclusion and was administered to patients participating in the cohort at that time and who were eligible for participating in the trial (n=86). We asked questions about four different topics: whether they had ever experienced flare-ups during the follow-up, what they did when they experienced a flare-up, what their GP did after being contacted and whether it was clear to them what they should do when they experienced flare-ups.

Patient and public involvement

It was neither appropriate nor possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research. The outcome measures of our study are based on the recommendations stated by the HOME initiative.[11] Patients were intensively involved during the development of the core outcome set and its measurement tools by this initiative. The results of our research will be disseminated to study participants through newsletters and infographics.

Table 2 POEM score of trial participants

	Randomised treatment	
	Fluticasone propionate (n=17)	**Hydrocortisone (n=15)**
Baseline, n=32	7.0 (5.5–14.5)	11.0 (8.0–16.0)

Variables are reported as median (IQR).
POEM, Patient-Oriented Eczema Measure.

Statistical methods

The calculated power for the trial, including secondary analyses and an assumed drop-out rate of 15%, gave a recommended sample size of 72 children per treatment arm (a total of 144). Descriptive statistics have been used to present baseline characteristics and the primary outcome, the POEM, for the 32 patients who participated in the trial. The response to the survey is also presented using descriptive statistics. Missing data were not included in the analyses.

RESULTS

Rotterdam Eczema Study

Inclusion took place from January 2018 to September 2020 through 53 general practices in the Netherlands and through open recruitment. A total of 367 patients were included in the cohort; 209 were recruited via general practices and 158 through social media (online supplemental figure 1). The 209 children recruited via general practices were eligible for the trial. Of these, 32 patients were eventually included in the trial and randomly assigned to a treatment. They had a mean age of 5.5 years (SD 4.8) and 40.6% were girls. In total, 15 patients were randomly assigned for treatment with hydrocortisone and 17 patients were randomly assigned to the fluticasone propionate group. For the baseline characteristics of the cohort, variables are reported as the mean (SD) and trial variables that were not normally distributed are reported

Table 1 Baseline characteristics

	Baseline, cohort, n=367 (100%)	**Baseline, cohort recruited via GP/ potentially eligible for trial, n=209 (100%)**	**Baseline, trial, n=32 (100%)**
Age in years, mean (SD)/median (IQR)	5.7 (5.0)	6.4 (5.2)	4.0 (2.0–9.8)
Sex, female, n (%)	200 (54.5%)	116 (55.5%)	13 (40.6%)
POEM, mean (SD)/median (IQR)	10.3 (6.1)	8.2 (5.6)	10.0 (6.0–15.8)
Randomised treatment, n (%)			
Hydrocortisone	–	–	15 (46.9%)
Fluticasone propionate	–	–	17 (53.1%)

GP, general practitioner; POEM, Patient-Oriented Eczema Measure.

as the median (IQR). At the trial baseline, the median POEM score was 10.5 (7.0–13.8) for the intervention group and 12.0 (8.0–17.5) for the control group (tables 1 and 2).

Survey

In total, 86 participants in the cohort who had been recruited via their GP and who were still in follow-up were invited in November 2020 to complete the survey. The other 123 patients had already finished follow-up of the cohort or had already taken part in the trial. The response rate was 80.2%; a total of 69 participants answered the survey. Of these 69 participants, 39 (56.5%) of them had suffered a flare-up during the follow-up period and only 12 of those 39 (30.7%) contacted their GPs as stated in the study protocol. Most of them started using TCS that had been prescribed before the inclusion in our study (n=20, 51.3%) or increased their use of an emollient (n=19, 48.7%). The majority of patients who contacted the GP (n=12) did not meet the inclusion criteria for the trial because their AD was mild or severe rather than moderate (n=8). Other reasons for not participating (free text) were 'we were unable to visit the GP because of COVID', 'the eczema was too bad' and 'the eczema was on the eyelids' (the two latter situations were exclusion criteria). Overall, most patients (or their parents) answered that they knew what they had to do in the event of an exacerbation of the eczema in order to participate in the trial (n=65, 92.8%). Patients' responses to this question (free text) included 'it was clear, but the doctor did not act properly', 'I didn't understand this properly' and 'we've had no contact with the GP's assistant since the start of the study' (table 3).

DISCUSSION

Summary

A total of 367 patients were included in the cohort of the Rotterdam Eczema Study, of whom 209 patients were recruited throughout GP practices and were potentially

Table 3 Survey and results for the 69 respondents

Question	Answer options	Total, n=69 (100%)
1a. In the period during which my child or I participated in the study, the eczema worsened one or more times (=a flare-up).	Yes	39 (56.5)
	No	30 (43.5)
1b. If yes, what did you do when the eczema got worse? (*multiple answers possible*)	Did nothing, the AD was not so severe	5
	Increased the use of emollients	19
	Started TCS ointment ourselves	20
	Contacted the GP	12
	Other, namely: (free text)	0
1c. When I contacted the GP, I mentioned that my child/I was participating in the Rotterdam Eczema Study.	Yes	12
	No	0
1d. If you contacted the GP, they: (*multiple answers possible*)	Thought the eczema was mild and started treatment	4
	Thought the eczema was severe and started treatment	4
	Was not available, I could not make an appointment	0
	Issued a repeat prescription	4
	Suggested enrolling in Part 2 of the study (the trial), which I did not want to do because: (*free text*)	0
	Other, namely: (*free text*)	4 answers*
2a. It was clear to me what I had to do in the event of an exacerbation of the eczema in order to participate in Part 2 of the study (the trial):	Yes	64 (92.8%)
	No	5 (7.2%)
2b. If no, what was unclear?	Other, namely: (*free text*)	*5 answers***

1b, 1c, 1d were fly-out questions that appeared if the answer to 1a was 'yes'. 2b was a fly-out question that appeared if the answer to 2a was 'no'.
* 'eczema was too bad', 'we were unable to visit the GP because of COVID', 'eczema was on the eyelids' and 'eczema was mild'
** 'it was clear, but the doctor did not act properly', 'I only take part in the cohort study, not in the trial', 'I guess I didn't understand this properly', 'we've had no contact with the GP's assistant since the start of the study' and 'I was especially confused by the informational e-mail we received about participating in the trial'
AD, atopic dermatitis; GP, general practitioner; TCS, topical corticosteroid.

eligible for the trial. Only 32 patients were ultimately selected for the trial and randomly assigned to a treatment arm. It was not possible to enrol enough participants despite reminders and additional information about the study procedure throughout the follow-up. Most of the participants did know what to do when they had a flare-up (92.8%). The majority of the patients in the cohort who completed the survey experienced a flare-up (56.5%); the main reason for failure to enrol a sufficient number of patients in the trial was that cohort participants did not contact their GPs when they had an AD flare-up. When participants did contact their GPs, most of them did not meet all the inclusion criteria for participation in the trial. The majority of the patients treated the flare-up themselves.

Strengths and limitations

A strength of the survey was that it gave us an understanding of the patients' behaviour when they experienced a flare-up. These findings have let us make suggestions that may lead to better and more effective ways of recruiting trial participants in future studies in primary care. The low rates of trial participation may be attributed to selection bias, as patients with an understanding of their condition and who were more proactive in starting treatment were more likely to be enrolled in the cohort and therefore did not join the trial. A limitation of the survey is that we did not ask in depth why participants did not contact their GP. This makes it more difficult to comprehend the main reason for the trial's failure fully.

Comparison with existing literature

Recruiting patients for RCTs in primary care is known to be difficult in a variety of ways.[7 8] One of the interventions suggested by the Cochrane evaluation of methods to increase recruitment to randomised trials is using an open-trial design; this was also part of our study design.[8] Furthermore, the Cochrane review suggests telephone follow-ups for those who do not reply to a postal invitation but our participants got a reminder in the weekly online survey to call their GP if their AD got worse. In retrospect, telephone reminders would probably have been more effective for our study. A recent study by Knapp *et al* found that multimedia information only (eg, animations and videos) increased the trial recruitment rate in children and young people compared with participant information sheets for trial recruitment.[12] We used printed participant information only. However, the children in our study were already participating in a cohort study but maybe would have been more able and more willing to participate in the trial if multimedia information had been given.

We used a case-finding method in our study to recruit patients through general practices. When it turned out that inclusion for the cohort was behind schedule, we started recruitment through social media and a newspaper.[6] Research by van der Worp *et al* showed largely comparable samples for recruitment throughout the media versus case-finding.[13] That study was carried out in a comparable setting in Dutch general practice. Baker *et al* found that paid and unpaid social media recruitment could be an efficient tool that can potentially assist recruitment to clinical trials in AD.[14] One solution could be to recruit solely through social media and at the same time increase the sample size of the cohort so that it would finally include more patients in the trial. However, to get a comparable patient selection, inclusion and exclusion criteria should be properly decided. To ensure that selection bias is minimised, it should be verified that the patient characteristics in primary care and open recruitment are identical. It should also be possible to overcome the logistical issue with medical supervision. When patients are recruited via their own GPs, the GP must have confirmed their willingness to take part in the research, and is responsible for the patient's treatment and management. The GP can provide prescriptions and is the point of contact if the treatment is not effective. When patients are recruited through social media, that responsibility needs to be transferred to a physician in the research team.

A good example is the Panoramic trial of Butler *et al*. This was a nationwide, multicentre, primary care, open-label, multigroup, prospective, platform adaptive trial of early treatments for COVID-19 in the UK. They successfully included more than 10 000 patients.[15] They included patients not only via the central trial team but also via hubs; these included GP Sites, Community Trusts and other health service providers, including government agencies for example, the UK Health Security Agency. A medically qualified professional, research nurse, nurse prescriber or prescribing pharmacist from the hub was able to complete all recruitment procedures, screening, baseline, informed consent and eligibility reviews. Furthermore, they also could provide the patient with the medication being studied. Although this trial had a larger budget and studied a potentially deadly disease with a high impact, it could be an interesting option to use the structure of hubs with medically qualified professionals to recruit patients for trials nationwide.

In our study, participants were told what to do in the event of an exacerbation of the AD in order to be included in the trial (92.8%), but a substantial number of patients did not contact their GPs when they experienced a flare-up (69.2%). Most of them started treating the flare-up themselves. This meant that participants did have a TCS at home, whereas the protocol stated that participants had to hand in any TCS they had at home during the cohort baseline visit if they did not use a TCS at baseline. They did not have to hand in the medication if they were doing maintenance therapy or treating a flare-up. Based on our baseline data, 49% of the children used a TCS at baseline, so this substantial group of participants probably had a TCS at home.[16] One of the reasons for not contacting their GPs could be that if patients experienced a flare-up, it was probably more convenient to start a TCS

they had at home than schedule a consultation with the GP. Or maybe they reconsidered participation when a flare-up of the AD occurred. In addition, an increase in AD symptoms might not have been noticed as a flare-up by parents/patients because it was assumed to be typical fluctuation of a well-known disease.

Furthermore, our window of inclusion covered the beginning of the COVID-19 pandemic. It is known that the number of consultations declined substantially compared with pre-pandemic levels.[17] It was stated in the survey that COVID-19 was one reason why patients could not visit the GP when experiencing a flare-up. It is likely that patients did not want to burden the healthcare system unnecessarily during the pandemic or that the appointment was scheduled after too many days. This could have led to higher rates of patients who started treating the flare-up themselves.

Also, the high burden for trial participants could be a reason for failure to enrol.[18] The burden of participating in our trial consisted of a consultation with the GP and three home visits.[6] Patients had to contact the practice themselves to arrange an appointment with their GP. They might have had to wait 1 or 2 days before they could arrange an appointment, especially during the COVID-19 period. Additionally, the multicentre design resulted in one or only a few patients from each participating GP practice. This could have led to less awareness among the GPs and/or GP assistants about what to do when a participant was experiencing a flare-up. This was also mentioned in the survey. Moreover, the consultation with the GP was needed for going through the inclusion and exclusion criteria of the trial and objectively assessing the severity of the AD; this could also be one of the barriers that hampered contact with the GP during a flare-up. This barrier could be resolved by transferring those responsibilities to the research team and making them also available during out-of-office hours. In addition, digital photographs could be used to remotely assess the severity of AD. Studies with these methods are promising.[19 20]

Because their AD was mild or severe rather than moderate, the majority of patients who contacted their GP did not satisfy the trial's inclusion criteria. One reason for this could be that our eligibility criteria were too narrowly defined. Narrow eligibility criteria and an overestimation of prevalence are known reasons for unsuccessful recruitment.[18 21] We selected children with moderate eczema because we did not want to overtreat or undertreat them with the intervention and control treatments. Another reason for poor recruitment could be that we overestimated the prevalence of moderate AD in children. However, the baseline data of the cohort showed that mean AD severity was moderate on the POEM scale, so this does not seem to have been the problem. The survey showed that 56.6% of the participants in the cohort experienced a flare-up. If we had been able to recruit the cohort sample size through the GP practices, it would have been feasible to reach the desired trial sample size given the numbers and severity of AD cases in the cohort.

Box 1 Summary of recommendations for future research in children in general practice with AD

Recommendations for future research

Conduct a feasibility study
Choose inclusion criteria carefully
Responsible physician/nurse should be in the research team to supervise the treatment
Assess severity of AD digitally (via photos)
Deliver randomised medication to the home
Patient recruitment through social media or mobile research team
Telephone reminders for cohort patients

Implications for future research

We would like to present some suggestions for an improved design and a more successful way to answer the important research question of whether starting with a potent TCS during a flare-up of AD is more efficacious than starting with a low-potency TCS in children in primary care. See the summary in box 1.

First, responsibility for the patients' AD should be transferred from their own GP through hubs to a physician in the research team or to a medically qualified professional such as a research nurse, as shown by Butler *et al*.[15] Second, we consider the recruitment method. As discussed above, our own study and the literature show social media recruitment to be an effective way of including patients.[13 14] Third, we suggest assessing the severity of AD digitally; the literature has shown that this is a promising alternative.[19 20] Finally, we recommend implementing a direct medication delivery service to patients to eliminate the need for pharmacy visits. However, the GP or study team should verify the inclusion and exclusion criteria before randomisation. Eliminating the need for the patient to schedule an appointment with their doctor and visit the pharmacy makes it possible to reduce the time between the onset of the flare-up and the start of the randomised treatment. However, these recommendations are not absolute and depend on several factors, including the available budget, the condition being studied and the target patient group. We advise conducting a feasibility study to test a design that incorporates these modifications.

CONCLUSION

Although the cohort part of the Rotterdam Eczema Study successfully included 367 children with AD, we were unable to reach the target for the trial. We hope that the lessons learnt from this study will be useful in developing future studies in young patients with AD who are being treated in primary care.

Contributors KFvH, GE and AMB conceived the study and initial study design in collaboration with PJEB and SGMAP. KFvH and AMB conducted the analyses. All the authors contributed to the drafting of this paper, led by KFvH and approved the final manuscript. KFvH is the guarantor and accepts full responsibillity for this work. The corresponding author attests that all listed authorsmeet authorship criteria and that no others meeting the criteria have been omitted.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Medical Ethics Committee (MEC) of the Erasmus Medical Center Rotterdam approved the protocol (MEC-2017-328). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Consent was not obtained from participants for data sharing. Authors will consider reasonable request to make relevant anonymised participant level data available.

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