Standardised training for endoscopic mucosal resection of large non-pedunculated colorectal polyps to reduce recurrence (*STAR-LNPCP study) a multicentre cluster randomised trial

Meulen, L.W.T.; Bogie, R.M.M.; Siersema, P.D.; Winkens, B.; Vlug, M.S.; Wolfhagen, F.H.J.; ... ; Moons, L.M.G.

Original research

Standardised training for endoscopic mucosal resection of large non-pedunculated colorectal polyps to reduce recurrence (*STAR-LNPCP study): a multicentre cluster randomised trial

Lonne W T Meulen ,[1,2] Roel M M Bogie,[1,2] Peter D Siersema,[3] Bjorn Winkens,[4,5] Marije S Vlug,[6] Frank H J Wolfhagen,[7] Martine Baven-Pronk,[8] Michael van der Voorn,[9] Matthijs P Schwartz,[10] Lauran Vogelaar,[11] Wouter H de Vos tot Nederveen Cappel,[12] Tom C J Seerden,[13] Wouter L Hazen,[14] Ruud W M Schrauwen,[15] Lorenza Alvarez Herrero,[16] Ramon-Michel M Schreuder,[17] Annick B van Nunen,[18] Esther Stoop,[19] Gijs J de Bruin,[20] Philip Bos,[21] Willem A Marsman,[22] Edith Kuiper,[23] Marc de Bièvre,[24] Yasser A Alderlieste,[25] Robert Roomer,[26] John Groen,[27] Marloes Bargeman,[28] Monique E van Leerdam ,[29,30] Linda Roberts-Bos,[31] Femke Boersma,[32] Karsten Thurnau,[33] Roland S de Vries,[34] Jos M Ramaker,[35] Frank P Vleggaar,[36] Rogier J de Ridder,[1] María Pellisé ,[37] Michael J Bourke ,[38] Ad A M Masclee,[1] Leon M G Moons [36]

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For numbered affiliations see end of article.

Correspondence to
Dr Leon M G Moons, Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, 3508 GA, Netherlands; L.M.G.Moons@umcutrecht.nl

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ABSTRACT

Objective Endoscopic mucosal resection (EMR) is the preferred treatment for non-invasive large (≥20 mm) non-pedunculated colorectal polyps (LNPCPs) but is associated with an early recurrence rate of up to 30%. We evaluated whether standardised EMR training could reduce recurrence rates in Dutch community hospitals.

Design In this multicentre cluster randomised trial, 59 endoscopists from 30 hospitals were randomly assigned to the intervention group (e-learning and 2-day training including hands-on session) or control group. From April 2019 to August 2021, all consecutive EMR-treated LNPCPs were included. Primary endpoint was recurrence rate after 6 months.

Results A total of 1412 LNPCPs were included; 699 in the intervention group and 713 in the control group (median size 30 mm vs 30 mm, 45% vs 52% size, morphology, site and access (SMSA) score IV, 64% vs 64% proximal location). Recurrence rates were lower in the intervention group compared with controls (13% vs 25%, OR 0.43; 95% CI 0.23 to 0.78; p=0.005) with similar complication rates (8% vs 9%, OR 0.93; 95% CI 0.64 to 1.36; p=0.720). Recurrences were more often unifocal in the intervention group (92% vs 76%; p=0.006). In sensitivity analysis, the benefit of the intervention on recurrence rate was only observed in the 20–40 mm LNPCPs (5% vs 20% in 20–29 mm, p=0.001; 10% vs 21% in 30–39 mm, p=0.013) but less evident in ≥40 mm LNPCPs (24% vs 31%; p=0.151). In a post hoc analysis, the training effect was maintained in the study group, while in the control group the recurrence rate remained high.

Conclusion A compact standardised EMR training for LNPCPs significantly reduced recurrences in community hospitals. This strongly argues for a national dedicated training programme for endoscopists performing EMR of ≥20 mm LNPCPs.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Endoscopic mucosal resection (EMR) of large non-pedunculated colorectal polyps (LNPCP) is accompanied by a high recurrence rate. In tertiary centres, recent advances have made it possible to reduce recurrence significantly. Results on community level are, however, unknown.

WHAT THIS STUDY ADDS

⇒ This study shows that implementation of a compact, standardised EMR training can improve results of EMR of LNPCPs on community level significantly. For LNPCPs ≥40 mm in size, this effect is less extensive than for LNPCPs 20–40 mm in size.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on these results, routine implementation of a standardised EMR training on a national level is advised to optimise outcomes of EMR of LNPCPs. For ≥40 mm LNPCPs, centralisation should be considered to increase annual exposure and optimise learning curves and outcomes.

Interestingly, in sensitivity analysis, this benefit was limited for LNPCPs ≥40 mm.

Trial registration number NTR7477.

INTRODUCTION

Large (≥20 mm) non-pedunculated colorectal polyps (LNPCPs) are prevalent in current endoscopy practice, especially after the introduction of colorectal cancer (CRC) screening programmes.[1] While endoscopic mucosal resection (EMR) is the preferred treatment for non-invasive LNPCPs, especially above the rectum, recurrence rates of up to 30% have been reported.[2 3] Recurrences need additional treatment, resulting in additional follow-up endoscopies, and may even necessitate surgery, increasing the burden for patients and healthcare resources.

Recurrences depend on the size and complexity of the lesion,[2–4] but also on the experience of the endoscopist. More recently, recurrence rates as low as 1.4% were obtained in expert centres by improved EMR techniques and adding adjuvant thermal ablation of post-EMR margins.[5 6] Although outcomes in expert centres appear to be good, recurrence rates at community level remain much higher.[1 7–9] Therefore, standardised training programmes and EMR assessment tools to ensure high-quality training are necessary to improve the management of LNPCPs on a national level.

Which format training should take remains uncertain. Bhurwal *et al* showed that overall rates of incomplete R1 resection and residual neoplasia at follow-up decreased to below 20–25% after 100 EMRs.[10] Yang *et al* evaluated EMR competence in six advanced endoscopy fellows and showed that only two of them (33%) achieved competence on key cognitive (ie, indications/contraindications, benefits, risks, limitations of the procedure, components of pre-endoscopic evaluation and postprocedural care) and technical aspects of colonic EMR during a 12-month fellowship.[11] It therefore seems unlikely that the current training and exposure of community endoscopists is sufficient to provide them with the requisite knowledge and skills to safely and adequately treat LNPCPs with EMR. This deficiency may lead to primary surgical referral and drive unnecessary completion surgery, with evidence of significant morbidity and costs.[12 13] Whether short-term, intensive training can improve outcomes among community endoscopists is currently unknown.

We evaluated whether standardised, stepwise training of community endoscopists in EMR of LNPCPs can decrease post-EMR recurrence rates at 6 months in a multicentre cluster randomised trial. A cluster design was used to avoid contamination between endoscopists within centres.

METHODS

This study was conducted in the Netherlands, where 69 hospitals are located, of which eight are university medical (tertiary) centres. A total of 30 hospitals participated in this cluster randomised trial. We hypothesised that a compact standardised EMR training for community endoscopists should reduce the risk of recurrence by 50%, from 20% in the control group to 10% in the intervention group. This study is reported according to the Consolidated Standards of Reporting Trials guidelines and extension for cluster randomised trials.[14]

Study design

In this multicentre cluster randomised trial, 59 community endoscopists from 30 hospitals participated. The hospitals were asked to nominate their endoscopists dedicated to EMR of LNPCPs within their centre. Sixteen hospitals delivered two participating endoscopists, whereas eight hospitals delivered only one endoscopist and another six hospitals delivered three or four endoscopists. To determine the experience of each participating centre, all participating endoscopists were asked to fill in a prerandomisation questionnaire about their experience as gastroenterologists and their dedication to large polypectomies (online supplemental table 1). Each endoscopist could score between 2 and 11, and this score was used as randomisation factor.

Stratified block randomisation on centre level was performed by LWTM, with varying block sizes of 4 and 6, using Sealed Envelope.[15] Strata used for randomisation were: (1) number of participating endoscopists per centre and (2) experience in a centre based on the sum value of prerandomisation questionnaires (online supplemental table 1).

Intervention and e-learning modules

Participating centres were randomly assigned to an intervention or control group. The intervention group received 2 days of teaching sessions by experts (MP, MB, LMGM) on EMR of LNPCPs, including lectures by experts, a hands-on session and case-based discussions. Furthermore, e-learning modules about all aspects of EMR were developed by experts in the field, based on predefined learning goals (online supplemental material 2). After the 2-day teaching sessions, all participants in the intervention group got access to an online platform where these e-learning modules could be viewed.

Endoscopists of both intervention and control groups received access to an e-learning regarding the identification of the post-EMR scar, differentiating recurrence from post-EMR scar clip artefact, and explaining the standardised protocol of scar biopsy used for this trial.

Source population

From April 2019 to August 2021, all consecutive non-invasive LNPCPs, suitable for EMR, were included in this study. Inclusion criteria were the patient's age of 18 years or older and the presence of an LNPCP suitable for EMR. Exclusion criteria were IBD, suspicion of submucosal invasion and inability to provide informed consent.

All patients provided written informed consent prior to the study. The study was registered at the International Clinical Trial Registry Platform (NTR7477). Due to reorganisation of the Dutch patient organisation, patients were not involved in in this research at their own request.

Patient, lesion and treatment characteristics

Patient characteristics such as age, gender, American Society of Anesthesiologists (ASA) classification, medication use and medical history were obtained from the patient's record charts. Lesion and treatment characteristics were documented by the endoscopists using a standardised report form. Lesion characteristics consisted of size, location, morphology, accessibility, enhanced imaging (Hiroshima/Kudo/Japanese NBI Expert Team (JNET) classification), presence of spontaneous bleeding, optical diagnosis with level of confidence and estimated risk of T1 CRC (using the OPTICAL model).[16] The SMSA score was calculated based on the registered Size, Morphology, Site and Access in the endoscopy reports.[17] Treatment characteristics consisted of injection fluid (colloid, dye, epinephrine), Kato lifting, piecemeal/en bloc, number of pieces, type of snare, presence of submucosal fibrosis, presence and adjunctive treatment

of residual tissue after snaring, margin thermal ablation, the difficulty of the procedure, presence and treatment of intraprocedural bleeding, and assessment and potential treatment of deep mural injury (DMI).

In addition to this standardised report form, endoscopists were asked to take photos of the different stages of the EMR in white light, with near focus and with advanced imaging.

In case there was more than one LNPCP present in a patient, we randomly included one of them in this study.

Post-EMR surveillance

Surveillance was performed after 6 months[2] by the same endoscopist or a colleague participating in the study. A standardised protocol was followed during the assessment of the EMR scar, which included photography of the scar in white light, with zoom/near focus and an advanced imaging technique such as narrow-band imaging, virtual chromoendoscopy or blue-light imaging. The scar was carefully assessed for recurrent neoplastic tissue and characteristics were documented (eg, size and location). All imaging of the scars was independently reviewed by a second reviewer, masked to treatment allocation. Recurrence was defined as all visible neoplastic tissue in and around the scar (within 5 mm). When endoscopic recurrence was present, this was treated and documented in the endoscopy report. When there were no signs of recurrence, biopsies were taken according to a standardised biopsy protocol: depending on the size and shape of the scar (eg, straight line or round), one to three biopsies were taken from the centre and at least one biopsy per quadrant in the periphery of the scar. Biopsies from the centre and periphery were separately presented for histological evaluation.

Outcomes

Primary outcome was recurrence rate after 6 months. Recurrence rates were compared between intervention and control groups. The secondary aims were to compare recurrence rates for different lesion size groups (20–29, 30–39 and ≥40 mm) and to compare endoscopic resection technical characteristics (eg, lifting fluid, number of pieces, adjunctive treatment, margin thermal ablation) and complication rates between the intervention and control groups. Complication was defined as any procedure-related event resulting in (1) presentation at the emergency department, (2) the need for admission or an unplanned start of analgetics or antibiotics, (3) the need for additional treatments such as repeated colonoscopy, endovascular treatment or surgery and (4) death. Full-thickness wall defects (Sydney DMI classifications IV and V) were also considered complications.

Early postpolypectomy bleeding was defined as GI bleeding within 24 hours. Delayed bleeding was defined as GI bleeding >24 hours after EMR. Perforation was defined as Sydney DMI type IV and type V or clinical presentation of perforation (abdominal pain with presence of free intra-abdominal air on CT of the abdomen). Postpolypectomy syndrome was defined as the clinical syndrome of abdominal pain, fever and leucocytosis, with the absence of a perforation.

Intraprocedural adverse events were defined as any unintentional event such as intraprocedural bleeding, or damage to the muscularis propria, which were successfully treated during the procedure without the need for postprocedural measures.

The Adverse Events Gastrointestinal Endoscopy (AGREE) classification was used to describe the clinical consequences of the intraprocedural adverse events and complications.[18]

Statistical analysis

For descriptive statistics, categorical variables are presented as numbers and percentages, and numerical variables as means with SD or medians with IQR. Pearson's χ^2 test and Fisher's exact test were used to compare groups regarding endoscopic resection characteristics. Generalised linear mixed models with logit link were used to assess differences in binary outcomes (recurrence and complication rate) between groups. A random intercept on centre level was included to account for the correlation between patients within the same centre. Since only one LNPCP per patient was included in these analyses, there was no clustering of LNPCPs within patients. As for the fixed part, next to group (intervention or control) we included the stratification variables (experience and number of participating endoscopists per centre), SMSA score, sessile serrated histology and ASA classification. No multiple imputation was used, as missing outcome data were accounted for by the maximum likelihood-based method, which assumes missing at random (MAR). To ensure MAR (missing values depend only on observed variables), variables related to missing values were included in the analysis model: SMSA score and ASA classification. The reasons for missings were recorded to check whether the missings are likely to be dependent on observed and/or unobserved variables, the latter implies missing not at random. The reasons showed that the missings were probably related to observed aforementioned variables, indicating that the MAR assumption is justifiable. As post hoc analyses, we evaluated whether the intervention effect depended on lesion size (20–29, 30–39, ≥40) by adding an interaction between group and lesion size to the model, where SMSA score was removed due to expected strong correlation with lesion size. A two-sided p value ≤0.05 was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics V.27.0.0.

Sample size consideration

The sample size was based on the estimated a priori risk for recurrence of approximately 20% after 6 months,[2 3] and the hypothesis that training will reduce this risk by 50%. After correction for the design effect (=1+(m-1)*ICC, where intraclass correlation coefficient (ICC)=0.025,[19] and the mean number of patients per endoscopist is 35; ie, m=35), 10% loss in efficiency due to the variation in the number of colonoscopies performed during the study period per endoscopist[20] and a 20% dropout risk for patients with LNPCP, the number of LNPCP cases required to detect a difference of 10% (20% local recurrence in the control group vs 10% in the intervention group) with a power of 90% and using a significance-level alpha of 5% is 683 per group.

RESULTS

Clusters

There were 30 clusters in this trial; 15 in the intervention group and 15 in the control group. Characteristics at cluster level are presented in online supplemental table 2.

Baseline characteristics

In total, 1412 consecutive LNPCPs were eligible for inclusion. Finally, a total of 1390 LNPCPs (98%) underwent EMR. In the remaining 2% of cases, LNPCPs were managed by endoscopic full-thickness resection, endoscopic submucosal dissection or primary surgery due to suspicion of CRC during reassessment.

From the 1277 lesions (90%) that underwent 6-month follow-up endoscopy, the post-EMR scar was identified in 1215

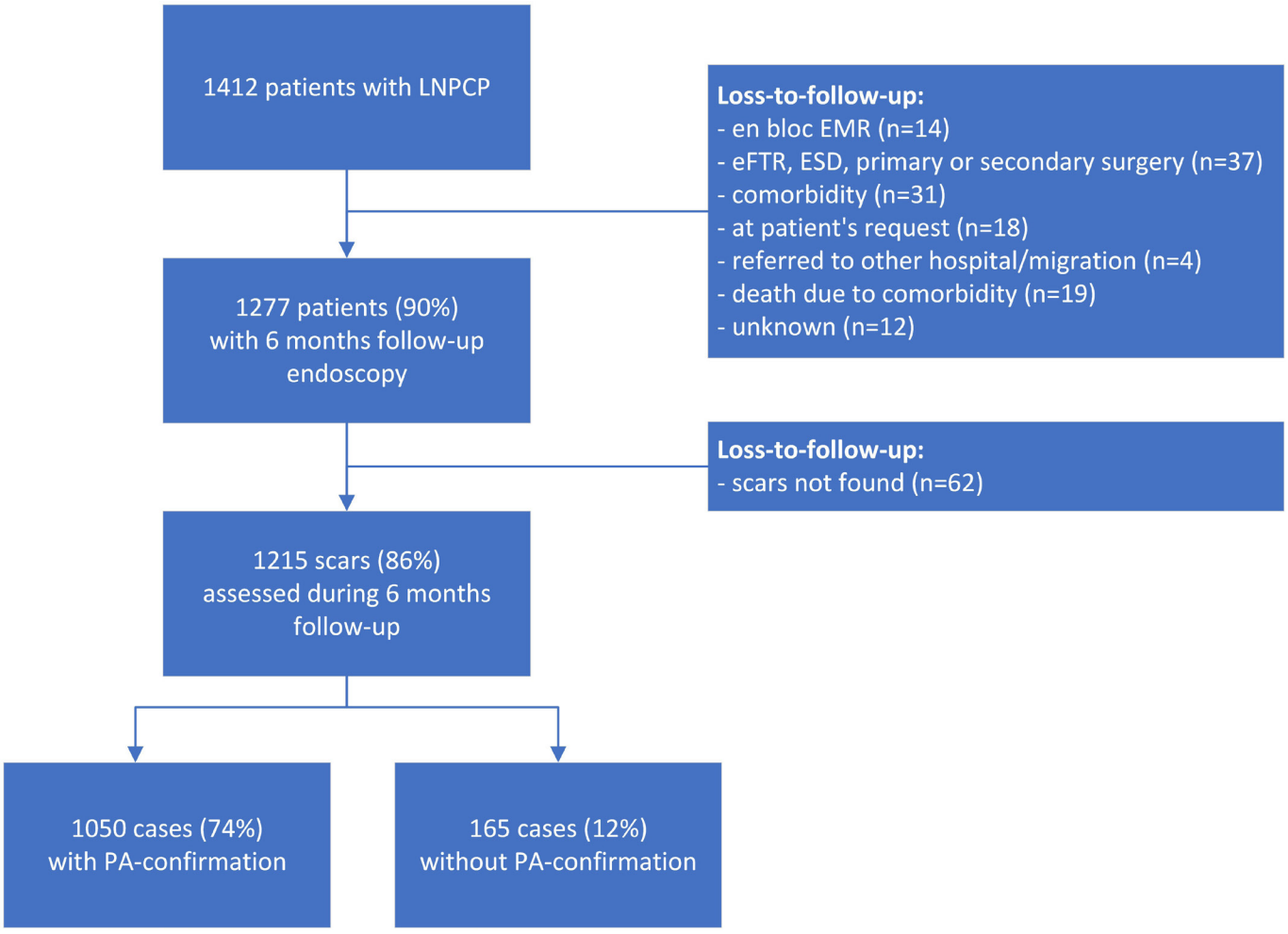

Figure 1 Study flow chart. eFTR, endoscopic full-thickness resection; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; LNPCP, large non-pedunculated colorectal polyp; PA, pathology.

(86%) and biopsied in 1050 cases (74%) (figure 1). There was no significant difference in the proportion of lesions that were loss to follow-up between the intervention and control groups.

Patient and lesion characteristics are presented in table 1. Mean age of the total group was 68 (SD 9) years and 45% was female. The median size of LNPCPs was 30 mm (p25–p75: 25–40), 64% were located in the proximal colon and 48% were SMSA IV.

There were no significant differences in experience and dedication of endoscopists between the intervention and control groups (online supplemental table 3). There were also no significant differences in centre characteristics between the intervention and control groups (online supplemental table 4).

Endoscopic resection technical characteristics

Differences in endoscopic resection technical characteristics between groups are shown in table 2. In the intervention group, the use of colloid lifting fluid instead of normal saline (87% vs 63%; p<0.001), the addition of epinephrine to the lifting fluid (73% vs 41%; p<0.001), identification of residual tissue after snaring (24% vs 18%; p=0.003), performing adjunctive treatment (100% vs 92%; p<0.001) and performing margin thermal ablation (92% vs 75%; p<0.001) were more common compared with the control group.

Recurrence rate

The overall recurrence rate after 6 months was 19%, with a significant difference between intervention group (13%) and control group (25%) (OR 0.43; 95% CI 0.23 to 0.78) (table 3). The overall recurrence rate increased with increasing lesion size, from 12% in 20–29 mm lesions to 15% in 30–39 mm lesions and 28% in ≥40 mm lesions.

Although the interaction between the intervention and size was not statistically significant (p=0.056), the difference in recurrence rate between the intervention and control groups decreased with increasing lesion size, from 15% difference (5% vs 20%) in 20–29 mm lesions (OR 0.20; 95% CI 0.08 to 0.52; p=0.001) to 11% (10% vs 21%) in 30–39 mm lesions (OR 0.36; 95% CI 0.16 to 0.81; p=0.013) and 7% (24% vs 31%) in ≥40 mm lesions (0.61; 95% CI 0.31 to 1.20; p=0.151).

In total, 200 recurrences were detected at 6 months. In most cases, recurrences occurred in proximal lesions (132/200; 66%) and SMSA IV lesions (132/200; 66%) (table 4). Recurrences were small, with a mean size of 6 mm, and were mostly unifocal (82%). Fewer multifocal recurrences were seen in the intervention group compared with the control group (8% vs 24%; p=0.006). Comparing intervention and control groups, the proportion of recurrences treated by conventional polypectomy was higher

Table 1 Baseline patient, colonoscopy and lesion characteristics

	Total (n=1412)	Intervention group (n=699)	Control group (n=713)
Patient characteristics			
Age in years, mean (SD)	68 (8.7)	68 (8.9)	68 (8.6)
Female gender, n (%)	638 (45)	326 (47)	312 (44)
Body mass index, mean (SD)	26.8 (4.9)	26.7 (4.5)	26.9 (5.3)
ASA classification, n (%)			
ASA I–II	1214 (86)	598 (86)	616 (86)
ASA III–IV	198 (14)	101 (14)	97 (14)
Anticoagulant use, n (%)	452 (32)	216 (31)	236 (33)
Colonoscopy characteristics			
Boston Bowel Preparation Score (BBPS) ≥2 per inspected segment, n (%)	1384 (98)	691 (99)	693 (97)
Indication colonoscopy, n (%)			
Screening	578 (41)	308 (44)	270 (38)
Surveillance	202 (14)	82 (12)	120 (17)
Symptomatic	410 (29)	230 (33)	180 (25)
Referred for intervention	222 (16)	79 (11)	143 (20)
Lesion characteristics			
Size in mm, mean (SD)	36 (16)	35 (14)	37 (18)
Size in mm, median (p25–p75)	30 (25–40)	30 (25–40)	30 (25–40)
Size groups, n (%)			
20–29 mm	448 (32)	240 (34)	208 (29)
30–39 mm	441 (31)	222 (32)	219 (31)
≥40 mm	523 (37)	237 (34)	286 (40)
Proximal location, n (%)	904 (64)	447 (64)	457 (64)
Paris type, n (%)			
Is	632 (45)	370 (53)	262 (37)
IIa	477 (34)	203 (29)	274 (38)
IIb	31 (2)	10 (1)	21 (3)
IIc	2 (0.1)	1 (0.1)	1 (0.1)
IIa+c	23 (2)	15 (2)	8 (1)
IIa+Is	247 (18)	100 (14)	147 (21)
SMSA score, n (%)			
SMSA II	78 (6)	45 (6)	33 (5)
SMSA III	652 (46)	341 (49)	311 (44)
SMSA IV	682 (48)	313 (45)	369 (52)
Granularity, n (%)			
Homogeneous granular	745 (53)	365 (52)	380 (53)
Non-granular	354 (25)	171 (25)	183 (26)
Granular with >10 mm nodule	292 (21)	153 (22)	139 (19)
Granular with non-granular area	21 (2)	10 (1)	11 (2)
Depression, n (%)	86 (6)	44 (6)	42 (6)
Hiroshima classification*, n (%)			
Hiroshima A	117 (8)	58 (8)	59 (8)
Hiroshima B	1138 (82)	577 (83)	561 (80)
Hiroshima C1	119 (9)	52 (8)	67 (10)
Hiroshima C2	13 (1)	5 (1)	8 (1)
Hiroshima C3	6 (0.4)	2 (0.3)	4 (0.6)
Spontaneous bleeding, n (%)	81 (6)	30 (4)	51 (7)

*19 cases missing Hiroshima classification.
ASA, American Society of Anesthesiologists; SMSA, Size, Morphology, Site and Access.

in the intervention group, while the proportion of recurrences treated by re-EMR was higher in the control group (p=0.003).

Recurrence rate at cluster level is presented in online supplemental figure 1A,B. No significant increase was observed during the 3 years after training (only pathology (PA)-confirmed scars (n=543) 12%-13%-16%, p=0.604; all assessed scars (n=613) 11%-12%-13%, p=0.736). For the control group, also no significant increase or decrease in recurrence rate was observed during the 3-year study period (only PA-confirmed scars (n=500) 24%-26%-26%, p=0.954; all assessed scars (n=593) 20%-22%-22%, p=0.789).

Adverse events and complications

The intraprocedural adverse event rate was similar in the intervention and control groups (29% vs 35%; p=0.258) (table 3). There were 443 EMR procedures with intraprocedural adverse events. In 431 (97%) of these procedures there was intraprocedural bleeding, which was a constraint for the overview during the procedure in only 44 (10%) of cases. In 19 (4%) of the EMR procedures there was a Sydney DMI type III mucosal injury (target sign).

The complication rate was similar in both groups (8% vs 9%; p=0.720) (table 3). Perforation was present in six cases (1%) in the intervention group and in five cases (1%) in the control group. In one case (intervention group), the perforation was not recognised during the procedure. This unrecognised perforation led to emergency surgical intervention to close the defect. In the other 10 cases, the perforation was closed with clips intraprocedural and led to hospital admission for >3 hours in only one case.

In only three of the 24 cases (13%) with perforation or post-polypectomy syndrome, antibiotic treatment was started.

Delayed bleeding developed in 56 cases, of whom 41 cases (73%) used anticoagulants. Clinical consequences of delayed bleeding were presentation at the emergency department in 37 cases (66%), transfusion of erythrocyte concentrates in 2 cases (4%) and endoscopic intervention in 17 cases (30%). In 11/17 (65%) cases, endoclips were used to stop active bleeding.

AGREE classification did not show any significant differences between groups (p=0.066; table 2).

DISCUSSION

In this multicentre cluster randomised trial, we showed that a compact structured EMR training of community endoscopists decreased the recurrence rate by almost 50% (13% vs 25%, OR 0.43; 95% CI 0.23 to 0.78; p=0.005). In addition, recurrences were more often unifocal in the intervention group compared with the control group (92% vs 76%; p=0.006). While the effect of a structured training on recurrence rates was evident in

Table 2 Endoscopic resection characteristics

	Total* (n=1390)	Intervention group (n=694)	Control group (n=696)	P value
Colloid lifting fluid, n (%)	1039 (74)	603 (87)	436 (63)	<0.001
Epinephrine added to lifting fluid, n (%)	794 (57)	508 (73)	286 (41)	<0.001
Piecemeal resection, n (%)	1323 (94)	667 (96)	656 (94)	0.106
Number of pieces, n (%)				0.305
2	99 (8)	45 (7)	54 (8)	
3	155 (12)	88 (13)	67 (10)	
4	176 (13)	94 (14)	82 (13)	
5–10	612 (46)	305 (46)	307 (47)	
>10	281 (21)	135 (20)	146 (22)	
Submucosal fibrosis present, n (%)	235 (17)	117 (17)	118 (17)	0.962
Residual tissue after snaring, n (%)	288 (21)	166 (24)	122 (18)	0.003
Adjunct treatment for residual tissue, n (%)	278/288 (97)	166/166 (100)	112/122 (92)	<0.001
Adjunct modality, n (%)				<0.001
Snare tip soft coagulation	86 (31)	56 (34)	30 (27)	
Argon plasma coagulation	24 (9)	2 (1)	22 (20)	
CAST	93 (34)	63 (38)	30 (27)	
Cold avulsion	48 (17)	31 (19)	17 (15)	
Hot avulsion	13 (5)	4 (2)	9 (8)	
Suck and snare	14 (5)	10 (6)	4 (4)	
Margin thermal ablation, n (%)	1165 (84)	640 (92)	525 (75)	<0.001
Margin thermal ablation modality, n (%)				<0.001
Snare tip soft coagulation	1049 (90)	630 (98)	419 (80)	
Argon plasma coagulation	116 (10)	10 (2)	106 (20)	
Intraprocedural bleeding, n (%)	431 (31)	198 (29)	233 (33)	0.129
Management IPB, n (%)				0.572
Snare tip soft coagulation	287 (67)	132 (67)	155 (67)	
Coagulation grasper	70 (16)	35 (18)	35 (15)	
Epinephrine injection	14 (3)	3 (2)	11 (5)	
Haemoclip	21 (5)	11 (6)	10 (4)	
STSC+haemoclip	30 (7)	13 (7)	17 (7)	
Coagulation grasper+haemoclip	6 (1)	3 (2)	3 (1)	
Epinephrine+haemoclip	3 (1)	1 (1)	2 (1)	
IPB constraint for overview, n (%)	44/431 (10)	15/198 (7)	29/233 (12)	0.096
Damaged muscularis propria, n (%)	98 (7)	52 (7)	46 (7)	0.409
Sydney DMI classification, n (%)				0.435
DMI type I	14/98 (14)	8/52 (15)	6/46 (13)	
DMI type II	55/98 (56)	32/52 (62)	23/46 (50)	
DMI type III	19/98 (19)	7/52 (14)	12/46 (26)	
DMI type IV	10/98 (10)	5/52 (10)	5/46 (11)	
Submucosal tattoo placed, n (%)	531 (38)	313 (45)	218 (31)	<0.001
Clips used, n (%)	293 (21)	129 (19)	164 (24)	0.023
Complication, n (%)				0.347
Early postpolypectomy bleeding	33 (2)	11 (2)	22 (3)	
Delayed bleeding	56 (4)	28 (4)	28 (4)	
Postpolypectomy syndrome	13 (1)	8 (1)	5 (1)	
Perforation	11 (1)	6 (1)	5 (1)	
AGREE classification†, n (%)				0.066
No adverse event	1280 (92)	642 (93)	638 (92)	
Grade I	82 (6)	35 (5)	47 (7)	
Grade II	6 (0.4)	6 (1)	0 (0)	
Grade IIIa	21 (2)	10 (1)	11 (2)	
Grade IIIb	1 (0)	1 (0)	0 (0)	

Continued

Table 2 Continued

	Total* (n=1390)	Intervention group (n=694)	Control group (n=696)	P value
Histology, n (%)				0.002
Sessile serrated lesion	258 (19)	105 (15)	153 (22)	
Adenoma	1090 (78)	569 (82)	521 (75)	
Tubular	394 (36)			
Villous	73 (7)			
Tubulovillous	623 (57)			
Superficial submucosal carcinoma	28 (2)	14 (2)	14 (2)	
Deep submucosal carcinoma	1 (0.1)	1 (0.1)	0 (0)	
Carcinoma (not specified)	13 (1)	5 (1)	8 (1)	
Dysplasia, n (%)				0.433
No dysplasia	139 (10)	62 (9)	77 (11)	
Low-grade dysplasia	982 (71)	503 (72)	479 (69)	
High-grade dysplasia	223 (16)	106 (15)	117 (17)	
Carcinoma	46 (3)	23 (3)	23 (3)	
R0 resection, n (%)	42 (3)	21 (3)	21 (3)	0.985

*1390 cases; 22 cases were directly referred for endoscopic full-thickness resection (eFTR), endoscopic submucosal dissection (ESD) or surgery.
†AGREE classification: classification for Adverse Events Gastrointestinal Endoscopy.[18]
CAST, cold-forceps avulsion with adjuvant snare-tip soft coagulation; DMI, deep mural injury; IPB, intraprocedural bleeding; STSC, snare tip soft coagulation.

lesions with a size of 20–29 mm (5% vs 20%, OR 0.20; 95% CI 0.08 to 0.52; p=0.001) and 30–39 mm (10% vs 21%, OR 0.36; 95% CI 0.16 to 0.81; p=0.013), there was a limited effect of this training on the outcomes of ≥40 mm lesions (24% vs 31%, OR 0.61; 95% CI 0.31 to 1.20; p=0.151). The complication rate was similar for intervention and control groups (8% vs 9%; p=0.720).

High-volume, highly skilled expert centres have shown the safety and efficacy of EMR[5 9]; however, there remains a substantial gap between these reported outcomes and the results in real-life clinical practice. It is still unclear when and how competency in EMR should be acquired. Although EMR is one of the most performed endoscopic interventions, a structured training in EMR during fellowship is mostly lacking. In the Netherlands, proficiency is mostly obtained in the years following training in a 'learning by doing' fashion, with only a few procedures performed together with a more experienced peer staff member. Dedicated fellowships to learn colorectal EMR during a prolonged period with a high number of cases per week are absent. A recent survey in the USA among gastroenterology fellows showed that formal education in EMR was lacking in nearly half of all fellows, and that basic insight in the procedure was missing in the same proportion.[21] Two studies evaluating competency of EMR in trainees showed that competency in EMR is related to procedure volume and lesion size, but that the predefined thresholds for competency are rarely met.[11 22] It is questionable whether teaching EMR should be limited to gastroenterologists in training, as the essential scope control is expected to develop to competent levels in the years after the fellowship or residency. In the current study, we evaluated a structured postgraduate training programme in a population of practising gastroenterologists, who were selected as dedicated EMR endoscopists within their centre and therefore likely to be exposed to LNPCPs after the training. Based on the findings in the current study, it seems efficient to implement a dedicated structured postgraduate training in EMR to dedicated endoscopists on a national level. This relatively low-intensity training had a significant impact on the recurrence rate but was unable to close the gap to outcomes on expert level completely. This training should therefore be supplemented by additional efforts, for example, the implementation of quality indicators for endoscopic resection of LNPCPs.[1] Monitoring and reporting 6-month recurrence rates as a quality indicator and providing endoscopists feedback on their individual numbers might contribute to

Table 3 Recurrence rate (after 6 months) and complication rate after endoscopic mucosal resection

Outcome	Intraclass coefficient*	Total	Intervention group	Control group	OR (95% CI); P value†
Recurrence rate, n (%) *Only PA-confirmed lesions*	0.11	200/1050 (19)	73/543 (13)	127/507 (25)	0.43 (0.23–0.78); 0.005
Recurrence rate, n (%) *All assessed scars‡*	0.07	200/1215 (16)	73/613 (12)	127/602 (21)	0.48 (0.29–0.81); 0.006
Complication rate, n (%)	0.00	113/1390 (8)	53/694 (8)	60/696 (9)	0.93 (0.64–1.36); 0.720
Intraprocedural adverse events, n (%)	0.07	443/1390 (32)	201/694 (29)	242/696 (35)	0.77 (0.50–1.21); 0.258

*Intraclass coefficient reflects the correlation between the outcomes of patients within the same centre.
†Generalised linear mixed models (with logit link), with random intercept on centre level and correction for stratification variables, SMSA (size, morphology, site and access) score, sessile serrated histology and American Society of Anesthesiologists (ASA) classification.
‡Including scars assessed as negative for recurrence, without PA confirmation; n=160.
PA, pathology.

Table 4 Characteristics of recurrences at 6 months after endoscopic mucosal resection

	Total (n=200)	Intervention group (n=73)	Control group (n=127)	P value
Initial lesion characteristics				
Proximal location, n (%)	131 (66)	43 (59)	88 (69)	0.137
SMSA score, n (%)				0.084
SMSA II	4 (2)	3 (4)	1 (1)	
SMSA III	64 (32)	18 (25)	46 (36)	
SMSA IV	132 (66)	52 (71)	80 (63)	
Recurrence characteristics				
Size in mm, mean (SD)	6 (4.5)	5 (3.9)	6 (4.9)	0.191
Unifocal or multifocal*, n (%)				0.006
Unifocal	152 (82)	60 (92)	92 (76)	
Multifocal	34 (18)	5 (8)	29 (24)	
Treatment, n (%)				0.003
Hot/cold avulsion	29 (15)	10 (14)	19 (15)	
Hot/cold polypectomy	103 (52)	46 (63)	57 (45)	
Re-EMR	46 (23)	7 (10)	39 (31)	
CAST	14 (7)	8 (11)	6 (5)	
eFTR	2 (1)	0 (0)	2 (2)	
Referral to another hospital	4 (2)	2 (3)	2 (2)	
Surgery	2 (1)	0 (0)	2 (2)	
Histology†, n (%)				0.075
Sessile serrated lesion	21 (11)	3 (4)	18 (15)	
Tubular adenoma	121 (62)	48 (66)	73 (60)	
Villous adenoma	6 (3)	4 (5)	2 (2)	
Tubulovillous adenoma	44 (22)	18 (25)	26 (21)	
Superficial submucosal carcinoma	1 (0.5)	0 (0)	1 (1)	
Deep submucosal carcinoma	1 (0.5)	0 (0)	1 (1)	
Dysplasia†, n (%)				0.132
No dysplasia	13 (7)	2 (3)	11 (9)	
Low-grade dysplasia	173 (89)	68 (93)	105 (87)	
High-grade dysplasia	6 (3)	3 (4)	3 (2)	
Carcinoma	2 (1)	0 (0)	2 (2)	

*14 missing cases; 8 in the intervention group and 6 in the control group.
†6 missing cases in the control group.
CAST, cold-forceps avulsion with adjuvant snare-tip soft coagulation; eFTR, endoscopic full-thickness resection; EMR, endoscopic mucosal resection; SMSA, Size, Morphology, Site and Access.

optimalisation of outcomes, and thereby an improvement in outcomes on a national level.

This was a low-intensity 2-day training, focusing on the important steps of EMR such as prevention of neoplasia by correct snare placement, recognition of residual adenoma at the margin as well as the base of the EMR defect, bleeding control, recognition of damage to the muscularis propria and management of non-lifting parts of the polyp. It showed a 50% recurrence risk reduction. This seems to be in contrast with the long learning curve as demonstrated by previous studies, in which endoscopists reach competency in EMR after a certain number of EMRs performed, ranging from 100 to 150.[11 22] Our training did not focus on the necessary motor skills such as scope handling, ability to torque to a 6 o'clock position, steady tip control, correct insertion technique, etc. As most of the participating endoscopists were already practising for many years, most of these motor skills were already obtained during daily practice. This may have facilitated the fast uptake of small treatment adjustments. Furthermore, as demonstrated by data from expert centres, only small procedural adjustments, for example, margin thermal ablation or recognition and treatment of residual neoplasia at the base of the EMR defect, can lead to remarkable reduction of recurrence rate.[9 23 24] This study may therefore give support to the notion that theoretical teaching of EMR should be paralleled with motor skill development, and that providing this training to physicians who need to obtain these motor skills might be less effective in reducing the recurrence rate.

While we have seen an evident effect of a compact training of community endoscopists on post-EMR recurrence rates, this effect seems limited for lesions of ≥40 mm in size. A recent randomised controlled study comparing underwater EMR versus conventional EMR showed a recurrence rate of 40% in the ≥40 mm polyps when removed with conventional EMR,[25] while a much lower recurrence rate was observed for 20–40 mm LNPCPs. Although size ≥40 mm was not related to recurrence within a cohort of LNPCPs treated with EMR with thermal margin ablation (EMR-T) as long as the whole margin was completely ablated, the subgroup of incomplete EMR-T was larger in size, showed more muscle injury, was more often referred for surgery and had a recurrence rate of 27%.[5] These ≥40 mm LNPCPs therefore reflect a specific subgroup of much higher complexity. As these ≥40 mm LNPCPs are less prevalent, the exposure of an individual endoscopist is likely to be low. In the current study, the mean annual exposure to these ≥40 mm LNPCPs was only seven cases per centre, with a range of 0–26 cases (data not shown). Since learning curve studies have shown that the quality of EMR only reaches acceptable levels after >100 procedures,[10] low exposure limits the effect of this training in this specific complex subgroup. The current 2-day training and e-learning focused on a standardised approach of EMR, with a clear focus on all essential elements involved in recurrence, but extensive hands-on training and proctorship such as in a dedicated 6–12 months fellowship was absent. It is likely that dedicated hands-on training on ≥40 mm LNPCPs will be necessary to increase competency to the desired level in this subgroup. Creating a national or regional infrastructure for EMR of ≥40 mm LNPCPs should focus on centralisation of these LNPCPs to be able to train new dedicated endoscopists and to retain competency due to a high annual exposure.

Several limitations should be emphasised. First, randomisation was performed on centre level instead of polyp level. Therefore, differences in polyp characteristics (such as SMSA score and histology) between the intervention and control groups were seen. These differences potentially could have caused confounding bias on our main outcome. However, we incorporated these potential confounding factors in our analysis, and this did not change the outcomes. Since the intervention was performed on endoscopist level, it was not possible to randomise on polyp level. Cluster randomisation was performed on centre

level to make sure cross-contamination between endoscopists within centres would not occur. Therefore, this design was the most appropriate and suitable to evaluate our hypothesis.

A second limitation is the uncertainty whether in all centres all consecutive LNPCPs are included. As in all prospective cohorts, it is unclear which cases were not included. We do believe that this effect is very limited. Selection of cases based on outcome is unlikely, given the fact that the recurrence rates of our cohort are in line with recurrence rates reported in other community-based cohorts.[7 26] Furthermore, both groups included comparable numbers of LNPCPs, with similar distribution of potential risk factors and histology. This makes positive selection in one of the groups unlikely. Technical success of EMR was not reached in 1.2% of the cases and did not significantly differ between intervention and control groups (1.1% vs 1.3%; p=0.076), which supports the assumption that there was no difference in case selection between groups.

A third limitation is that although the training shows a significant decrease in recurrence rate, it is very difficult to pinpoint which items of the training added the most to this success. During the teaching sessions, many aspects of performing an EMR were taught. As the procedures itself were not recorded and evaluated, it remains unknown which aspects actually have lingered or how they have been brought into practice. It was not possible to determine which recorded parameters were most important to the outcome. It is therefore likely that the many observed differences together sum up to the current result. Furthermore, unregistered practice variation may also have added up to the result. This makes it difficult to focus future training on those specific items which are the most important for decreasing recurrences. We observed a variation in recurrence rate between centres in the intervention group. We also observed that the centres with persisting high recurrence rate after training were characterised by a low annual exposure to LNPCPs and a low uptake of the e-modules. So it seems likely that exposure and dedication are important factors in improving outcomes of EMR.

A fourth limitation is that it is uncertain whether enthusiastic participants might have attended additional courses regarding EMR or large polypectomies in general. However, in the region in which the study was performed, no in-person courses were given during the study period because of the COVID pandemic. Therefore, it is unlikely that this might have influenced study outcomes. Participants of the control group received the structured EMR training after completion of the clinical trial. This was implemented to make sure participants of the control group would stay motivated to complete the clinical trial. There were no additional inclusions or measures after training of the control group. While this would be interesting, our stratified cluster randomisation should have led to comparable groups, which enabled us to evaluate the effects of this compact EMR training.

The fifth limitation concerns the relatively high proportion of cases needing an auxiliary method to achieve complete removal of all neoplastic tissue. Residual neoplasia after snaring was seen in 24% and 18% of the cases in the intervention and control group, respectively. It is to be expected that a closer examination of the post-EMR defect would result in an increased detection of residual neoplasia. However, according to current guidelines, this additional detected neoplasia should and could be removed with additional snaring techniques. It remains unclear why adjunctive treatments were applied in such high numbers, and how this is related to the competency of the individual endoscopists. However, retrospective and prospective series in tertiary hospitals also show the application of auxiliary modalities in 19–21% of cases.[27 28]

In conclusion, in this national, multicentre cluster randomised trial including more than 1400 LNPCPs, a compact training in EMR significantly reduced the recurrence rate at 6 months with more than 50%. This strongly argues for a national dedicated training programme for endoscopists performing EMR. While this effect was evident for 20–39 mm lesions, this was limited in ≥40 mm lesions. Due to the low annual exposure in the participating centres, centralisation of ≥40 mm lesions should be considered.

Author affiliations
[1]Department of Gastroenterology and Hepatology, Maastricht University Medical Centre+, Maastricht, The Netherlands
[2]GROW School for Oncology and Reproduction, Maastricht University, Maastricht, The Netherlands
[3]Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands
[4]Department of Methodology and Statistics, Maastricht University, Maastricht, The Netherlands
[5]CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands
[6]Department of Gastroenterology and Hepatology, Dijklander Hospital, Hoorn, The Netherlands
[7]Department of Gastroenterology and Hepatology, Albert Schweitzer Hospital, Dordrecht, The Netherlands
[8]Department of Gastroenterology and Hepatology, Groene Hart Hospital, Gouda, The Netherlands
[9]Department of Gastroenterology and Hepatology, Haga Hospital, Den Haag, The Netherlands
[10]Department of Gastroenterology and Hepatology, Meander Medical Centre, Amersfoort, The Netherlands
[11]Department of Gastroenterology and Hepatology, Diakonessenhuis, Utrecht, The Netherlands
[12]Department of Gastroenterology and Hepatology, Isala Clinics, Zwolle, The Netherlands
[13]Department of Gastroenterology and Hepatology, Amphia Hospital, Breda, The Netherlands
[14]Department of Gastroenterology and Hepatology, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands
[15]Department of Gastroenterology and Hepatology, Bernhoven, Uden, The Netherlands
[16]Department of Gastroenterology and Hepatology, Sint Antonius Hospital, Nieuwegein, The Netherlands
[17]Department of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, The Netherlands
[18]Department of Gastroenterology and Hepatology, Zuyderland Medical Centre, Sittard-Geleen, The Netherlands
[19]Department of Gastroenterology and Hepatology, Haaglanden Medical Centre, Den Haag, The Netherlands
[20]Department of Gastroenterology and Hepatology, Tergooi Hospital, Hilversum, The Netherlands
[21]Department of Gastroenterology and Hepatology, Hospital Gelderse Vallei, Ede, The Netherlands
[22]Department of Gastroenterology and Hepatology, Spaarne Gasthuis, Haarlem, The Netherlands
[23]Department of Gastroenterology and Hepatology, Maasstad Hospital, Rotterdam, The Netherlands
[24]Department of Gastroenterology and Hepatology, VieCuri Medical Centre, Venlo, The Netherlands
[25]Department of Gastroenterology and Hepatology, Rivas Zorggroep, Gorinchem, The Netherlands
[26]Department of Gastroenterology and Hepatology, Franciscus Gasthuis en Vlietland, Rotterdam, The Netherlands
[27]Department of Gastroenterology and Hepatology, Sint Jansdal Hospital, Harderwijk, The Netherlands
[28]Department of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, The Netherlands
[29]Department of Gastrointestinal Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[30]Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands
[31]Department of Gastroenterology and Hepatology, Laurentius Hospital, Roermond, The Netherlands
[32]Department of Gastroenterology and Hepatology, Gelre Hospitals, Apeldoorn, The Netherlands

[33]Department of Gastroenterology and Hepatology, Hospital group Twente, Almelo, The Netherlands
[34]Department of Gastroenterology and Hepatology, Deventer Hospital, Deventer, The Netherlands
[35]Department of Gastroenterology and Hepatology, Elkerliek Hospital, Helmond, The Netherlands
[36]Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, The Netherlands
[37]Department of Gastroenterology, Hospital Clinic de Barcelona, Barcelona, Spain
[38]Department of Gastroenterology and Hepatology, Westmead Hospital, Westmead, New South Wales, Australia

Contributors Study concept and design: LWTM, LMGM, AAMM, MB, MP, PDS. Acquisition of data: all authors. Analysis and interpretation of data: LWTM, BW, LMGM. Drafting of the manuscript: LWTM, LMGM. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: LWTM, BW. Study supervision: LWTM, AAMM, LMGM. Guarantor: LMGM.

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ORCID iDs
Lonne W T Meulen http://orcid.org/0000-0001-5205-5466
Monique E van Leerdam http://orcid.org/0000-0002-5719-3208
María Pellisé http://orcid.org/0000-0001-9739-4998
Michael J Bourke http://orcid.org/0000-0001-5047-312X
Leon M G Moons http://orcid.org/0000-0002-6913-9954

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