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Interventions to improve the quality of screening-related colonoscopy: protocol for a systematic review and network meta-analysis of randomised controlled trials

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ABSTRACT

Introduction Colonoscopy quality can vary depending on endoscopist-related factors. Quality indicators, such as adenoma detection rate (ADR), have been adopted to reduce variations in care. Several interventions aim to improve ADR, but these fall into several domains that have traditionally been difficult to compare. We will conduct a systematic review and network meta-analysis of randomised controlled trials evaluating the efficacies of interventions to improve colonoscopy quality and report our findings according to clinically relevant interventional domains.

Methods and analysis We will search MEDLINE (Ovid), PubMed, EMBASE, CINAHL, Web of Science, Scopus and Evidence-Based Medicine from inception to September 2022. Four reviewers will screen for eligibility and abstract data in parallel, with two accordant entries establishing agreement and with any discrepancies resolved by consensus. The primary outcome will be ADR. Two authors will independently conduct risk of bias assessments. The analyses of the network will be conducted under a Bayesian random-effects model using Markov-chain Monte-Carlo simulation, with 10 000 burn-ins and 100 000 iterations. We will calculate the ORs and corresponding 95% credible intervals of network estimates with a consistency model. We will report the impact of specific interventions within each domain against standard colonoscopy. We will perform a Bayesian random-effects pairwise meta-analysis to assess heterogeneity based on the I^2 statistic. We will assess the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation framework for network meta-analyses.

Ethics and dissemination Our study does not require research ethics approval given the lack of patient-specific data being collected. The results will be disseminated at national and international gastroenterology conferences and peer-reviewed journals.

PROSPERO registration number CRD42021291814.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A comprehensive search strategy will be employed to capture all relevant randomised controlled trials (RCTs) of interventions to answer our study question.
⇒ The certainty of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation framework.
⇒ Compared with prior network meta-analyses (NMAs) reporting comparisons across multiple domains of interventions in screening colonoscopy, our approach is strengthened by the performance of an all-encompassing NMA of RCTs reported by domains, where the efficacies of similar interventions (for instance, intraprocedural techniques) are compared.
⇒ A limitation of our approach is the exclusion of observational studies which could potentially miss important novel approaches, technologies or devices not yet studied in the form of a randomised trial.
⇒ While our choice to exclude conference abstracts was deliberate given their potential for unclear reporting of methodology, a limitation of this choice is ensuing potential publication bias; to mitigate this, we will test for evidence of publication bias.

INTRODUCTION

An estimated 150 000 new cases of colorectal cancer (CRC) and 50 000 associated deaths were estimated to occur in 2021.[1] While resection of premalignant adenomatous polyps identified on screening-related colonoscopy has been demonstrated to decrease mortality from CRC,[2 3] colonoscopy quality can vary significantly based on endoscopist-related factors.[4] Consequently, several quality indicators have been widely adopted to improve colonoscopy quality and reduce variations in care.[5–8] In addition, these quality indicators aim to minimise risk of serious adverse events (AEs) in colonoscopy, which, though rare, can occur.[9]

Adenoma detection rate (ADR), defined as the proportion of screening-related colonoscopies during which one or more adenoma is detected, is arguably the most well-established colonoscopy quality indicator.[5–8] A strong argument for the use of ADR as a primary quality indicator is its established inverse correlations with postcolonoscopy CRC (PCCRC) and CRC-related death.[10] Despite its importance, reported ADRs vary widely between endoscopists due to modifiable and unmodifiable factors.[11 12] Furthermore, there is an absence of clear evidence-based guidance regarding strategies to improve ADR. Given the importance and endoscopist-level variability in ADR as well as other colonoscopy quality metrics, such as cecal intubation rate (CIR),[11 12] there is an urgent need to systematically characterise colonoscopy quality improvement strategies.

Several interventions exist that aim to improve ADR. Broadly, these can be categorised into several domains, including preprocedural and periprocedural considerations (eg, optimised bowel cleansing[13] and sedation regimens[14]), endoscopist-directed interventions (eg, directed audit and feedback[15] or educational courses[16]), intraprocedural techniques (eg, dynamic positional changes[17] or second-look examination[18]), endoscopy technologies (eg, advanced imaging[19] or computer-aided detection, CADe[19]), disposable assistive devices (eg, cuffs[20] or rings[21]) and additive substances (eg, hyoscine-*n*-butylbromide[22]).

Prior meta-analyses have assessed the impacts of these strategies on ADR and other colonoscopy quality metrics.[15 18] Few studies, however, have compared the relative impacts of multiple similar interventions using network meta-analyses (NMAs). The NMAs that exist have reported comparisons across several interventional domains,[19 23] resulting in substantial heterogeneity in interventions, patient populations and study methodology. These limitations create challenges in interpreting the data and preclude the provision of meaningful guidance for practising endoscopists regarding colonoscopy quality improvement. To address these gaps, we will conduct an overarching systematic review and NMA of randomised controlled trials (RCTs) evaluating interventions to improve colonoscopy quality.

METHODS

Overview and objectives

We will conduct this systematic review and NMA according to the guidelines for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions.[24] Our protocol has been registered a priori on PROSPERO (CRD42021291814).

The primary objective of this study is to determine the impact of various interventions on ADR when compared with standard colonoscopy. The secondary objectives are to determine the impact of the same interventions, on other quality indicators and detection parameters, including polyp detection rate (PDR), ADR subtypes (including but not limited to sessile serrated lesion detection rate and locational ADR), missed adenoma rate, CIR, withdrawal time, sedation requirements, patient satisfaction metrics, AE rates and unplanned healthcare encounters (UHEs), in addition to assessing these comparisons within clinically relevant subgroups determined a priori and described below. No research ethics approval is required for this study given the lack of patient-specific data being collected.

Eligibility criteria

We will include studies that meet *all* of the following criteria: (1) patients are adults (age≥18) undergoing screening-related colonoscopy; (2) interventions include any of the following categories or any other category deemed to be relevant: preprocedural and periprocedural parameters (eg, bowel preparation, numbers and types of observers, sedation regimens), endoscopist-directed interventions (eg, directed audit and feedback, educational courses), intraprocedural techniques (eg, dynamic positional changes, second-look segmental examination, retroflexed segmental examination, water immersion), endoscopy technologies (eg, advanced imaging modalities, CADe), disposable assistive devices (eg, cuffs, rings, caps) and additive substances (eg, hyoscine-*n*-butylbromide, natural/herbal additives); (3) the comparator is one of either (A) 'standard colonoscopy' (SC), defined as white light colonoscopy performed with high-definition colonoscopes in primary a screening-related population (defined below) without the aid of strategies used in intervention groups specific to the domain being assessed or (B) any of the other interventions described; (4) one or more of the primary or secondary outcomes is reported (ADR or its subtypes, PDR, CIR, withdrawal time, sedation requirements, AE rates, UHE rates); and (5) the study type is an RCT. Studies will be considered to assess a screening population if they met all the following criteria[12] : (A) ≤15% of the study cohort falls outside the age range 40–80; (B) ≤15% of the cohort are inpatients at the time of the procedure; (C) ≤15% of the cohort is undergoing colonoscopy for non-screening-related indications, such as active gastrointestinal symptoms or surveillance related to inflammatory bowel disease.

A study will be excluded from the final review if it meets any of the following criteria: (1) it is an observational study, case report or series, narrative or systematic review, or meta-analysis; (2) the comparator is either unclear or not considered to represent SC for the purposes of comparisons within the domain in question; (3) there is an absence of any relevant reported outcomes; (4) it assesses upper endoscopies and/or flexible sigmoidoscopies as part of the study cohort; (5) it assesses colonoscopy outcomes exclusively in trainees; (6) it assesses colonoscopies in a high-risk population such as those with hereditary polyposis syndromes; (7) it was published prior to the year 2000, as it may contain data from non-high-definition colonoscopies and (8) it is not published in full manuscript form.

Search strategy and terms

We designed a comprehensive search strategy with a health research librarian (MV) to query the electronic databases MEDLINE (Ovid), PubMed, EMBASE, CINAHL, Web of Science, Scopus and Evidence-Based Medicine from inception to September 2022. Each interventional domain outlined above will inform a separate search. A combination of free-text and Medical Subject Heading (MeSH) terminology will be employed in the search strategy, along with appropriate synonyms and spelling variations. The full electronic search strategy is provided ine online supplemental materials.

Study selection and data abstraction

All citations will be imported into Covidence (Melbourne, Australia) and all duplicate entries will be removed. A team of 4 reviewers (RK, RB, NG and MAS) will perform initial screening, full-text exclusion and data abstraction. Each reviewer will be assigned approximately an equal number of citations at each screening stage, with a vote of 'both include' or 'both exclude' by the two reviewers resulting in inclusion or exclusion, respectively. All potential discrepancies will be resolved by a third vote by either senior study author (SCG or NF).

All included citations from the first stage will undergo duplicate full-text assessment with a subsequent inclusion or exclusion by two reviewers of the same team of four (RK, RB, NG and MAS), with discrepancies again resolved by the senior authors. Data will then be abstracted in duplicate by two authors (RK and RB) into standardised forms containing: (1) study identification (eg, authorship, year of publication, country of origin), (2) study design parameters and risk of bias assessments, (3) endoscopist demographics, (4) patient demographics (eg, age, sex, comorbidities), (5) descriptions of the intervention and comparators, (6) bowel preparation regimens and (7) outcomes. We will also collect data on relevant subgroups where available.

Outcome definitions

The primary outcome is ADR. Secondary outcomes are PDR, ADR subtypes, adenoma per colonoscopy (APC), APC subtypes, missed adenoma rates, CIR, withdrawal time, sedation requirements, AE rates, UHE rates and patient satisfaction. ADR and APC subtypes will include right-sided ADR, defined as the proportion of colonoscopies in which at least one adenoma is found in the right colon,[25] advanced ADR, defined as the proportion of exams with one or more adenoma ≥10 mm in size or with high-grade dysplasia or a villous component,[26] and sessile serrated ADR, defined as the portion of exams with one or more sessile serrated adenomas,[27] in addition to all according subtypes for the APC metric.

Risk of bias

Two authors (RK and RB) will conduct risk of bias assessments in parallel for all studies included in the final review. Assessment of randomised studies will be performed using the Cochrane Risk of Bias tool, version 2 (RoB 2).[28] Discrepancies will be resolved by consensus.

Statistical analysis, sensitivity and subgroup analyses

We will perform a Bayesian random-effects pairwise meta-analysis to assess heterogeneity based on the I^2 statistic. If substantial heterogeneity is observed, we will address heterogeneity by carrying out meta-regression on relevant covariates using random effects models and by excluding studies. We will assess the transitivity assumption of the NMA with two approaches. First, we will examine the distribution of effect modifiers of the interventions across studies, such as sex and/or gender, family history of polyps and/or CRC, differences in procedural indication, quality of bowel preparation and definitions of 'standard' colonoscopy, to make sure that no significant differences exist in these factors. Second, we will carry out a test of inconsistency to determine whether there is statistical evidence of overall inconsistency. The presence of inconsistency will be addressed with either subgroup analysis or meta-regression.

The main analyses of the network will be conducted under a Bayesian random-effects model using Markov-chain Monte-Carlo simulation, with 10 000 burn-ins and 100 000 iterations. We will calculate the ORs and corresponding 95% credible intervals of network estimates with a consistency model. The ranking probabilities of the interventional domains will be evaluated with a plot of surface under the cumulative ranking curves and a league table of the relative effects between all interventions. Publication bias will be evaluated with a comparison-adjusted funnel plot. Local incoherence will be assessed by comparing the direct estimates to the indirect estimates obtained through a node-splitting method. All analysis will be performed using the *BUGSnet* and *gemtc* R packages.[29 30]

For the primary analyses, results will be separated into interventional domains previously outlined: preprocedural and periprocedural parameters, endoscopist-directed interventions, intraprocedural techniques, endoscopy technologies, disposable assistive devices, additive substances or other interventions not foreseen by our study team that could feasibly comprise their own homogeneous domain. These domains are summarised in table 1. We will report the impact of specific interventions within each domain against standard colonoscopy for each available outcome.

We will perform sensitivity analyses to assess: low (< 25%) vs high study attrition/ drop-out rates, results from studies published prior to 2015 vs in 2015 or later (to account for gradual overall improvements in colonoscopy quality over time),[31] results from North American versus European versus Asian studies, results from per-protocol versus intention-to-treat analyses, results from studies with clear and similar descriptions of comparator arms versus others, results from only those studies with even more restrictive screening-related criteria (<5% rather than <15% as described above), and results from all studies

Table 1 Examples of domains of interventions to improve the quality of screening-related colonoscopy

Domain	Potential interventions	Potential comparators
Periprocedural parameters	Split dose bowel preparation	Day before bowel preparation
	Split dose bowel preparation	Same day bowel preparation
	Sodium picosulphate bowel preparation	Polyethylene glycol bowel preparation
	Simethicone (in bowel preparation)	Standard bowel preparation
	Patient education on bowel preparation	No patient education
	Propofol sedation	Opioid and benzodiazepine sedation
	Nurse observer or other second observer	Single observer
Endoscopist parameters	Educational interventions	No interventions
	Audit and feedback (report cards)	No audit and feedback (report cards)
Intraprocedural techniques	Water exchange or water immersion	Air or CO_2 insufflation
	Dynamic position changes	No position changes
	Second inspection on forward view	Standard inspection
	Right sided retroflexion	Second inspection on forward view
	Right sided retroflexion	Standard inspection
	'Two-handed' technique (with assistant)	'One-handed' technique
	Resection of polyps on insertion	Resection of polyps on withdrawal
	>9 min withdrawal time	6–9 min withdrawal time
	Monitoring of withdrawal time	No monitoring of withdrawal time
	Segmental timed withdrawal	Standard inspection with 6–8 min total withdrawal
Endoscopic technologies	Linked colour imaging (LCI)	Narrow-band imaging (NBI)
	LCI	White light imaging
	NBI	White light imaging
	i-Scan imaging	White light imaging
	Autofluorescence imaging	White light imaging
	Any enhanced optical imaging	Standard colonoscopy
	High-definition colonoscopy	Standard colonoscopy
	Artificial intelligence/computer-aided detection	Standard colonoscopy
	Use of ultrathin colonoscopes	Standard colonoscopy
	Full spectrum endoscopy	Standard colonoscopy
Disposable assistive devices	Endocuff-assisted colonoscopy	Standard colonoscopy
	Endorings-assisted colonoscopy	Standard colonoscopy
	Endocuff vision (ECV)-assisted colonoscopy	Standard colonoscopy
	ECV-assisted colonoscopy	AmplifEYE-assisted colonoscopy
	AmplifEYE-assisted colonoscopy	Standard colonoscopy
	Cap-assisted colonoscopy	Standard colonoscopy
Additive substances	Methylene blue	No additives
	Hyoscine-N-butylbromide	No additives
	Peppermint oil	No additives

versus only those without high risks of bias according to RoB 2.[28] We will also perform subgroup analyses, where possible, to assess: relevant patient subgroups (including age, sex, ethnicity/race and comorbidities), indications for colonoscopy (including faecal immunochemical test-positive patients vs surveillance vs initial screening vs others), bowel preparation quality, extent of trainee participation, sedation practices, colonoscopy completion rates and endoscopist specialty and experience.

Certainty of the evidence

We will assess the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework[32] and will specifically follow

their guidance for NMA.[33] Two reviewers with experience in using GRADE (GIL and NF) will independently and in a blinded fashion (with interventions and comparator groups concealed) rate each GRADE domain for each comparison, including the overall risk of bias, publication bias, inconsistency, indirectness, imprecision,[34] incoherence[35] and violation of transitivity.[36] To help inform the ultimate GRADE ratings, all study authors who perform colonoscopy will be surveyed individually to provide their minimum clinically meaningful thresholds for all outcomes, in absolute differences.

Patient and public involvement

No patients or public were involved with study design, and none will be involved in the interpretation of results.

DISCUSSION

This systematic review and NMA will provide a contemporary evaluation of the comparative efficacies of interventions designed to improve colonoscopy quality using the highest available form of input evidence. This study will inform evidence-based guidelines and is a crucial step toward improving patient outcomes.

Although colonoscopy is an extremely common procedure, variations in the quality of screening-related colonoscopy exist can result in incomplete procedures, missed lesions, AEs and/or PCCRC.[11] Thus, it is the obligation of endoscopists performing screening-related colonoscopy to be aware of interventions to improve the quality of this procedure. Furthermore, up-to-date knowledge of these interventions is critical to endoscopy unit managers, healthcare decision-makers and gastrointestinal and endoscopy societies to provide recommendations on the best available options to improve care.

Prior meta-analyses have summarised the effects of interventions that aim to improve or optimise colonoscopy quality.[13–15] However, few studies have attempted to compare the magnitudes of effects of multiple similar interventions by performing NMAs. In the few NMAs that do exist assessing this question, comparisons have been reported across multiple interventional domains,[19 32] with potential heterogeneity in interventions, patient populations and study methodology. Our study proposes to mitigate these issues by reporting the results of an overarching, all-encompassing NMA of RCTs according to domains, where the efficacies of similar interventions (for instance, intraprocedural techniques) are compared with standard colonoscopy and reported together.

Though our protocol was designed to mitigate sources of bias using rigorous methodology, there are limitations with our approach. Like any meta-analysis, the certainty of pooled estimates is dependent on the quality of input studies. For this reason, we are only including RCTs, which represent the highest starting point for study quality. We acknowledge that this approach will exclude observational studies assessing novel interventions not yet studied in an RCT. Another limitation is the possibility of pooling outcome estimates using variable definitions of 'standard colonoscopy' (the comparator) across studies and domains. To mitigate this, we will review study-specific descriptions of comparator arms in detail and perform sensitivity analyses to exclude studies with unclear or dissimilar descriptions of the comparator arm. Finally, will exclude conference abstracts from being eligible. Though this decision potentially exposes our study to publication bias, we contend that the lack of detailed methodology often found in conference proceedings can introduce heterogeneity to our findings.

To summarise, we anticipate that our study will bridge an important knowledge gap relating to the relative efficacies of interventions to improve colonoscopy quality. Our results can have an immediate impact on patients and endoscopists and downstream impact on clinical practice guidelines and healthcare decision making. Future research should use these high-quality data to perform cost-effectiveness analyses of interventions within each domain.

ETHICS AND DISSEMINATION

Our study does not require research ethics approval given the lack of patient-specific data being collected. The results will be disseminated to local, national and international gastroenterology and endoscopy societies, and submitted to national and international gastroenterology conferences and peer-reviewed journals.

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Contributors NF, SCG and GIL were involved in the conception and design of the study. RK, MV, YR, RB, NG, MAS, DB, GIL, SCG and NF were involved in developing the analysis plan. RK and NF drafted the article. RK, MV, YR, RB, NG, MAS, DB, GIL, SCG and NF critically revised the article for important intellectual content and approved the final version of the article.

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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.

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