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Anaesthesia – Protocol

Evaluation of the McGrath MAC® and Macintosh Laryngoscope for tracheal intubation in 2000 patients undergoing general anaesthesia: The randomised multicentre EMMA trial study protocol

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ABSTRACT

Introduction: The direct laryngoscopy technique using a Macintosh blade is the first choice globally for most anaesthetists. In case of an unanticipated difficult airway, the complication rate increases with the number of intubation attempts. Recently, video laryngoscopy has become a widely accepted method for securing an airway by tracheal intubation because it enables the visualisation of the glottis without a direct line of sight. Several studies and case reports have highlighted the benefit of the video laryngoscope in the visualisation of the glottis and found it to be superior in difficult intubation situations. The aim of this study is to compare the first-pass intubation success rate using the McGrath MAC® (McGrath) video laryngoscope compared with conventional direct laryngoscopy in surgical patients.

Methods and analysis: The EMMA trial is a multicentre, open-label, patient-blinded, randomised controlled trial. Consecutive patients requiring tracheal intubation are randomly allocated to either the McGrath video laryngoscope or direct laryngoscopy using the Macintosh laryngoscope. The expected rate of successful first-pass intubation is 95% in the McGrath group and 90% in the Macintosh group. Each group must include a total of 1000 patients to achieve 96% power for detecting a difference at the 5% significance level. Successful intubation with the first attempt is the primary endpoint. The secondary endpoints are the time to intubation, attempts for successful intubation, the necessity of alternatives, visualisation of the glottis using the Cormack & Lehane score and percentage of glottic opening score and definite complications.

Ethics and dissemination: The project was approved by the local ethics committee of the Medical Association of the Rhineland Palatine state and Westphalia-Lippe. The results of this study will be made available in the form of manuscripts for publication and presentations at national and international meetings.

Trial registration: ClinicalTrials.gov NCT 02611986.

Strengths and limitations of this study

- This trial aims to determine whether video laryngoscopy is superior to direct laryngoscopy in daily anaesthesia practice.
- The plan is to include 2000 patients in this multicentre, open-label, randomised controlled superiority study.
- All training levels of anaesthesiologists (trainee, specialist, expert) are included.
- Selected patients with an expected “easy” airway are evaluated.
- Only one type of video laryngoscope using a Macintosh-like blade is evaluated. The results cannot be transferred to other kinds of video laryngoscopes (e.g., curved blade, channelled blade).

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

(A) Securing the airway by tracheal intubation with direct laryngoscopy is an established and preferred technique in emergency settings and clinical anaesthesia practice. The limitations of direct laryngoscopy are well known. To achieve a learning curve with a 90% probability of performing a successful intubation, more than 57 attempts are required to develop enough experience with the technique.[2,3] To obtain optimal visualisation of the glottis, direct laryngoscopy requires alignment of the oropharyngeal-laryngeal axes.

However, the first-pass success rate of intubation in emergency settings ranges from 40 to 80%,[4-9] in intensive care units from 55 to 68% [10,11] and in the operating room from 63 to 85%.[12-15] Several studies have shown a correlation between increased complications and more than two intubation attempts.[16-18]

Indirect video laryngoscopy has become a widely accepted method for learning the techniques of airway management because it enables an optimised view of the glottis without a direct line of sight.[19-21] Thus, video laryngoscopy plays an important role in the management of patients with unanticipated airway difficulties or failed tracheal intubation. The use of video laryngoscopy (VL) is associated with a reduction in airway complications in clinical emergency and anaesthesia practice.[18,22] Despite the optimised visualisation of the glottis, the duration of tracheal intubation can be prolonged, and intubation attempts can fail.[21-24] Compared to direct laryngoscopy, the learning curve associated with the video laryngoscope is steep.[25] Video laryngoscopy varies in the design of the curved or angulated blade, mobility, size of the monitor display and operation of the micro camera on the blade.

Over the last 10 years, several studies and a recent Cochrane review [26] have compared different video laryngoscopes to direct laryngoscopy or to each other, focusing on endotracheal intubation (ET) in emergency settings or in patients undergoing elective surgery in an operating room. The results suggested advantages in superior visualisation of the glottis,[19,21,23] a higher first-pass success rate [4,11,19,24], and reduction of airway complications as well as benefits in those patients with a difficult airway.[20-23] However, most of these studies had methodological weaknesses, including studies with small sample sizes,[6,13,19-21,24] evaluation in intensive care units

[4,7,10,11,27,28] or emergency departments,[5,6,8,9] manikin studies [19,20,23] and inclusion of patients who were anticipated to have a difficult airway.[12,19-21,23]

Studies conducted more recently have suggested advantages with video laryngoscopy but either failed to routinely use neuromuscular blockade[4] or included patients with highly specific characteristics.[9] Special study characteristics are listed in Table 1.

(B) We chose to study the McGrath® MAC (McGrath; Covidien, Dublin, Ireland) video laryngoscope because it is a portable, relatively inexpensive device with a Macintosh-based blade similar to that in the Macintosh laryngoscope (DL; Stoss Medica, Wiesbaden, Germany). It therefore provides both a direct view of the glottis and an indirect view on the monitor display, which can be beneficial in the case of oropharyngeal mismatch. Our specific choice of the McGrath video laryngoscope was based on the following considerations:

- The Macintosh-based curved blade of the McGrath is comparable to the Macintosh blade;
- The video display of the McGrath allows visualisation of the glottis by the operator along with study measurement or teaching by a consultant when tracheal intubation is performed by an inexperienced provider; and
- The McGrath is available with a disposable blade in different sizes and allows a swift change to treat more patients consecutively.

The aim of this study is to evaluate whether the use of the McGrath (vicarious for Macintosh- like blade video laryngoscopes) improves the first-pass success rate compared with the DL in surgical patients with an expected normal airway undergoing general anaesthesia. We hypothesise that tracheal intubation using the McGrath decreases the frequency of failed intubation and airway complications.

Table 1. Recapitulation of previous studies on endotracheal intubation with videolaryngoscopy in different study settings.

First author	Device	Operators	Centre	Design	N	First-pass Success (DL vs. VL)	*p* value	Comments
Data shown a higher First-pass Success rate with the Videolaryngoscopy								
Silverberg et al. [4]	GS	Attending's	Monocentre	Randomised	117	40% vs. 74%	< 0.001	ICU
Park et al. [5]	GS	Non-anaesthesiologists	Monocentre	Randomised	82	55.9% vs. 91.8%	< 0.001	ED
Ahmadi et al. [6]	GS	Residents	Monocentre	Randomised	97	60.9% vs. 87.5%	0.036	ED
Mosier et al. [7]	GS, CMAC	Non- anaesthesiologists residents/ attending	Monocentre	Non-randomised	234	60.7% vs 78.6%	0.009	ICU
Sakles et al. [8]	GS	Resident	Monocentre	Randomised	822	57% vs. 75%	0.03	ED
Noppens et al.[10]	CMAC	Residents	Monocentre	Prospective	274	55% vs. 79%	0.03	ICU
Kory et al.[11]	GS	Non- anaesthesiologists	Monocentre	Retrospective	128	68% vs. 91%	0.01	ICU
Noppens et al.[19]	McGrath S5	Residents	Monocentre	Prospective	67	69% vs. 95%	< 0.001	
Savoldelli et al. [22]	GS, McGrath S5, Airtraq	Mixed	Monocentre	Randomised	60	63% vs. 88% vs. 100% vs. 88%	< 0.001	Manikin-study
Kasuya et al. [37]	McGrath	Anesthesia trainees	Monocentre	NR	NR	78.6% vs. 92.8%	< 0.001	
Data shown a similar or higher First-pass Success rate with Direct Laryngoscopy								
Yeatts et al.[9]	GS	Mixed	Monocentre	Randomised	623	80% vs. 81%	0.46	ED
Piepho et al.[12]	CMAC	Residents	Monocentre	Prospective	52	79% vs. 81%	0.8	
Ruetzler et al.[21]	CMAC,GS, McGrath S5, KV, Airtraq	Mixed	Monocentre	Randomised	27	96.7% vs. 100% vs. 44.4% vs. 77.8 vs. 88.9% vs. 100%	< 0.001	Manikin-study
Piepho et al.[24]	McGrath S5, GS	Paramedics	Monocentre	Randomised	30	94.4% vs. 97.7%	> 0.05	Manikin-study
Purugganan et al.[36]	McGrath, C-MAC	Residents	Monocentre	Randomised	130	95% vs. 87% vs. 91%	0.4	

Mixed (Residents/ Attending's); ED (Emergency Department); ICU (Intensive Care Unit); CMAC= C-MAC (Storz, Germany); GS= GlideScope (Verathon, USA); BO= Bonfils (Storz, Germany); McGrath= McGrath (Medtronic, Irland); McGrath Series 5= McGrath (Medtronic, Irland); KV= King Vision (Kingssystems, USA); Airtraq (Airtraq, USA); AWS= Airway-scope (Pentax, Japan); NR (Not reported)

Study aims and objectives

Primary objective: Comparing the initial or first-pass success rate of endotracheal intubation with the McGrath video laryngoscope to DL using a Macintosh blade in patients undergoing elective surgery and requiring tracheal intubation.

Secondary objective: Comparing the clinical performance of both devices, view of the glottis, influence of neuromuscular agents, correlation between clinical experiences in airway management and success rates.

Trial design

The EMMA trial is a multicentre, open-label, randomised controlled superiority trial.

METHODS: PARTICIPANT SELECTION, INTERVENTIONS AND OUTCOMES

Study setting

The EMMA trial is currently started in eight Divisions of Anaesthesiology in two hospitals (one university and one general hospital). Another centre All laryngoscopists are anaesthetists with different levels of clinical experience using direct and video laryngoscopy. After a specific introduction to the study protocol, all anaesthetists from the study centres participated in this trial.

Eligibility criteria

Inclusion criteria

Patients having elective surgery with general anaesthesia and requiring mechanical ventilation via an endotracheal tube are recruited.

Exclusion criteria

Patients are not included in this study if they have one or more of the following:

- More than one predictor of an anticipated difficult airway (e.g., BMI > 40 kg/m^2, unanticipated difficult airway in the medical history (e.g., C&L ≥ III), reduction of the atlanto-occipital joint extension < 35°, reduced thyromental distance < 6 cm or Mallampati class ≥ III);
- Age < 18 years;
- ASA class IV;
- Pregnant or breastfeeding;
- Participation in other studies;

- Unable to provide informed written consent or under guardianship;
- Urgent surgical intervention; and
- At high risk for aspiration (e.g. delayed gastric emptying, incompetent lower oesophageal sphincter, oesophageal diseases).

Intervention

Concomitant treatments in both groups

First, patients admitted requiring elective tracheal intubation are evaluated for predictors of anticipated difficult intubation (body mass index, head extension, thyromental distance, Mallampati class, mouth opening and previous difficult airway (e.g., C&L ≥ III). The expertise of the participating anaesthesiologists ranges from "beginner" (residents) to "expert" (consultants). Every anaesthesiologist participating in this study has a clinical experience with at least 25 intubations using DL and at least five intubations using video laryngoscopy. All anaesthetists received hands-on training and theoretical introduction to the use of the McGrath VL and direct laryngoscopy. Tracheal intubation is performed in both groups following the protocol outlined below (Figure 1).

(A) All patients are monitored for ECG, oxygen saturation (SO_2), and arterial blood pressure (non-invasive or invasive as appropriate). Pre-oxygenation is achieved using the device chosen by the provider based on patient characteristics and clinical standard operating procedure (EtO_2 > 80%). In our anaesthesia practice, we use the Pallas® / Primus® (Dräger Lübeck, Germany) anaesthesia respiratory system:

- Tidal volume breathing with normal breaths for at least 3 min or with eight deep breaths over 60 seconds (8 DB 60 sec);[29,30]
- Anaesthesia ventilator in pressure support (PS) mode (PS 8 mbar, PEEP 5 mbar and FiO_2 1.0). [30,31]

(B) After sufficient pre-oxygenation, anaesthesia is induced with sufentanil (0.2 – 0.5 $\mu g.kg^{-1}$) and propofol (2 – 3 $mg.kg^{-1}$), and anaesthesia is maintained with either propofol infusion (TIVA) or volatile anaesthetics. After the patient is deeply anaesthetised, the neuromuscular transmission is monitored using acceleromyography of the adductor pollicis. The individual choice of neuromuscular blocking agent depends on the temporal duration of the surgery, necessary of

perioperative neurological monitoring, absence of allergies and organ failures. The following agents and specific dosages are used:

- Mivacurium (0.2 $mg.kg^{-1}$);
- Atracurium (0.5 $mg.kg^{-1}$);
- Rocuronium (0.3 - 0.6 $mg.kg^{-1}$); and
- Succinylcholine (1 - 2 $mg.kg^{-1}$).

The train-of-four (TOF) is used for continuous quantitative monitoring of neuromuscular transmission. Complete muscle relaxation is confirmed in the absence of tactile and measured twitches in response to maximal TOF stimulation of the ulnar nerve at the adductor pollicis. The importance of obtaining adequate neuromuscular blockade will emphasise with study personnel.

(C) The laryngoscopy attempt begins with a TOF count of 0/4 and is performed using the device indicated by default randomisation:

- Macintosh laryngoscope (DL) or
- McGrath® MAC video laryngoscope (McGrath) – initially as an indirect laryngoscope. However, direct laryngoscopy can be performed at the discretion of the anaesthetist.

The provider selects the method for visualisation of the glottis, either direct or indirect, using the McGrath monitor. The anaesthetist should achieve the best possible view of the laryngeal structures. External laryngeal manipulations (ELM) could be used to improve the view of the glottis to achieve a C&L I or II. The size of the endotracheal tube and the size of the blade are dependent on the standard operating procedure of the hospital (blade size in both groups: #3 for average patients and #4 for very tall patients (> 190 cm height); standard ET size: 7.0 ID used for female patients and 7.5 ID for male patients). The method of visualisation of the glottis and size of the ET/ blade is recorded in the case report form (CRF).

(D) The laryngoscopy attempt is defined as successful if the tracheal tube is placed (confirmed by persistent end-tidal carbon dioxide) with a single blade insertion within 120 seconds and without manipulation of the laryngoscope by another provider. The "time to intubation" is defined as the time from the insertion of the device into the mouth until confirmation of the first wave of CO_2 of the anaesthesia respirator. The anaesthesia nurse measures the intubation time using the built-in timer on the anaesthesia respirator. We also analyse two time periods before final placement:

- "Time to view": defined as the time when the blade tip passing the incisors until visualisation of the glottis; and
- "Placement of the ET": defined as the time from insertion of the ET until the black mark on the ET is threaded between the vocal cords.

If this first attempt fails, the provider makes a second laryngoscopy attempt with the same device. Mask ventilation is recommended between the attempts. A malleable stylet is allowed at the second attempt to reduce the risk of multiple intubation attempts. A total of two laryngoscopy attempts are allowed. If DL fails, the clinician changes to a preferred technique (e.g., McGrath, S-Guide®, rigid stylet) and records the direct and/or screen view of the McGrath. If McGrath fails after two attempts, the clinician is advised to proceed with a preferred rescue technique (e.g., C-MAC® D-Blade, SGA, iLMA, fibreoptic, rigid stylet). The limitation of two intubation attempts and choice of an alternative technique is recommended by the study protocol and is in accordance with the clinical standard.[32] If ELM techniques, such as BURP (specific pressure applied to the cricoid cartilage), are required during laryngoscopy, they are recorded in the CRF. In all cases, an additional individual who is not involved in patient care (either a postgraduate student or a study nurse) is present during induction of anaesthesia to record the study parameters.

Outcome measures

(a) Primary outcome measure

The primary outcome measure is successful intubation within 120 seconds (time to ventilation) with the first-pass attempt.

(b) Secondary outcome measure

- Laryngoscopy Technique: Whether direct or indirect glottic visualisation is used in the McGrath group is recorded
- Different times for successful tracheal intubation
  - Time to view (defined as the time when the blade tip passing the incisors until glottic view)
  - Time to place the ET (defined as the time when the blade tip passing the incisors until the black mark on the ET is threaded through the vocal cords)
  - Total time to successful placement (defined as the time from insertion of

the device until the first carbon dioxide wave on the anaesthesia respirator)

- Number of laryngoscopy attempts
- Failures/ crossovers to other rescue techniques (e.g., SGA, iLMA, fibreoptic)
- External laryngeal manipulations (e.g., BURP, cricoid pressure)
- Glottic view with the Cormack & Lehane grade (C&L) and percentage of glottic opening score (POGO)
- Intubation difficulty score (IDS-Score) [33]
- If McGrath is used, occurrence of fogging is recorded
- Complications (e.g., desaturation < 90% SaO_2, dental or soft tissue trauma)
- Degree of ease or difficulty of tracheal intubation based on the Likert scale (0=easy to 10=difficult) [34,35]

(c) Subgroup analysis

- Demographics
  - Patient (age, gender, BMI, ASA class)
  - Airway difficulty score (ADS score) [36]
  - Provider analysis (clinical experience, education status, experience in direct and indirect laryngoscopy)
- Type of neuromuscular blocking agent
- Endotracheal tube (ET) with or without malleable stylet when using McGrath
- Type of surgery (e.g., thyroidectomy, neck dissection)

Participant timeline

The schedule of enrolment and intervention is shown in Figure 1, and the participant timeline is described in Table 2.

Table 2. Participant timeline.

	Study Period					
	Enrolment	Intervention	Intubation			Extubation
Timepoint	D_0	D_1	D_1 (Time to view)	D_1 (Time to place)	D_1 (Time to ventilation)	D_{1-2}
Eligibility Assessment	X					
Informed consent	X					
Randomisation	X					
Demographic data and physical Examination	X					
Preoxygenation		X				
Induction of Anaesthesia		X				
TOF measurement		X				
Time measurement			X	X	X	
Glottic View			X			
Intubation success					X	
Complications			X	X	X	X

D= Day; D_0= Day of Enrolment / Allocation; D_1= Day of Surgery; D_2= Intensive care unit (ICU) stay

Recruitment

Patient inclusion started in November 2016 in the Division of Ear, Nose and Throat surgery at University Medical Centre, Mainz, Germany, and inclusion of other divisions over the course of time is planned. The history and physical examinations of all patients scheduled for surgery are screened preoperatively for predictors of difficult airway. Patient recruitment is conducted by one of the study physicians. Patients are included if they require orotracheal intubation with an ET under general anaesthesia with neuromuscular agents.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation

After eligibility is confirmed and written informed consent is obtained, enrolled participants are randomised 24 hours before the intervention. A web-based service (QuickCalcs, GraphPad Software, La Jolla, CA, USA) is used for allocating patients to either DL or McGrath.

Sequence generation

The randomisation sequence is generated by a study nurse in the Clinical Research Unit who is not involved in patient recruitment. The software used to collect the data in the CRF automatically allocated the patients, thereby ensuring concealment and anonymity.

Blinding

Blinding to the type of laryngoscopy is only possible for the patient. The performing anaesthesiologist is informed of treatment group prior to induction of anaesthesia.

METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

Data collection and management

The study data are recorded on a specific paper-based case report form (CRF). Prior to measurement, the data from each patient are collected by study personnel. All outcome measurements are recorded during and after the evaluation on the CRF. Any protocol deviations are recorded either on the CRF or in the medical records; a clinical research assistant ensures that all protocol deviations and adverse events are recorded in the database. If adverse events are observed, the ethics committee will be informed in writing.

Every allocated subject will be coded with a specific patient number. After measurement is completed, the study data will be entered into a premade computer-based table (Microsoft Excel, Version 14.0, Microsoft Corporation, Redmond, Washington, USA). The completed CRF will be secured in the Clinical Research Unit for the next 15 years.

Statistics

For statistical analysis, GraphPad Prism (Version. 6.0 for MAC; GraphPad Software, La Jolla, CA, USA) will be used. Data are expressed as the median (interquartile range [IQR]) for non-Gaussian variables. The statistical analysis will conform to the CONSORT statement for non-pharmacological interventions.

Description of the patient groups at baseline

The baseline features of the patients will be described using absolute numbers (n) and percentages for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables. We will use the Pearson correlation coefficient to compare patient specifics (e.g., BMI, ADS score) between the groups at the baseline.

Analysis of the primary outcome

A chi-squared test will be used to compare the success rate between the two groups. Multiple regression analysis of subgroup factors will allow the determination of important factors affecting successful first-time intubation comparing DL with McGrath. Relationships between the experience of the provider and the first-attempt intubation rate or time to intubation will be analysed as paired samples with Bonferroni correction for multiple comparisons. The differences will be considered statistically significant if the p-value is less than 0.05.

Analysis of the secondary outcomes

Comparison of the view of the glottis, overall intubation time and the Likert scale score will be analysed by the Wilcoxon`s Rank Sum test.

Subgroup analysis

We will perform a separate analysis of the specific type of surgery (e.g., thyroidectomy, neck dissection), influence of neuromuscular agents and/or patients with difficult intubation, defined as more than two attempts or IDS score > 5.

Sample Size

A sample size calculation was based on achieving successful tracheal intubation on the first attempt within 120 seconds (time to ventilation) compared to more than one attempt. We determined the power of the study by assuming a first-pass success rate of 85% (DL)[14,15] and 90% (McGrath).[37,38] On the basis of the current first-pass success rate, we hypothesised that an increase of 5% by skilled laryngoscopists in the McGrath group compared to the DL group would be a relevant improvement in airway management. We determined that the inclusion of 1000 patients per group would show relevant differences. With 1000 patients, an increase from 85% - 90% (DL) and 90% to 95% (McGrath) in the first-pass success rate can be observed with a power of 96% at the 1.67% significance level.

VI. METHODS: MONITORING

Data monitoring

Prior to the start of patient enrolment, the study physicians and the clinical research assistants are involved in the study protocol and data collection in CRFs. All documents required for the study (e.g., informed consent, CRF baseline and perioperative) are available in the operating room, where the study measurement begins. The CRF is prepared and managed by the investigator. Because this is an investigator initiated trial (IIT), the principal investigator meets with clinical research assistants to discuss any problems in data collection and protocol compliance and to evaluate study progress. This study is proposed, managed and will be analysed in accordance with the ICH Guideline for GCP (good clinical practice) E6 (R2) and following the requirements of German law. All persons (e.g., investigator, study assistants) are obliged to follow these rules.

Harms

The study may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the type of laryngoscope used. Reporting of severe adverse events (SAE) will be per local Research Ethics Committee (REC) standard operating procedures. SAEs will include the following when occurring as a result of airway

manipulation (cardiac arrest, acute circulatory failure, death, vocal cord injury, oesophageal rupture). The principal investigator informs the REC about the SAE. No specific reporting procedure for unexpected serious adverse events is planned.

Auditing

The Clinical Research Unit of the Department of Anaesthesiology, University Medical Centre Mainz reviews the screening form and clinical data at regular intervals.

ETHICS AND DISSEMINATION

Research ethics approval

This study is conducted in adherence with the current version of the Declaration of Helsinki and GCP Guidelines. The initial research project was approved by the ethics committee (Medical Association of the State of Rhineland Palatinate, Germany) in October 2015 (Registration Nr.: 837.296.15 (10064); NCT 02611986). It was also approved by the Medical Association Westphalia, Lippe, Germany, in March 2016 (Registration Nr.: 2016-110-b-S).

Consent or assent

Prior to the trial, patients must consent orally and in writing after the possible consequences of the clinical study are explained in an understandable way. All documents must be written in German and comprehensible. According to German law, only a physician can have the conversation with the participant. The patient receives a copy of the signed patient information and informed consent. A patient may withdraw from the study at any time if he is unwilling to continue in the trial. In this case, the data from a patient who requests full withdrawal will not be considered in the data analysis.

Confidentiality

All original documents will be kept in the Clinical Research Unit for the next 15 years.

Declaration of interests

Neither the Department of Anaesthesiology of the University Medical Centre of the Johannes Gutenberg University-Mainz, Germany nor any of its employees received any compensation for this work. No funding or competing interests are declared.

None of the authors have financial interests or received honoraria or paid expert testimony. None of the authors have any personal relationships with people or organisations that could inappropriately influence (bias) this work. Covidien®, which produces the McGrath video laryngoscope, had no role in the study design and will have no role in its conduct, data collection, analysis, or interpretation, or the decision to submit the results for publication.

DISCUSSION

To our knowledge, the EMMA trial is one of the largest such randomised, multicentre trials. Several studies have suggested that video laryngoscopy and direct laryngoscopy using a Macintosh blade had similar intubation success rates.[9,20,21,24] The weaknesses of the existing research include the study setting (e.g., manikin-based study or measurement in ICU)[10,11,20,21] and study design (e.g., inadequate sample size or variables in anaesthesia induction).[4,6,24] Furthermore, the clinical experience of the user was not usually taken into account.[5,7,11,24,27] To our knowledge, the EMMA study is the only clinical, multicentre, randomised study with 2000 patients comparing video laryngoscopy and direct laryngoscopy for the first attempt tracheal intubation. This trial has an open-label design; blinding of the operator is not feasible. However, the primary outcome measure is the presence of the inflection on the expired capnography curve to ensure that the ET is in the tracheal position. The main outcome of other studies was the duration of the intubation attempt. For detailed information about the overall intubation time, we divide the overall time into three time periods, from insertion of the laryngoscope until the first ventilation. The visualisation of the glottis is another preferred outcome parameter in several airway studies, but a good view of the glottis cannot be associated with successful or faster tracheal intubation.[21,22] Furthermore, the number of attempts constitutes a relevant factor for increased airway complications (e.g., risk of aspiration, tissue/ mucosal damage) and desaturation during the intubation process.[15-17]

In conclusion, if our main hypothesis is confirmed, video laryngoscopy might become the reference standard in the operating room. The expected benefits of this practice include improved instruction of airway management and influence of neuromuscular

agents for the intubation procedure as well as improved patient safety in terms of decreased airway complications (e.g., hypoxemia, aspiration).

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Contributors

MK and RN designed the trial and prepared the manuscript. TP, IT and CA participated in designing the EMMA trial. IS wrote the statistical analysis plan and estimated the sample size. None of the authors have financial interests or received honoraria or paid expert testimony. None of the authors have any personal relationships with people or organisations that could inappropriately influence (bias) this work. The authors alone are responsible for the content and writing of the paper.

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No funding or competing interests are declared.

Patient consent

Obtained.

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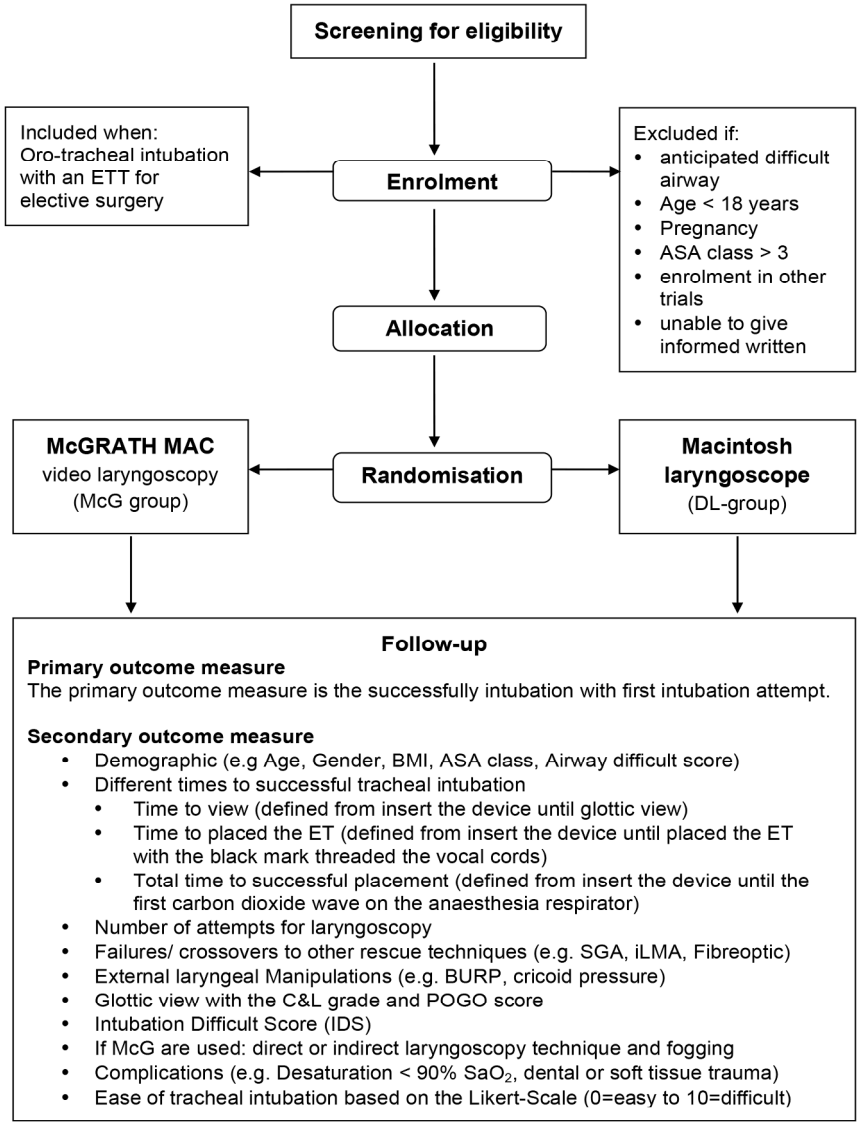
TABLE AND FIGURE

Figure 1. Study flow-chart.

Table 1. Recapitulation of previous studies on endotracheal intubation with video laryngoscopy in different study setting.

Table 2. Participant timeline.

Figure 1: Study flow-chart



Study flow-chart

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4,17
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,19
	5b	Name and contact information for the trial sponsor	1-2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1,19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17-19

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6,13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12,13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12,13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14,15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6,9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14,16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16,17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13-14
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17,19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	n/a
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Evaluation of the McGrath MAC and Macintosh Laryngoscope for tracheal intubation in 2000 patients undergoing general anaesthesia: The randomised multicentre EMMA trial study protocol

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Anaesthesia – Protocol

Evaluation of the McGrath MAC® and Macintosh Laryngoscope for tracheal intubation in 2000 patients undergoing general anaesthesia: The randomised multicentre EMMA trial study protocol

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ABSTRACT

Introduction: The direct laryngoscopy technique using a Macintosh blade is the first choice globally for most anaesthetists. In case of an unanticipated difficult airway, the complication rate increases with the number of intubation attempts. Recently, McGrath MAC® (McGrath) video laryngoscopy has become a widely accepted method for securing an airway by tracheal intubation because it allows the visualisation of the glottis without a direct line of sight. Several studies and case reports have highlighted the benefit of the video laryngoscope in the visualisation of the glottis and found it to be superior in difficult intubation situations. The aim of this study was to compare the first-pass intubation success rate using the (McGrath) video laryngoscope compared with conventional direct laryngoscopy in surgical patients.

Methods and analysis: The EMMA trial is a multicentre, open-label, patient-blinded, randomised controlled trial. Consecutive patients requiring tracheal intubation are randomly allocated to either the McGrath video laryngoscope or direct laryngoscopy using the Macintosh laryngoscope. The expected rate of successful first-pass intubation is 95% in the McGrath group and 90% in the Macintosh group. Each group must include a total of 1000 patients to achieve 96% power for detecting a difference at the 5% significance level. Successful intubation with the first attempt is the primary endpoint. The secondary endpoints are the time to intubation, attempts for successful intubation, the necessity of alternatives, visualisation of the glottis using the Cormack & Lehane score and percentage of glottic opening score and definite complications.

Ethics and dissemination: The project was approved by the local ethics committee of the Medical Association of the Rhineland Palatine state and Westphalia-Lippe. The results of this study will be made available in the form of manuscripts for publication and presentations at national and international meetings.

Trial registration: ClinicalTrials.gov NCT 02611986.

Strengths and limitations of this study

- This trial aims to determine whether video laryngoscopy is superior to direct laryngoscopy in daily anaesthesia practice.
- The plan is to include 2000 patients in this multicentre, open-label, randomised controlled superiority study.
- All training levels of anaesthesiologists (trainee, specialist, expert) are included.
- Selected patients with an expected normal airway are evaluated.
- One type of video laryngoscope using a Macintosh-like blade is evaluated. The results cannot be transferred to other kinds of video laryngoscopes (e.g., hyperangulated blade, channelled blade).

INTRODUCTION

Background and rationale

(A) Securing the airway by tracheal intubation with direct laryngoscopy is an established and preferred technique in emergency settings and clinical anaesthesia practice. The limitations of direct laryngoscopy are well known. To achieve a learning curve with a 90% probability of performing a successful intubation, more than 57 attempts are required to develop enough experience with the technique.[1,2] To obtain optimal visualisation of the glottis, direct laryngoscopy requires alignment of the oropharyngeal-laryngeal axes.

However, the first-pass success rate of intubation in emergency settings ranges from 40 to 80%,[3-7] in intensive care units from 55 to 68% [8-10] and in the operating room from 63 to 85%.[11-14] Several studies have shown a correlation between increased complications and more than two intubation attempts.[15-17]

Indirect video laryngoscopy has become a widely accepted method for learning the techniques of airway management because it enables an optimised view of the glottis without a direct line of sight.[18-20] Thus, video laryngoscopy plays an important role in the management of patients with unanticipated airway difficulties or failed tracheal intubation. The use of video laryngoscopy is associated with a reduction in airway complications in clinical emergency and anaesthesia practice.[17,21] Despite the optimised visualisation of the glottis, the duration of tracheal intubation can be prolonged, and intubation attempts can fail.[20-23] Compared to direct laryngoscopy, the learning curve associated with the video laryngoscope is steep.[24] Video laryngoscopy varies in the design of the curved or angulated blade, mobility, size of the monitor display and operation of the micro camera on the blade.

Over the last 10 years, several studies have compared different video laryngoscopes to direct laryngoscopy or to each other, focusing on endotracheal intubation (ET) in emergency settings or in patients undergoing elective surgery in an operating room. The results suggested advantages in superior visualisation of the glottis,[18,20,22] a higher first-pass success rate [3,10,18,23], and reduction of airway complications as well as benefits in those patients with a difficult airway.[20-22] However, most of these studies had methodological weaknesses, including studies with small sample sizes,[5,12,18-20,23] evaluation in intensive care units [3,6,9,10,25,26] or emergency departments,[4,5,7] manikin studies [19,20] and inclusion of patients who were anticipated to have a difficult airway.[11,18-22]

Studies conducted more recently have suggested advantages with video laryngoscopy but either failed to routinely use neuromuscular blockade,[3] in contraindication to current guidelines, or included patients with highly specific characteristics.[4,7] Special study characteristics are listed in Table 1.

(B) We chose to study the McGrath® MAC (McGrath; Covidien, Dublin, Ireland) video laryngoscope because it is a portable, relatively inexpensive device with a Macintosh-based blade similar to that in the Macintosh laryngoscope (DL; Stoss Medica, Wiesbaden, Germany). It therefore provides both a direct view of the glottis and an indirect view on the monitor display, which can be beneficial in the case of oropharyngeal mismatch. Our specific choice of the McGrath video laryngoscope was based on the following considerations:

- The Macintosh-based curved blade of the McGrath is comparable to the Macintosh blade;
- The video display of the McGrath allows visualisation of the glottis by the operator along with study measurement or teaching by a consultant when tracheal intubation is performed by an inexperienced provider; and
- The McGrath is available with a disposable blade in different sizes and allows a swift change to treat more patients consecutively.

The aim of this study is to evaluate whether the use of the McGrath improves the first-pass success rate compared with the DL in surgical patients with an expected normal airway undergoing general anaesthesia. We hypothesise that tracheal intubation using the McGrath decreases the frequency of failed intubation and airway complications.

Table 1. Recapitulation of previous studies on endotracheal intubation with videolaryngoscopy in different study settings.

First author	Device	Operators	Centre	Design	N	First-pass Success (DL vs. VL)	*p* value	Comments
Data shown a higher First-pass Success rate with the Videolaryngoscopy								
Silverberg et al. [3]	GS	Attending's	Monocentre	Randomised	117	40% vs. 74%	< 0.001	ICU
Park et al. [4]	GS	Non-anaesthesiologists	Monocentre	Randomised	82	55.9% vs. 91.8%	< 0.001	ED
Ahmadi et al. [5]	GS	Residents	Monocentre	Randomised	97	60.9% vs. 87.5%	0.036	ED
Mosier et al. [8]	GS, CMAC	Non- anaesthesiologists residents/ attending	Monocentre	Non-randomised	234	60.7% vs 78.6%	0.009	ICU
Sakles et al. [6]	GS	Resident	Monocentre	Randomised	822	57% vs. 75%	0.03	ED
Noppens et al.[9]	CMAC	Residents	Monocentre	Prospective	274	55% vs. 79%	0.03	ICU
Kory et al.[10]	GS	Non- anaesthesiologists	Monocentre	Retrospective	128	68% vs. 91%	0.01	ICU
Noppens et al.[18]	McGrath S5	Residents	Monocentre	Prospective	67	69% vs. 95%	< 0.001	
Savoldelli et al. [21]	GS, McGrath S5, Airtraq	Mixed	Monocentre	Randomised	60	63% vs. 88% vs. 100% vs. 88%	< 0.001	Manikin-study
Kasuya et al. [37]	McGrath	Anesthesia trainees	Monocentre	NR	NR	78.6% vs. 92.8%	< 0.001	
Data shown a similar or higher First-pass Success rate with Direct Laryngoscopy								
Yeatts et al.[7]	GS	Mixed	Monocentre	Randomised	623	80% vs. 81%	0.46	ED
Piepho et al.[11]	CMAC	Residents	Monocentre	Prospective	52	79% vs. 81%	0.8	
Ruetzler et al.[20]	CMAC,GS, McGrath S5, KV, Airtraq	Mixed	Monocentre	Randomised	27	96.7% vs. 100% vs. 44.4% vs. 77.8 vs. 88.9% vs. 100%	< 0.001	Manikin-study
Piepho et al.[23]	McGrath S5, GS	Paramedics	Monocentre	Randomised	30	94.4% vs. 97.7%	> 0.05	Manikin-study
Purugganan et al.[36]	McGrath, C-MAC	Residents	Monocentre	Randomised	130	95% vs. 87% vs. 91%	0.4	

Mixed (Residents/ Attending's); ED (Emergency Department); ICU (Intensive Care Unit); CMAC= C-MAC (Storz, Germany); GS= GlideScope (Verathon, USA); BO= Bonfils (Storz, Germany); McGrath= McGrath (Medtronic, Irland); McGrath Series 5= McGrath (Medtronic, Irland); KV= King Vision (Kingssystems, USA); Airtraq (Airtraq, USA); AWS= Airway-scope (Pentax, Japan); NR (Not reported)

Study aims and objectives

Primary objective: Comparing the initial or first-pass success rate of endotracheal intubation with the McGrath video laryngoscope to DL using a Macintosh blade in patients undergoing elective surgery and requiring tracheal intubation.

Secondary objective: Comparing the clinical performance of both devices, view of the glottis, influence of neuromuscular agents, correlation between clinical experiences in airway management and success rates.

Trial design

The EMMA trial is a multicentre, open-label, randomised controlled superiority trial.

METHODS: PARTICIPANT SELECTION, INTERVENTIONS AND OUTCOMES

This manuscript was written in accordance with the SPIRIT guidelines.[27]

Study setting

The EMMA trial is performed in eight Divisions of Anaesthesiology in two hospitals (one university and one general hospital). All laryngoscopists are anaesthetists with different levels of clinical experience using direct and video laryngoscopy. After a specific introduction to the study protocol, all anaesthetists from the study centres participated in this trial.

Eligibility criteria

Inclusion criteria

Patients having elective surgery with general anaesthesia and requiring mechanical ventilation via an endotracheal tube are recruited.

Exclusion criteria

Patients are not included in this study if they have one or more of the following:

- More than one predictor of an anticipated difficult airway (e.g., BMI > 40 kg/m^2, unanticipated difficult airway in the medical history (e.g., C&L ≥ III), reduction of the atlanto-occipital joint extension < 35°, reduced thyromental distance < 6 cm or Mallampati class ≥ III);
- Age < 18 years;
- ASA class IV;

- Pregnant or breastfeeding;
- Participation in other studies;
- Unable to provide informed written consent or under guardianship;
- Urgent surgical intervention; and
- At high risk for aspiration.

Intervention

Concomitant treatments in both groups

First, patients admitted requiring elective tracheal intubation are evaluated for predictors of anticipated difficult intubation (body mass index, head extension, thyromental distance, Mallampati class, mouth opening and previous difficult airway (e.g., C&L ≥ III). The expertise of the participating anaesthesiologists ranges from "beginner" (residents) to "expert" (consultants). All anaesthetists received hands-on training and theoretical introduction to the use of the McGrath VL and direct laryngoscopy. Tracheal intubation is performed in both groups following the protocol outlined below (Figure 1).

(A) All patients are monitored for ECG, oxygen saturation (SO_2), and arterial blood pressure (non-invasive or invasive as appropriate). In the McGrath group, a malleable stylet in a "hockey-stick" shape is always used for tube placement.

Pre-oxygenation is achieved using the device chosen by the provider based on patient characteristics and clinical standard operating procedure (EtO_2 > 80%). In the study locations a Pallas® / Primus® (Dräger Lübeck, Germany) anaesthesia respiratory system is used:

- Tidal volume breathing with normal breaths for at least 3 min or with eight deep breaths over 60 seconds (8 DB 60 sec);[28,29]
- Anaesthesia ventilator in pressure support (PS) mode (PS 8 mbar, PEEP 5 mbar and FiO_2 1.0).[29,30]

(B) After sufficient pre-oxygenation, anaesthesia is induced with sufentanil (0.2 – 0.5 $\mu g.kg^{-1}$) and propofol (2 – 3 $mg.kg^{-1}$), and anaesthesia is maintained with either propofol infusion (TIVA) or volatile anaesthetics. After the patient is deeply anaesthetised, the neuromuscular transmission is monitored using acceleromyography of the adductor pollicis. The individual choice of neuromuscular blocking agent depends on the temporal duration of the surgery, necessary of

perioperative neurological monitoring, absence of allergies and organ failures. The following agents and specific dosages are used:

- Mivacurium (0.2 $mg.kg^{-1}$);
- Atracurium (0.5 $mg.kg^{-1}$);
- Rocuronium (0.3 - 0.6 $mg.kg^{-1}$); and
- Succinylcholine (1 - 2 $mg.kg^{-1}$).

The train-of-four (TOF) is used for continuous quantitative monitoring of neuromuscular transmission. Complete muscle relaxation is confirmed in the absence of tactile and measured twitches in response to maximal TOF stimulation of the ulnar nerve at the adductor pollicis. The importance of obtaining adequate neuromuscular blockade was emphasised with study personnel.

(C) The laryngoscopy attempt begins with a TOF count of 0/4 and is performed using the device indicated by default randomisation:

- Macintosh laryngoscope (DL) or
- McGrath® MAC video laryngoscope (McGrath) - direct laryngoscopy or indirect laryngoscopy can be performed at the discretion of the anaesthetist.

The provider selects the method for visualisation of the glottis, either direct or indirect, using the McGrath monitor. The anaesthetist should achieve the best possible view of the laryngeal structures. External laryngeal manipulations (ELM) could be used to improve the view of the glottis to achieve a C&L I or II. The size of the endotracheal tube and the size of the blade are dependent on the standard operating procedure of the hospital (blade size in both groups: #3 for average patients and #4 for very tall patients (> 190 cm height); standard ET size: 7.0 ID used for female patients and 7.5 ID for male patients). The method of visualisation of the glottis and size of the ET/ blade is recorded in the case report form (CRF).

(D) The laryngoscopy attempt is defined as successful if the tracheal tube is placed (until the black mark on the ET was threaded between the vocal cords) with a single blade insertion within 120 seconds and without manipulation of the laryngoscope by another provider. The “time to intubation” is defined as the time measured from the opening of the patient’s mouth until the ET passed the vocal cords. An anaesthesia nurse measures the intubation time using the built-in timer on the anaesthesia respirator. We also analyse two time periods until final placement:

- "Time to view": defined as the time from insertion of the device until visualisation of the glottis;
- "Time to intubation": defined as the time from insertion of the device until the ET passed through the vocal cords; and
- "Time to ventilation": defined as the time from insertion of the ET until the time from the insertion of the device into the mouth until confirmation of the first wave of CO_2 of the anaesthesia respirator.

An intubation attempt is defined as an introduction of the laryngoscope blade into the mouth and its removal regardless of whether an ET was successfully inserted. If this first attempt fails, the provider makes a second laryngoscopy attempt with the same device. Mask ventilation is recommended between the attempts. A total of two laryngoscopy attempts are allowed. If DL fails, the clinician changes to a preferred technique (e.g., McGrath, S-Guide®, rigid stylet) and records the direct and/or screen view of the McGrath. If McGrath fails after two attempts, the clinician is advised to proceed with a preferred rescue technique (e.g., C-MAC® D-Blade, SGA, iLMA, fibreoptic, rigid stylet). The limitation of two intubation attempts and choice of an alternative technique is recommended by the study protocol and is in accordance with the clinical standard.[31] If ELM techniques, such as BURP (specific pressure applied to the cricoid cartilage), are required during laryngoscopy, they are recorded in the CRF. In all cases, an additional individual who is not involved in patient care (either a postgraduate student or a study nurse) is present during induction of anaesthesia to record the study parameters.

Outcome measures

(a) Primary outcome measure

The primary outcome measure is successful intubation within 120 seconds (time to ventilation) with the first-pass attempt.

(b) Secondary outcome measure

- Laryngoscopy Technique: Whether direct or indirect glottic visualisation was used in the McGrath group is recorded
- Different times for successful tracheal intubation
  - Time to view (defined as the time from insertion of the device until glottic view)

- Time to intubation (defined as the time from insertion of the device until the ET passed through the vocal cords)
- Time to ventilation (defined as the time from insertion of the device until the first carbon dioxide wave on the anaesthesia respirator)

- Number of laryngoscopy attempts
- Failures/ crossovers to other rescue techniques (e.g., SGA, iLMA, fibreoptic)
- External laryngeal manipulations (e.g., BURP, cricoid pressure)
- Glottic view with the Cormack & Lehane grade (C&L) and percentage of glottic opening score (POGO)
- Intubation difficulty score (IDS-Score) [32]
- If McGrath is used, occurrence of fogging is recorded
- Comparing the level of training with intubation success
- Complications (e.g., desaturation < 90% SaO_2, dental or soft tissue trauma)
- Degree of ease or difficulty of tracheal intubation based on the Likert scale (0=easy to 10=difficult) [33,34]

(c) Subgroup analysis

- Demographics
  - Patient (age, gender, BMI, ASA class)
  - Airway difficulty score (ADS score) [35]
  - Provider analysis (clinical experience, education status, experience in direct and indirect laryngoscopy)
- Type of neuromuscular blocking agent
- Train-of-four (TOF) count when inserting the laryngoscope
- Type of surgery (e.g., thyroidectomy, neck dissection)

Participant timeline

The schedule of enrolment and intervention is shown in Figure 1, and the participant timeline is described in Table 2.

Table 2. Participant timeline.

	Study Period					
	Enrolment	Intervention	Intubation			Extubation
Timepoint	D_0	D_1	D_1 *(Time to view)*	D_1 *(Time to intubation)*	D_1 *(Time to ventilation)*	D_{1-2}
Eligibility Assessment	X					
Informed consent	X					
Randomisation	X					
Demographic data and physical Examination	X					
Preoxygenation		X				
Induction of Anaesthesia		X				
TOF measurement		X				
Time measurement			X	X	X	
Glottic View			X			
Intubation success					X	
Complications			X	X	X	X

D= Day; D_0= Day of Enrolment / Allocation; D_1= Day of Surgery; D_2= Intensive care unit (ICU) stay

Recruitment

Patient inclusion started in 2016 in the Division of Ear, Nose and Throat surgery at University Medical Centre, Mainz, Germany, and inclusion of other divisions over the course of time is planned. The history and physical examinations of all patients scheduled for surgery are screened preoperatively for predictors of difficult airway. Patient recruitment is conducted by one of the study physicians. Patients are included if they require orotracheal intubation with an ET under general anaesthesia with neuromuscular blocking agents.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation

After eligibility is confirmed and written informed consent is obtained, enrolled participants are randomised 24 hours before the intervention. A web-based service (QuickCalcs, GraphPad Software, La Jolla, CA, USA) is used for allocating patients to either DL or McGrath.

Sequence generation

The randomisation sequence was generated by a study nurse in the Clinical Research Unit who is not involved in patient recruitment. The software used to collect the data in the CRF automatically allocated the patients, thereby ensuring concealment and anonymity.

Blinding

Blinding to the type of laryngoscopy is only possible for the patient. The performing anaesthesiologist is informed of treatment group prior to induction of anaesthesia.

METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

Data collection and management

The study data are recorded on a specific paper-based case report form (CRF). Prior to measurement, the data from each patient are collected by study personnel. All outcome measurements are recorded during and after the evaluation on the CRF. Any protocol deviations are recorded either on the CRF or in the medical records; a clinical research assistant ensures that all protocol deviations and adverse events are recorded in the database. If adverse events are observed, the ethics committee will be informed in writing.

Every allocated subject will be coded with a specific patient number. After measurement is completed, the study data will be entered into a premade computer-based table (Microsoft Excel, Version 14.0, Microsoft Corporation, Redmond, Washington, USA). The completed CRF will be secured in the Clinical Research Unit for the next 15 years.

Access to data

Data safety, data quality and statistical analysis will be managed by the two principal investigators, who are responsible for notifying any issues that may arise during the whole prospective study. Data is collected and stored according to GCP guidelines and is available to all participating study sites. Any issue occurring during the clinical trial will be reported to the principal investigators.

Statistics

For statistical analysis, GraphPad Prism (Version. 6.0 for MAC; GraphPad Software, La Jolla, CA, USA) will be used. Data are expressed as the median (interquartile range [IQR]) for non-Gaussian variables. The statistical analysis will conform to the CONSORT statement for non-pharmacological interventions.

Description of the patient groups at baseline

The baseline features of the patients will be described using absolute numbers (n) and percentages for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables. We will use the Pearson correlation coefficient to compare patient specifics (e.g., BMI, ADS score) between the groups at the baseline.

Analysis of the primary outcome

A chi-squared test will be used to compare the success rate between the two groups. Multiple regression analysis of subgroup factors will allow the determination of important factors affecting successful first-time intubation comparing DL with McGrath. Relationships between the experience of the provider and the first-attempt intubation rate or time to intubation will be analysed as paired samples with Bonferroni correction for multiple comparisons. The differences will be considered statistically significant if the p-value is less than 0.05.

Analysis of the secondary outcomes

Comparison of the view of the glottis, overall intubation time and the Likert scale score will be analysed by the Wilcoxon`s Rank Sum test. Comparing the different level of training with the intubation success with the Spearman's rank correlation coefficient.

Subgroup analysis

We will perform a separate analysis of the specific type of surgery (e.g., thyroidectomy, neck dissection), influence of neuromuscular agents and/or patients with difficult intubation, defined as more than two attempts or IDS score > 5.

Sample Size

A sample size calculation was based on achieving successful tracheal intubation on the first attempt within 120 seconds (time to ventilation) compared to more than one attempt. We determined the power of the study by assuming a first-pass success rate of 85% (DL)[13,14] and 90% (McGrath).[36,37] On the basis of the current first-pass success rate, we hypothesised that an increase of 5% by skilled laryngoscopists in the McGrath group compared to the DL group would be a relevant improvement in airway management. We determined that the inclusion of 1000 patients per group would show relevant differences. With 1000 patients, an increase from 85% - 90% (DL) and 90% to 95% (McGrath) in the first-pass success rate can be observed with a power of 96% at the 1.67% significance level.

VI. METHODS: MONITORING

Data monitoring

Prior to the start of patient enrolment, the study physicians and the clinical research assistants were involved in the study protocol and data collection in CRFs. All documents required for the study (e.g., informed consent, CRF baseline and perioperative) are available in the operating room, where the study measurement begins. The CRF is prepared and managed by the investigator. Because this is an investigator initiated trial (IIT), the principal investigator meets with clinical research assistants to discuss any problems in data collection and protocol compliance and to evaluate study progress. This study is proposed, managed and will be analysed in accordance with the ICH Guideline for GCP (good clinical practice) E6 (R2) and following the requirements of German law. All persons (e.g., investigator, study assistants) are obliged to follow these rules.

Harms

The study may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the type of laryngoscope used. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalisation or prolongation of existing hospitalisation, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

Reporting of severe adverse events (SAE) will be per local Research Ethics Committee (REC) standard operating procedures. SAEs will include the following when occurring as a result of airway manipulation (e.g. cardiac arrest, acute circulatory failure, death, vocal cord injury, oesophageal rupture). The principal investigator informs the REC about the SAE. No specific reporting procedure for unexpected serious adverse events is planned.

Auditing

The Clinical Research Unit of the Department of Anaesthesiology, University Medical Centre Mainz reviews the screening form and clinical data at regular intervals.

ETHICS AND DISSEMINATION

Research ethics approval

This study is conducted in adherence with the current version of the Declaration of Helsinki and GCP Guidelines. The initial research project was approved by the ethics committee (Medical Association of the State of Rhineland Palatine, Germany) in October 2015 (Registration Nr.: 837.296.15 (10064); NCT 02611986). It was also approved by the Medical Association Westphalia, Lippe, Germany, in March 2016 (Registration Nr.: 2016-110-b-S).

Consent or assent

Prior to the trial, patients must consent orally and in writing after the possible consequences of the clinical study are explained in an understandable way. All documents must be written in German and comprehensible. According to German law, only a physician can have the conversation with the participant. The patient

receives a copy of the signed patient information and informed consent. A patient may withdraw from the study at any time if he is unwilling to continue in the trial. In this case, the data from a patient who requests full withdrawal will not be considered in the data analysis.

Confidentiality

All original documents will be kept in the Clinical Research Unit for the next 15 years. The study data will be handled as requested by the German Federal Data Protection Act, which implements the Directive 95/46/EC on data protection (Data Protection Directive). All original records will be kept on file at the trial sites or coordinating data managing centre for 15 years. The cleaned electronic trial database file will be anonymised and kept on file for 15 years.

Declaration of interests

Neither the Department of Anaesthesiology of the University Medical Centre of the Johannes Gutenberg University-Mainz, Germany nor any of its employees received any compensation for this work. No funding or competing interests are declared. None of the authors have financial interests or received honoraria or paid expert testimony. None of the authors have any personal relationships with people or organisations that could inappropriately influence (bias) this work. Covidien®, which produces the McGrath video laryngoscope, had no role in the study design and will have no role in its conduct, data collection, analysis, or interpretation, or the decision to submit the results for publication. The findings of this study will be presented at conferences and disseminated through publication in a peer reviewed journal.

DISCUSSION

To our knowledge, the EMMA trial is one of the largest such randomised, multicentre trials. Several studies have suggested that video laryngoscopy and direct laryngoscopy using a Macintosh blade had similar intubation success rates.[7,11,20,23] The weaknesses of the existing research include the study setting (e.g., manikin-based study or measurement in ICU)[9,10,19,20] and study design (e.g., inadequate sample size or variables in anaesthesia induction).[3,5,23] Furthermore, the clinical experience of the user was not usually taken into account.[4,6,10,23,25] To our knowledge, the EMMA study is the only clinical, multicentre, randomised study with

2000 patients comparing video laryngoscopy and direct laryngoscopy for the first attempt tracheal intubation. This trial has an open-label design; blinding of the operator or the patient are not feasible. However, the primary outcome measure is the presence of the inflection on the expired capnography curve to ensure that the ET is in the tracheal position. The main outcome of other studies was the duration of the intubation attempt. For detailed information about the overall intubation time, we divide the overall time into three time periods, from insertion of the laryngoscope until the first ventilation. The visualisation of the glottis is another preferred outcome parameter in several airway studies, but a good view of the glottis cannot be associated with successful or faster tracheal intubation.[20,21] Furthermore, the number of attempts constitutes a relevant factor for increased airway complications (e.g., risk of aspiration, tissue/ mucosal damage) and desaturation during the intubation process.[14-17]

In conclusion, if our main hypothesis is confirmed, video laryngoscopy might become the reference standard in the operating room. The expected benefits of this practice include improved instruction of airway management and influence of neuromuscular agents for the intubation procedure as well as improved patient safety in terms of decreased airway complications (e.g., hypoxemia, aspiration).

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Contributors

MK and RN designed the trial and prepared the manuscript. TP, IT and CA participated in designing the EMMA trial. IS wrote the statistical analysis plan and estimated the sample size. None of the authors have financial interests or received honoraria or paid expert testimony. None of the authors have any personal relationships with people or organisations that could inappropriately influence (bias) this work. The authors alone are responsible for the content and writing of the paper.

Funding and competing interests

No funding or competing interests are declared.

Patient consent

Obtained.

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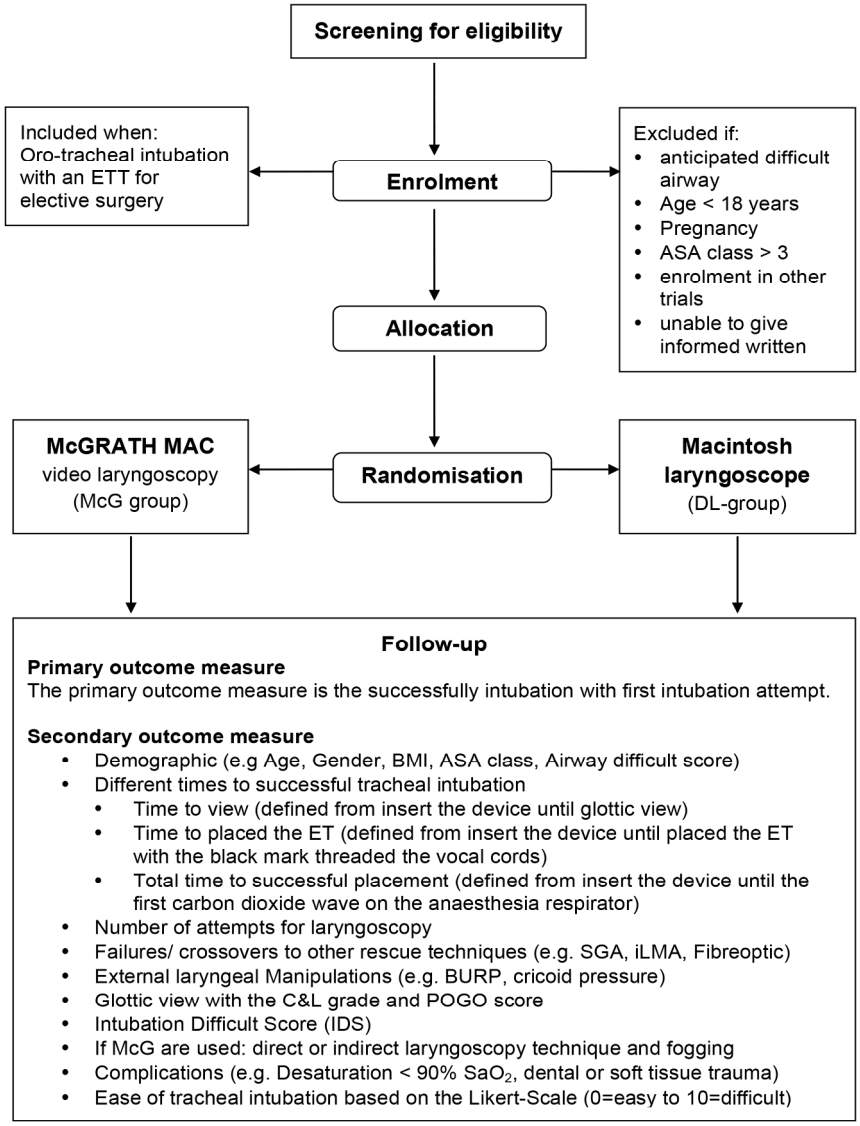
TABLE AND FIGURE

Figure 1. Study flow-chart.

Table 1. Recapitulation of previous studies on endotracheal intubation with video laryngoscopy in different study setting.

Table 2. Participant timeline.

Figure 1: Study flow-chart



Study flow-chart

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4,17
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	18,20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,19
	5b	Name and contact information for the trial sponsor	1-2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18,19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13,14,16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	6,8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8,17,18
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8,17,18
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11,13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12,13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16,19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13,14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17,18
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14,19
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	14,19
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15,16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14,15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	n/a

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17,18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14,17,18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18,20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15,18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	4,18
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17,18
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.