# Research protocol

## **Safety of uninterrupted peri-procedural direct-acting oral anticoagulation during colonoscopy (SuDOC trial)**

**Principal Investigators:**

Shweta Sharma1, Dr Nicholas Tutticci1

1QEII Jubilee Hospital, Department of Gastroenterology, Brisbane, Queensland

## **Introduction**

Post-polypectomy bleeding is an important and feared adverse event after colonic polypectomy. The incidence, however, is low and the frequency of intervention required is even lower.1,2 Post-polypectomy bleeding, whether immediate or delayed, rarely results in the need for surgery or death.3 The risk of bleeding after poly resection ranges from 0.3 to 10% depending on factors such as polyp size, type of polyp and the technique of removal.4Thromboembolic complications on the other hand, despite also being uncommon (<1%), can have devastating outcomes including permanent disability and major cardiac event.5,6 Individual risk of dictated by patient co-morbidities, indication for anticoagulation and timing since last thrombotic event. Optimal peri-procedural anticoagulation strategy aims to balance these risks.

Specifically with regards to safety of anticoagulation, studies evaluating post-polypectomy bleeding and thromboembolic risk have found that there is a longer hospital stay in patients who interrupt their anticoagulation.7 The two available options for oral anticoagulation include warfarin and direct-acting oral anti-coagulants (DOACs). Horiuchi *et al.* in 2014 assessed the risk of performing small (<10mm) cold snare polypectomy with uninterrupted warfarin. They conducted a prospective randomised controlled study and concluded that the risk is lower in cold snare polypectomy compared to conventional polypectomy. Additionally, the risk of delayed bleeding in the cold snare polypectomy group was negligible at 0%.8

In our centre, we are currently continuing DOACs for colonoscopies in selected patients on a case-by-case basis. If there is any bleeding, it is usually immediate causing some technical interference but allowing the opportunity for haemostasis to be achieved during the procedure.

In a recently published prospective single centre observational cohort study from Japan, Yabe *et al.,* investigated the risks of procedure-related bleeding in patients with or without anti-thrombotic therapy. Consistent with our experience, they found a low rate of immediate and delayed bleeding requiring endoscopic treatment in patients on DOACs with cold-snare polypectomy. Prophylactic clipping was not routinely performed.9

Currently, American Society of Gastrointestinal Endoscopy (ASGE; 2016), the British Society of Gastroenterology/European Society of Gastrointestinal Endoscopy (BSG/ESGE; 2021) as well as the joint Asian Pacific Association of Gastroenterology (APAGE) and Asian Pacific Society for Digestive Endoscopy (APSDE) practice guidelines from 2018 deem all polypectomy as a “higher risk procedure”. Hence, interruption of DOAC therapy from 1-4 day period is recommended with acknowledgment of low-quality of evidence to support the claim.4,10,11

Reviewing our local guidelines, Queensland Health anticoagulation guidelines last renewed in 2014 recommend minimum 1-3 day period of withholding DOACs prior to a procedure associated with low risk of bleeding. The guidelines do not clarify whether a colonoscopy with polypectomy is considered a low or a high risk procedure. This lack of precision is secondary to the fact that available data guiding local and international guidelines is sparse and heterogenous. The definitions of immediate and delayed post-polypectomy bleeding are often ill-defined or overall inconsistent. There is also absence of standardized endoscopic technique and the use of haemostatic clipping. Adding to the ambiguity, the recommendation to withhold DOACs for polypectomy as per the above guidelines is universal regardless of patient comorbidities, age, polypectomy size, proceduralist experience or technique used despite all these factors playing an important role in individual bleeding risk.

The 2017 American College of Cardiology Clinical Expert Consensus has defined the two determinants of risk as the incidence and implications, i.e. associated sequelae of a procedure.12 Advances in the last decades have made colonoscopies safer, rendering previous guidelines obsolete and due for revision. This is also reflected in the newer literature where colonoscopies are now being classed as a “low risk” procedure.13,14 The guidelines, however, lag behind latest evidence and consequently, their adherence remains inconsistent.

Clarity of individual risk is essential as those with moderate to high risk of thromboembolic events are also those who are most likely to require colonoscopies. DOACs are increasingly prescribed in this group. Data suggests that those with higher cardiovascular risk for instance are at a higher risk of polyposis.15,16 They are more likely to require polypectomies and surveillance colonoscopies with multiple periods of temporary anticoagulation cessation through their lifetime resulting in a more cumulative thrombosis risk.

Further studies are prudent to fill-in the gaps in our knowledge to allow case by case structured decision-making. As the number of patients receiving DOACs for treatment or prevention of cardiovascular or cerebrovascular diseases increases, data to support nuanced anticoagulation management is essential.

## **Aims**

a. Aim/hypothesis

* Our aim is to demonstrate non-inferiority of uninterrupted DOAC in terms of peri-procedural complications in patients on DOAC therapy for risk of thrombosis compared to temporary anticoagulation interruption prior to elective colonoscopy and polypectomy.
* We hypothesize that in patients on regular DOAC therapy, undergoing elective colonoscopy and polypectomy, uninterrupted anticoagulation with DOACs is safe and does not increase the risk of peri-procedural complications.

## **Method**

### **Study setting and duration**

The study will be undertaken at the Queen Elizabeth II (QEII) Jubilee hospital in Brisbane, Australia. This is a medium metropolitan public health care service. The population is ethnically diverse. Procedures are conducted with Anaesthetist delivered sedation and standard split dose GlycoPrep-C® bowel preparation.

To ensure standardization, all procedures in this study will be performed by three nationally accredited consultant Gastroenterologists including the study investigator or a senior endoscopy fellow under direct supervision. All colonoscopies will be performed by endoscopists who each perform more than 500 colonoscopies per year.

On average, each of the three Gastroenterologists perform 8-10 colonoscopies per week at QEII. We anticipate the recruitment to be ongoing for the initial six months of the study unless the recruitment is slow and the study period needs to be prolonged for unexpected reasons.

Standard cessation of medications for 7 days at QEII hospital prior to colonoscopies include:

* Fish oil supplements
* Ginko-Biloba
* Iron supplements
* Glucosamine
* Fibre supplements

### **Study type/design**

### This will be a randomized controlled single-center cohort study with the plan to enroll consecutive patients undergoing elective colonoscopies. An equal number of patients will be allocated to both the groups with an additional 5-10% recruitment to account for potential drop-out rate. This will be a single blinded study where clinicians performing the endoscopy will be blinded to treatment allocation.

Phase I and II

The study will be performed in two phases with the aim to substantiate our anecdotal experience with 100 participants in each arm in Phase I. The intention is to identify logistical bottlenecks and to adequately power/determine sample size for Phase II. An independent Data Safety Review will be performed post recruitment of 25 patients per am before proceeding with further data collection.

Given our anecdotal experience of low rate of complication, we are expecting the Phase II estimated sample size to be high but will aim to use the data from Phase 1 to determine the appropriate size.

### **Participants**

Exclusion by default

Patients who would automatically be excluded in this study would be those who are not suitable for DOAC therapy. These include those with a body mass index above 40 or weight greater than 120kg. Additionally, patients with decompensated cirrhosis, coagulopathy or thrombocytopenia, previous thrombotic or bleeding event on DOACs, mechanical valves, creatinine clearance (CrCl) <30 mL/min (<25 mL/min for apixaban) based on the Cockcroft-Gault formula or on dialysis will be excluded. Patients who have had an ischaemic stroke or angioplasty in last 6 months would also be predictably excluded given concurrent antiplatelet therapy in this group.

Inclusion criteria

* Patients undergoing elective colonoscopy
* Chronically anticoagulated with DOACs (Apixaban/Dabigatran/Rivaroxaban)
* Ages between 18 and 80 years

Exclusion criteria

* Individual characteristics:
  + Concurrent antiplatelet therapy prescribed
  + Discharge location distance from the hospital of greater than 100 kilometres
  + Individuals unable to give consent
  + Patients with renal impairment (defined as eGFR <45)
* Continuation of anticoagulation is not advised:
  + Prior peri-procedural bleeding requiring anticoagulation cessation/intervention/hospitalisation
* Interruption to anticoagulation not recommended:
  + Thromboembolic event in the preceding 3 months
  + Active malignancy
* Procedure planned to be performed by alternative clinician not participating in the study
* Endoscopic factors:
  + Emergency procedure
  + Concurrent endoscopy being performed on same day
  + Planned therapeutic procedure (i.e. large polypectomy/endo-mucosal resection/endoscopic submucosa dissection/dilatation)
  + Expected high burden of polyps (i.e. known polyposis syndrome not yet completed clearance colonoscopy)

**Recruitment**

The recruitment/introduction to the study will occur at three possible points of contact with the patients:

1. Gastroenterology physician clinic
2. Nurse practitioner clinic
3. Bowel prep clinic (nurse/principal investigator present)

Patients reviewed in Gastroenterology outpatient clinic by medical officer/Gastroenterologist/Anaesthetist

(introduction to the study)

Patients on surveillance registry

Direct referrals – review with nurse practitioner

(introduction to the study)

Bowel prep clinic (nurse practitioner)

(consent + randomisation)

Uninterrupted DOAC group

Interrupted DOAC group

Day of procedure (1 week – 3 months post consent)

(confirm protocol followed)

Routinely, patients are given information about anticoagulation cessation in clinic at the time of bowel preparation. At this stage, patients will have a detailed discussion with a team member or principal investigator regarding the study protocol. They will have time to read through the protocol and ask questions. A Physician/Gastroenterology registrar will be available during this process to answer any questions and inform of their right to withdraw from the study at any time.

The consent can be obtained by either the investigator, nurse/team member, or Gastroenterologist. The randomisation to each group, however would be performed by the bowel prep nurse to ensure endoscopist blinding, i.e. there is a possibility that the Gastroenterologist consenting the patient could be the one performing the procedure eventually.

After review in clinic, the patients typically have the colonoscopy between one week to three months. A copy of the signed consent form will be provided to the participant at their clinic appointment. The original copy will be stored at the QEII Jubilee Hospital Registrar office. No recruitment will not occur on the day of the procedure.

In patients of non-English speaking background, a formal face-to-face interpreter for their native language will be present on the day of introduction to the study, recruitment/consent as well as on the day of the procedure.

We intent to aim for 200-220 participants for Phase I to account for the potential 5-10% drop-out.

**COVID-19**

Given the current COVID-19 pandemic, some of the patients are not being reviewed in person but are receiving all paperwork via mail and are communicating with the health professionals via telephone until the day of the procedure. By default, the procedural consents are being performed on the phone with exactly the same information provided to patients on the phone as would be provided face to face. The patients are providing phone consent in this situation and formally signing documents on the day of the procedure. This will be specifically documented in iEMR.

Patients with advanced age/hearing deficit or language barriers are routinely seen face-to-face.

The same standard would be applied for patients who are unable to attend a number of face to face appointment due to the pandemic restriction. Post phone consent, the paperwork will be mailed to the patient and a further confirmation phone call will be made once the paperwork has been received. No consent will be done on the day of the procedure but if the consent has been obtained on the phone, the patients will be able to confirm on the day of the procedure.

**Declined consent**

In order to avoid selection bias, patients who do not wish to be involved in the study but meet the inclusion criteria will be asked a series of questions. If they do not wish to answer any questions, this will be documented as an unidentified individual (please see page 6 of PICF).

If they are willing to answer questions, they will be questioned about their reason for declining, reason for anticoagulation, age and sex. The rationale is to avoid obtaining biased data by unintentionally excluding certain subgroups.

**Randomisation**

Two study arms:

1. Standard of care arm:

* If the DOAC is a twice a day dose, the patients will omit three doses of the medication, i.e. they will not take the medication on the day of and the day prior to the procedure.
* If, the medication is taken once a day (morning or evening), they will omit the medication on the day prior to the procedure as well as the day of the procedure.
* Anticoagulation will be re-commenced at the next scheduled dose more than 24 hours after the procedure
  + If DOAC taken twice a day, they will re-commence after missing the dose on the evening of the procedure and the morning after. They will resume the evening dose day after the procedure.
  + If DOAC taken once a day, they will omit the day after the procedure then resume the next day.

1. Intervention arm:

* The DOAC will not be stopped.

An equal number of unlabelled sealed envelopes will be available for randomly picking and allocating to each group once consent has been obtained. The patients will be divided into the standard of care and intervention arm (see above).

Post randomisation, pre-prepared sealed envelopes will be available to open at the time of recruitment. These will only be opened once the patient has given consent for participation. This envelope will also include a form where a patient identifier label will be placed identifying which arm of the study the patient falls in. The form will be attached to the copy of the consent form stored at QEII hospital.

At the QEII hospital, a standard booking form is used for all patients booked for any endoscopic procedure. Post recruitment and allocation, this standard booking form will be flagged with a coloured sticker to ensure this is clear on the day of the procedure. The patients will also be flagged using a standardised flagging method using iEMR (“*Power trials”)*. This method allows a message to appear on patient record suggesting their trial participation when the present for their procedure or post procedure to any Queensland hospital using iEMR.

**Day of procedure**

The endoscopist will be made aware that the patient is a participant of this study however will be blinded to the arm. The patient’s timing of cessation of anticoagulation will be confirmed by the admitting nursing staff and be recorded on a standard form (see Patient procedure day questionnaire). This form will be attached to the patient’s original paperwork.

During the procedure, Paris classification will be used to define the overall polyp morphology, whereby an elevated (>2.5 mm above the surrounding normal mucosa) sessile lesion is described as 0-Is. A pedunculated polyp is described as 0-1p and sessile lesions <2.5 mm are classed as 0-IIa (slightly elevated), 0-IIb (flat), or 0-IIc (slightly depressed). Excavated lesions are classed as 0-III (Lambert et al 2003). In lesions with mixed classification, the dominant morphology is listed first. Laterally spreading lesions are defined as superficial lesions >10mm in size with further classification according to the surface topography (granular versus non-granular).

All colorectal polyps amenable to endoscopic removal at index colonoscopy as per clinical care will be removed using cold-snare polypectomy (CaptivatorTM Cold or SnareMaster Plus) or hot-snare (CaptivatorTM II). The transected polyp will be sucked into a trap or via the scope to the anus. The method of resection, i.e. hot versus cold, en-bloc versus piecemeal or the inject-and-resect technique using methylene blue with or without epinephrine will be at the discretion of the proceduralist.

Intraprocedural bleeding is defined as bleeding persisting for greater than 60 seconds during the procedure requiring endoscopic intervention. Usual methods of controlling intra-procedural bleeding include application of clips, thermal treatment or injection of submucosal epinephrine. Routine prophylactic clip closure will follow current clinical practice at our facility where routine clip closure is performed for hot polypectomy sites but not cold polypectomy. If decision to proceed with clipping, this will be performed using Instinct® Endoscopic clip or ResolutionTM Clip.

Patients will follow standard post procedure recovery in stages 1 and 2 in the unit. Written post-procedural instructions will be provided as per usual practice post coloscopy on potential problems and contact details for advice.

Patients are encouraged to call the hospital for advise if they experience any symptoms to suggest overt gastrointestinal bleeding post procedure. If the patient were to present to any other hospital in Queensland, a standardised flagging method will be employed using iEMR (“*Power trials”)* to allow a message to appear on patient record suggesting their trial participation.

**Proceduralist feedback**

At the end of the procedure, the proceduralist will receive a paper questionnaire from the principal investigator around endoscopic features of bleeding in that case. To allow the proceduralist time to complete the questionnaire, the form will be collected by the principal investigator from the proceduralist at the end of their endoscopist list.

The three endoscopists have volunteered to participate in this study all read and approved this research protocol. The purpose of including this is to ensure that clinician decision making was not affected by the patient’s participation in this study.

### **Need for repeat colonoscopy**

It is generally not advisable to remove a large (>20mm) adenomatous non-pedunculated polyp when incidentally identified on index colonoscopy.17 Typically at this stage, optical evaluation is performed to help technique selection and planning. It is also standard practice to perform procedure in stages when a large number of polyps are identified on index colonoscopy that cannot be removed on the same day. Lastly, intervention is delayed in the setting of inadequate bowel preparation where polypectomy is not deemed safe. In these scenarios, patients require a planned repeat colonoscopy with extra time allocation and extended bowel preparation. This decision is subjective and would be at endoscopist’s discretion. The rationale for planned repeat procedure will be recorded.

If no polypectomy was performed, the subject will still be included in the intention-to-treat analysis however excluded from the evaluable protocol-compliant analysis.

### **Unblinding**

The Gastroenterologists performing the procedure will be blinded. Events where unblinding may be necessary may include:

1. Bleeding during the procedure (intraprocedural bleeding [IPB]) or after it (clinically significant post-endoscopic bleeding (CSPEB) not manageable with endoscopic intervention.
2. Accidental unblinding where the endoscopist is unintentionally informed about the treatment arm the patient belongs to.

As per the Guideline for Good Clinical Practice, the code will only be broken in accordance with the protocol. The principal investigators will be promptly informed and reason/details of the event will be documented. The investigator will describe on the clinical records the treatment that follows in case of an unexpected adverse event. Physicians not familiar with the clinical study will not have the permission to break the blind.

If unblinded, the subject will still be included in the intention-to-treat analysis however excluded from the evaluable protocol-compliant analysis.

### **Definitions**

Intraprocedural bleeding (IPB): bleeding that does not spontaneously resolve within 60 seconds during the procedure requiring endoscopic intervention

Clinically significant post-endoscopic bleeding (CSPEB): any bleeding occurring after the completion of the procedure requiring emergency department presentation, subsequent hospitalisation, transfusion, or re-intervention (repeat colonoscopy, angiography, or surgery)

Self-limited bleeding: managed on an outpatient basis that does not require formal medical assessment

### **Data collection**

|  |  |
| --- | --- |
| **Patient factors** | **Procedure details** |
| Demographics: age, sex | Indication  Insertion time + subjective difficulty of insertion  Need for repeat colonoscopy & rationale |
| Anticoagulation: dose and type of DOAC, indication | Polyp size, Paris and NICE classification, location (right vs left), number, resection technique (hot vs cold) |
| Diagnosis of hypertension | Intraprocedural bleeding +/- use of haemostatic clips or alternative strategies for haemostasis |
| Charlson comorbidity index† | Histological diagnosis |
|  | Proceduralist and duration of experience |
|  | Total withdrawal time |
|  | Complications within 30-day of procedure (bleeding or thrombotic event) |

†Charlson comorbidity index is a surrogate used to predict 10-year survival in patients with multiple comorbidities including age, myocardial infarction, heart failure, peripheral vascular disease, ischaemic stroke or transient ischaemic attack, dementia, chronic obstructive airways disease, connective tissue disease, peptic ulcer disease, chronic liver disease, diabetes mellitus, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, AIDS.

**Patient feedback**

It is standard practice to send a message to patients using short message service (SMS) at the 30-day mark post procedure. The outcome of this is followed and recorded by a dedicated surveillance registered nurse and flagged for the proceduralist.

In addition to the above, study participants will receive a structured telephone interview at 30 days. Any delayed bleeding will be recorded, and data will be collected on the timing in relation to the procedure angiographic embolization or surgery, admission to hospital, and any mortality. Additionally, any thrombotic event including stroke, cardiac ischaemic event or venous thromboembolism will be recorded. Further, their feedback and perspective towards cessation of anticoagulation for the procedure will be sought.

We will attempt to contact the participant on three occasions. In the event that the patient cannot be reached and the potential outcome unknown, subject will still be included in the intention-to-treat analysis however excluded from the evaluable protocol-compliant analysis.

### **Outcome**

Primary

* Intraprocedural bleeding (IPB) or clinically significant post-endoscopic bleeding (CSPEB)
* Need for intervention during the procedure to stop bleeding

Secondary

* Hospitalisations within 30 days of index polypectomy
* Thromboembolic event (stoke; myocardial infarction; peripheral thrombus)
* Covariates of interest: patient factors/comorbidities and procedural factors that determine individual risk
* Patient acceptance or beliefs regarding anticoagulation.
* Proceduralist accuracy in predicting whether the patient has interrupted their anticoagulation.

### **Analysis**

All data collected will be de-identified and will remain strictly confidential. Data handling will comply with the Australian Code for the Responsible Conduct of Research 2007.

Access to the data will be granted to all clinicians involved in data collection. Post collection of the data, as per protocol, all records for non-drug trials should be kept for a minimum of 5 years’ post study closure.

Statistical support will be provided through Metro South MSH Biostatistics Clinic.

### **Ethics**

The research project will be conducted in full conformance with principles of the “Declaration of Helsinki”, Good Clinical Practice (GCP) and within the laws and regulations of Australia and Metro South Hospital and Health Service.

No investigators from outside Queensland Health will be involved in the study. No identifiable patient data will be shared outside the Department. All patient data collected and stored for the purpose of this study will be done so in accordance with the Information Privacy Act, Code of Conduct and Australian Code of Responsible Conduct of Research 2007 and the confidentiality agreement between MSH Biostatistics Clinic and Queensland Health.

This is a ‘Greater than low risk’ project and appropriate Human Research Ethics Application approval will be sought. The Phase I of the trial will be performed in two stages where post 20 cases in each arm, an Independent Safety Review Committee including two experts in the field and one statistician will be set up prior to commencement of further recruitment. Only once approved by the committee, the rest of the participants will be recruited.

Based on the results of Phase I of the trial, a repeat Ethics Approval for Phase II will be sought.

The consent paperwork will be stored in a locked drawer in a locked room at the Gastroenterology office in the endoscopy unit where there is a dedicated space for storage for confidential research paperwork. The consent forms will only be held until the completion of data collection and will be shredded using the hospital confidential paperwork pathway.

The verbal explanation of the research project and the participant information sheets and consent forms will make it clear that the participant does not have to take part in the study in order to receive treatment for their condition. As is routinely the case in consenting the patients prior to colonoscopies, their risk of continuation and discontinuation of DOAC will be explained to the patient by a consultant Gastroenterologist.

The voluntary nature of consent is described verbally and in writing and it will be made very clear that the participant’s relationship with their clinician and other health care professionals and with hospital involved will not be affected by their decision to take part or not to take part in the project. All participants will be reassured that their decision to participate in the study will not impact on their present or future health care at this hospital or their relationship with the researcher or health team members at this or any other hospital.

### **Resource requirements**

Operational and Finance impact of this study has been reviewed by the Head of Department and Facility Manager sign off will be sort for governance authorization.

There is no financial cost associated with this project. No additional staff appointments are needed to complete this study. Data will be collected by existing staff members in their own time.

The results will be presented at the QEII Hospital research audit, submitted for presentation at state or national scientific meetings and submission to a peer reviewed journal for consideration of publication.

If results of the study encourage further research an addition research application will be submitted to the HREC for consideration.

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