Management and Outcomes of Perioperative Care among European Diabetic Patients: (MOPED): A prospective observational, international cohort study

Study protocol

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Sponsor/Funder

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Contents

SYNOPSIS

Principal Investigator	Prof. Donal J Buggy, Mater University Hospital, University College Dublin, Ireland
Title	Management and Outcome after Perioperative Care among European Diabetic Patients (MOPED)
Short Title	MOPED
Trial Registration	NCT04511312
Protocol Version	V 1.0
Background & Rationale	Diabetes is common (about 20m patients in Europe), and patients have more surgical interventions than the general population. There are plausible pathophysiology and clinical mechanisms that diabetes patients are at increased risk of postoperative complications. When postoperative complications occur in the general population, they increase one-year mortality or major adverse events up to one year later. This is likely to be worse in diabetic patients. There is variation in practice guidelines in different countries in the perioperative management of diabetic patients undergoing major surgery, and whether this may affect postoperative outcome has not been investigated on a large scale. Neither is it known whether postoperative outcome differs depending on subgroups of diabetic patients, particularly whether different strata of preoperative glycaemic control affects outcome. If confirmed in this study, personalised perioperative management of diabetic patients may be enabled.
Objectives	Main Objectives: To conduct the first major European epidemiological study on the perioperative management of diabetic patients undergoing surgery and their 30-day postoperative patient-centered outcome; To evaluate subgroup outcomes, particularly strata of preoperative glycaemic control. Specific Objectives: To address the following research questions: 1. What is the epidemiology of diabetic patients undergoing surgery across Europe: Are there major variations in perioperative glycaemic control? Does management practice vary between centres and between nations? 2. What is the extent and patient-centered impact of postoperative complications among diabetic patients up to 30 days after surgery in Europe? 3. To undertake sub-group analysis comparing these outcomes among *Diabetes Mellitus Type 1, Diabetes Mellitus Type 2, and other diabetic patients; *Patients with different strata (levels) of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mol; *Patients who received different anaesthetic techniques: -Volatile versus total intravenous anaesthesia; regional versus general anaesthesia (GA) and

	*Diabetics of longer duration have higher risk of intraoperative hypotension due to autonomic neuropathy.
Outcomes	Primary endpoint: Days at Home at 30 days after surgery (DAH-30) Secondary endpoints: Comprehensive Complications Index (CCI) score, Quality of Recovery (QoR-15) Day 1 if applicable, 30-day mortality, Length of Hospital Stay, Incidence of specific major adverse events (as listed exhaustively see Appendix 11 'Definitions of Outcomes') Tertiary endpoints: Time to resumption of normal diabetes therapy (insulin or oral hypoglycaemics and diet), Incidence of Diabetic Ketoacidosis or Hypoglycaemia, Incidence and duration of use of IV Insulin Infusion Therapy, Change in diabetic management at 30 days Intraoperative and postoperative management techniques of diabetes therapy will be documented, including capillary blood glucose levels before, during and <2hr after surgery.
Inclusion & Exclusion Criteria	**Inclusion criteria:** Diabetic patients aged 18 years or over (all classes except gestational diabetes) undergoing surgery (defined as requiring any general anaesthesia technique or any specific regional anaesthetic technique or a combination). Ambulatory, elective or emergency surgery and patients who receive postoperative care in intensive care or high dependency units will be included. Pre-defined subgroups of diabetic patients will be highlighted for later analysis. **Exclusion criteria**: Patients who are not diabetic; Patients with gestational diabetes; Patients undergoing minor surgery, i.e. surgery under local anaesthetic infiltration alone with or without monitored sedation alone or surgery not as defined in the inclusion criteria above.
Project Measurements	Patients' consent will be requested to allow documentation of their perioperative course and 30-day outcome as outlined in the outcome measures. Apart from routine clinical care, no intervention is planned.
Number of Participants	5,000
Duration	In each participating centre, recruitment of new patients will continue for a period of 12 months after their registration with ESAIC as a participating centre, until the target 5,000 patients is reached. Follow up duration to 30 days after surgery.
Centres	This will be an international, multicentre prospective observational study. Any centre where colleagues can enrol and collect the data outlined in a minimum of n=45 patients are welcome to participate.

Statistical Considerations	Up to 5% of the population of Europe is thought to have diabetes. About 30m surgeries are performed in Europe per annum, therefore perhaps 1.5m diabetics have surgery in Europe per annum. It is proposed to evaluate a pragmatic sample of 5,000 European diabetic patients across at least 50 centres in a minimum of 10 nations. Centres undertaking surgery for diabetic patients will be invited to contribute patients. It is envisaged that this target number would be enrolled over a two-year period from initial roll-out, with up to a further 12 months needed for final data acquisition, cleaning and analysis. A sample size of 5,000 should be sufficient to avoid over-fitting and variance inflation for up to 63 factors or interactions. In addition, a sample size of 5,000 will have 90% power to find a small standardised difference of 0.10 as significant at $P<0.05$ for up to 63 independent hypotheses in comparing subsets of interest.
Risk-Benefit analysis	There is no risk to patients participating in this study other than any risk associated with their perioperative care. Individual patients will not benefit from the study, but the knowledge gained from the overall evaluation will inform best practice in this previously under-researched field.

List of Abbreviations

AKI	Acute kidney injury
ASA classification	American Society of Anaesthesiologists Physical Status classification system
CCI	Comprehensive Complications Index
CRF	Case report Form
CTN	Clinical Trial Network
CVA	Cerebrovascular accident
DAH-30	Days at home at 30 days
DVT	Deep vein thrombosis
eCRF	Electronic Case Report Form
ESAIC	European Society of Anaesthesiology and Intensive Care
GA	General anaesthesia
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation - Good Clinical Practice
ICU	Intensive care unit
IRB	Internal review board
MI	Myocardial infarction
MINS	Myocardial injury after noncardiac surgery
NC	National Coordinator
PE	Pulmonary embolism
PI	Principal Investigator
PIS	Patient Information Sheet
PPC	Postoperative pulmonary complication
QoR-15	Quality of Recovery 15

SAE	Serious adverse event
SC	Steering committee
SOP	Standard operational procedure
SORT	Surgical Outcome Risk Tool
SSI	surgical site infection

1. ADMINISTRATIVE STRUCTURE

1.1 The Steering-Writing Committee

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1.2 Sponsorship

MOPED is funded by a grant from the ESAIC Clinical Trials Network.
No other institution will be involved in conducting this study.
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2. ETHICAL AND REGULATORY ASPECTS

2.1 Ethical Conduct of Study

The research project will be carried out in accordance to the research plan and the principles enunciated in the current version of the Declaration of Helsinki (amendment 2013) by the World Medical Association and the ICH-GCP Guidelines E6(R2). Specific national and local regulatory authority's requirements will be followed as applicable.

2.2 Risk categorisation

MOPED is a prospective cohort study asking patients to assent to documentation of their perioperative clinical course and progress, and a 10 minute follow-up telephone call, if discharged, at 30 days post surgery. No research related interventions are anticipated and all patients will receive routine care according to the standards laid out in each institution.

2.3 Institutional Review Board (IRB) and Competent Authorities (CA) or equivalent

In all cases, prior to study initiation, the local Principal Investigator (PI) at each centre must submit the study documents to the responsible IRB or equivalent for ethical judgment and obtain document of proof that the study has been subject to IRB review and given approval/favourable opinion and exemption of patient consent if applicable.

If informed consent is not required by the local IRB, an explicit, written exemption must be obtained from the IRB. No substantial changes will be made to the protocol without prior IRB approval, except where necessary to eliminate apparent immediate hazards to study participants.

In the unlikely event of premature study end or interruption of the study, a report will be sent to the IRB within 15 days, or as required. The regular end of the study is reported to the IRB within 90 days, the final study report shall be submitted within one year after study end, , or as required. It is the local PI responsibility to communicate with their local IRB within their local timelines.

2.4 Participant Information and Informed Consent

Written, informed consent, using the approved Informed Consent Form (ICF), will be sought from each patient prior to inclusion unless an explicit, written exemption by the responsible IRB is provided. Patient Information Leaflet (PIL) and any other written information to be provided to the patients as well as advertisement for subject recruitment (if used) must be subject to IRB review and given approval/ favourable opinion.

If applicable, patients´ consent will be sought as follows: Prior to surgery, the patients will be presented with the IRB-approved PIL providing information for participant to make an informed decision about their participation in the study, i.e. explaining the nature of the study, its purpose, the general lack of any procedures involved, the expected duration, the potential risks and benefits and any discomfort participation may entail. (see Appendix 2 Patient Information Sheet, Appendix 3 Patient Informed Consent Form).

Each participant will be informed that their participation in the study is voluntary and that he/she may withdraw from the study at any time and without explanation, that withdrawal of consent will not affect his/her subsequent medical assistance and treatment and that no further data will be collected, while already collected, encoded data will be pseudonymised and analysis may be performed up to the point of data collection.

The participant will be informed that his/her medical records will be examined by authorised individuals other than their treating physician. The participant will read the statement and will have the opportunity to ask questions before signing and dating the ICF, and will be given a copy of the signed document. Patients will confirm that they were given adequate time to reach a decision. The ICF must also be signed and dated by the investigator (or designee) and it will be retained as part of study records.

Diabetic patients listed for both elective and emergency surgery will be approached by a member of the research team and invited to participate.

While for elective patients, consent may be obtained in a preoperative clinic up to 90 days prior, for emergency surgery diabetic patients' consent may be requested on the ward, immediately prior to coming to theatre on the day of surgery and up until hospital discharge.

There is even less knowledge currently about the management and outcomes of diabetic patients undergoing *emergency* surgery, who are acknowledged to be a particularly high-risk group, compared to diabetic patients undergoing elective surgery. Therefore, including a cohort of these patients is particularly important to evaluate risk factors for adverse outcomes which may be mitigated. There is also anecdotal evidence that practice of managing these patients varies widely between nations and individual centres.

The only difference from normal care will be the 10 minutes phone call follow-up at 30 days post surgery. If patients are still in hospital on Day 30, this 30 day data may be collected on

the ward. Patients in hospital overnight will be asked to give their responses to the Quality of Recovery score (QoR-15) Day 1 postoperative only, which takes 3-5 minutes.

The sponsor provides templates of the Patient Information Sheet and Consent Form in English.(See appendices). All translations and adaptation of the Appendices should be sent to ESAIC (the sponsor) for validation. SOP and guidance published by the Sponsor should be followed in this regard.

2.5 Participant privacy

The investigator affirms and upholds the principle of the participant's right to privacy and shall comply with applicable privacy laws. Specifically, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers and only pseudonymised data will be recorded in the central database.

For data verification purposes, authorised representatives of the sponsor or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.6 Early termination of project

MOPED is an observational cohort study. Therefore, premature termination of the study resulting from ethical or safety concerns is most unlikely. In case of insufficient participant recruitment, the study period may be extended to reach the calculated sample size of 5,000 patients.

2.7 Amendments, Changes

Only the steering Committee (SC) or persons delegated by the SC are entitled to amend the protocol. National Coordinating Investigators and Local Principal Investigators (PI) will receive timely notification of changes and will be required to submit amendments locally. Written documentation of the amendments' approval will be provided to the sponsor and substantial amendments of the protocol will be only implemented after approval of the responsible IRB.

In consideration of the observational nature of the study, the necessity of protocol deviations to protect the rights, safety and well-being of human subjects without prior approval of the sponsor and the IRB appears remote. Such deviations must be documented and reported to the sponsor and the IRB as soon as possible.

All non-substantial amendments like administrative changes will be communicated to the IRB as necessary by the PI. It is the local PI responsibility to communicate with their IRB.

2.8 Background

The incidence of diabetes is increasing globally, including within Europe. There is an estimated 20million diabetic patients in Europe, which is likely to increase, thereby adding to societal demands on European health services.[1] Diabetic patients are more likely to have surgical interventions than the general population.[2] There are plausible pathophysiology and clinical mechanisms that diabetics are at increased risk of postoperative complications.[3,4] When postoperative complications occur in the general population, they increase mortality or increase risk of major adverse cardiovascular events (Myocardial

Infarction, Cerebrovascular Accident, Pulmonary embolism) at 30-days and up to one year later.[5-7] In addition, diabetes is an independent risk factor for surgical site infections [6].

There is variation in practice guidelines in different countries in the perioperative management of diabetic patients undergoing major surgery, but this has not been documented on a large scale.[3,7,8] Given the multiplicity of guidelines and differing recommendations, it is unsurprising that variability of 'real-world' clinical practice with regard to perioperative management of oral antihyperglycemic medications and insulin therapy has been noted in audits such as the National Confidential Enquiry into Patient Outcome and Death (NCEPOD).[9]

Further, although it is recognised that diabetic patients are at increased risk of postoperative complications[5-8], this has not been recently evaluated, especially in light of ongoing developments in perioperative care, such as Enhanced Recovery Programmes.[7] While a quality improvement intervention study has shown that maintaining tight preoperative glycaemic control improves postoperative glycaemic control[8], it is not known if this reduces postoperative morbidity overall. Further, whether certain anaesthetic techniques may be associated with better or worse outcomes after major non-cardiac surgery is unknown.

2.9 Rationale for the research project

National bodies in Europe and elsewhere differ in their guidelines on management of diabetic patients undergoing surgery and small observational studies confirm wide variability in practice and perioperative management between centers.[1-3] Whether this variability in practice affects postoperative outcome among diabetic patients in countries across Europe has not been investigated.

Further, our sub-group analysis will provide novel data on how patients with different strata (levels) of preoperative glycemic control progress in the postoperative period. Poor pre-operative glycaemic control is associated with postoperative complications in retrospective studies [10,11]. If this study confirms an association between poor preoperative glycaemic control and adverse outcomes, then the beginning of personalised perioperative medicine for diabetic patients will be enabled. For example, it is known from intensive care medicine that patients with better pre-admission glycaemic control (HbA1c < 53 mmol.mol) have worse outcomes if they develop hyperglycaemia, compared with patients whose pre-existing glycaemic control was already poor (HbA1c > 69 mmol.mol) [4,11]. If this pattern was reflected in the perioperative management of diabetic patients, it would enable a more personalized approach in the perioperative period. Similarly, whether our other subgroups outlined differ in postoperative outcomes is unknown.

This large, multicentre, international prospective observational study will address these urgent research questions and so create a platform for better management and outcomes for patients undergoing surgery with this high risk, highly prevalent condition, which is increasing in incidence in the European population.

2.10 Risk-Benefit Assessment

MOPED is a prospective cohort study of the medical management and outcome of diabetic patients during and after surgery. Therefore, risks are limited to data protection. Data protection will be guaranteed through encoding and the use of a secured database with restricted access by individual log-in and gradated user rights. Further, only pseudonymised data will be stored centrally. The database will be hosted on servers physically located in the European Union and data can only be transferred to servers located in member States of the European Union or in third countries which level of personal data protection has been

determined as adequate by the European Commission (based on General Data Protection, EU Regulation 2016/679, Article 45).

3. OBJECTIVES, ENDPOINTS/OUTCOMES AND OTHER STUDY VARIABLES

3.1 Objectives

1. To document, in a large scale observational, epidemiological study, the perioperative glycaemic management of established diabetic patients undergoing every type of surgery with anaesthesia in Europe.
2. To document the type, incidence and severity of all postoperative complications occurring up to 30 days postoperatively.
3. To document the impact of all complications by determining the number of days at home at 30 days (DAH-30, primary outcome), Comprehensive Complications Index (CCI) score, based on the Clavien-Dindo scale and other secondary outcomes.
4. To undertake sub-group analysis comparing these outcomes among:

- DM1, DM2 and Other Diabetes ('Other" includes Maturity Onset Diabetes of the Young, (MODY) and LADA and any other type of diabetes).

- Patients with different strata of pre-operative glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol. mmol;[11]

- Patients who received different anaesthetic techniques:
  - Volatile versus total intravenous anaesthesia.
  - Regional versus general anaesthesia (GA) and
  - Patients receiving combined GA and regional anaesthesia versus GA alone.

A list of the a priori hypotheses is listed in Appendix 9.

3.2 Primary and secondary endpoint/outcome(s)

Primary endpoint: Days at Home at 30 days (DAH-30) [12,13]

Secondary endpoints:
Comprehensive Complications Index (CCI) score, based on Clavien-Dindo scale; [14,15]

Quality of Recovery scale (QoR-15), only taken from patients who are in hospital the day after surgery, I.e. Day 1 postoperatively [16], 30-day mortality,

Length of Stay in Hospital, Length of Stay in ICU if applicable.

Incidence of specific major adverse events as listed in European Perioperative Clinical Outcomes Definitions manuscript[18], (see Appendix 11 'Definitions of Outcomes') (MI, MINS, AKI, PPC, CVA, PE, DVT, AKI, Postoperative pulmonary infection (PPI);

Tertiary end-Points:
Intraoperative and postoperative management techniques of diabetes therapy will be documented, including fasting capillary/ABG blood glucose levels before, and <3hr after surgery. Also, peak blood glucose recorded during surgery, if available.

Also: incidence of diabetic ketoacidosis (defined as presence of the triad of: glucose > 12 mmol.L; ketonaemia > 3.0 mmol.L and lactaemia > 2.0 mmol.L);

Incidence and duration of use of IV Insulin Infusion Therapy.
Incidence of hypoglycaemia (glucose < 4 mmol/l or severe < 2,5 mmol/l).

4. PROJECT DESIGN

4.1 Type of research and general project design

MOPED is a prospective, observational, international, multicentre cohort study.

4.2 Study centres and role of national and local PIs

Any hospital in Europe (as defined by the World Health Organisation) is welcome to participate as a study centre. Non-European centres may be accepted upon request to the SC. Centres will be asked to enrol a minimum of 45 patients (up to 200) over a recruitment period of up to 18 months from the date of the centre's registration with ESAIC. No more than one quarter (25%) of a centre's patients can be day cases (ambulatory anaesthesia). Study centre registration occurs online via the dedicated "Call for Centres form" on the ESAIC website. Within the overall Europe-wide period of recruitment planned for MOPED (at least 18 months), the start of recruitment for individual centres is soon as possible after centre registration with ESAIC, provided that there is prior IRB approval. Recruitment will continue until enrolment of the planned sample size (n=5,000).

National coordinating investigators are anaesthesiologists appointed by ESAIC and the SC to lead the project within individual countries and their responsibility includes:
• Identify centres in their country and recruit local PIs in participating hospitals;
• Assist in the translation of required study documents;
• Ensure that all necessary national or regional regulatory approvals are in place prior to start of patient inclusion;
• Assist and train the Local PI and monitor the conduct of the study according to ICH-GCP;
• Ensure good communication with ESAic headquarters and the participating sites in his/her countries during all study steps including data cleaning.

Local PI may be anesthesiologists, surgeons or diabetes physicians working in perioperative medicine in each participating institution who will have the following responsibilities:

- Provide leadership for the study in their institution;
- Ensure all relevant regulatory/ethical approvals are in place for their institution;
- Ensure adequate training of all relevant staff prior to data collection;
- Supervise enrolment, daily data collection, and assist with problem solving;
- Adjudicate events
- Ensure timely completion of eCRF, follow-up assessments, and data cleaning queries. The Local PI is the main person responsible for ensuring integrity of data collection. By signing the data on eCRF Local PI confirms the data integrity;
- Communicate with ESAIC headquarters and the relevant National Coordinating Investigator during all study steps including data cleaning.

Maintain and update their investigator's site file according to the recommendation of the ICH-GCP Guidelines E6(R2).

4.3 Procedures

At screening day ("day -90" to "day of surgery", i.e. within 3 months of planned day of surgery), patients will be screened and be asked for consent (see 2.4). (see Appendix 2 'Patient Information Sheet' and Appendix 3 'Patient Consent Form'). For emergency surgery, diabetic patients' consent may be requested on the ward, immediately prior to coming to theatre on the day of surgery and up until hospital discharge.

If patients remain in hospital on the day of surgery, some data will be documented on the first day postoperatively ("Postop Day 1"), including QoR-15 quality of recovery score, taking 3-5 minutes.

Some patient data will also be recorded on Day of Discharge, provided the patient is discharged within 30 days of their surgery.

At Day 30 after surgery, data will be collected by telephone if the patient has been discharged. If still in hospital, patient data will be collected on the ward on Day 30.

There is some flexibility with the timing of data collection. Example: If Day of Discharge or follow-up Day 30 falls on a weekend, follow up may be conducted the next available working day. Similarly, if the patient cannot be contacted on Day 30, the patient should be contacted the next available day, e.g. Day 31. In this case, all outcomes recorded should be those that occurred up to and including Day 30 after surgery.

Table 1: Summary table of the timings of assessments

When	Action/Parameters Collected
Day-90 to Day 0	Screening Inclusion/Exclusion criteria Consent if elective Patient and diabetes baseline data Screening failure tracking SORT score
Day 0	Emergency patient screening and consent* Diabetes and patient baseline data if not already Surgical parameters SORT score Anaesthetic and PACU parameters
Day 1 Post-Op	QoR-15 Glucose and insulin parameters over 24 hr since surgery
Day of Discharge	Postoperative morbidity / complications CCI score
Day 30 Post-Op	DAH-30 (primary outcome) Mortality Postoperative morbidity / complications CCI score Length of Stay Diabetes parameters post surgery

*Consent can be taken from patients undergoing emergency surgery up until the day of hospital discharge

4.4 Recruitment and Screening

The PI or designee will screen the surgical schedule for eligible patients. This may include screening patients attending the preoperative clinic if the surgery is planned within three months. Because of the minimal interference to normal clinical care which this study

proposes, patients may also be invited to participate on the day of surgery, provided they receive this request on the ward before coming to theatre.

This is justified because there is even less knowledge currently about the management and outcomes of diabetic patients undergoing *emergency* surgery, who are acknowledged to be a particularly high-risk group, than diabetic patients undergoing elective surgery. Therefore, including a cohort of emergency surgery diabetic patients is particularly important to evaluate risk factors for adverse outcomes which may be mitigated. There is also anecdotal evidence that practice of managing these patients varies widely between nations and individual centres. The Surgical Outcome Risk Tool (SORT) will be used to indicate surgical risk [17]

4.5 Methods of minimising bias

In every centre, all diabetic patients undergoing surgery, (except where there is only conscious sedation, with or without local anaesthetic infiltration or topical anaesthesia to the eye) are eligible. Centres are invited to enrol their target number of patients (depending on number of investigators in their team) from the date of registration of their centre with ESAIC and all approvals being in place, for up to 12 months. No other exclusion criteria apply, even emergency surgery patients are eligible. Therefore, we do not believe that significant risk of bias exists.

5. PROJECT POPULATION

5.1 Inclusion criteria:

- Diabetic patients 18 years or over (all classes except gestational diabetes) undergoing surgery (defined as requiring any general anaesthesia technique or any specific regional anaesthetic technique or a combination). Ambulatory, elective or emergency surgery and patients who receive postoperative care in intensive care or high dependency units will be included. Pre-defined subgroups of diabetic patients will be highlighted for later analysis.

5.2 Exclusion criteria:

- Patients who are not diabetic;
- Patients with gestational diabetes;
- Patients undergoing surgery without a specific anaesthetic technique,

i.e. surgery under local anaesthetic infiltration or topical anaesthesia alone with or without monitored sedation alone or surgery not as defined in the inclusion criteria above.

Examples: Diabetic patient for cataract surgery. If anaesthetic technique will be simply topical anaesthesia, patient is excluded, whether or not there is monitored sedation.

If diabetic patient scheduled for cataract surgery with peribulbar or sub-tenon block, they are included.

5.3 Criteria for withdrawal / discontinuation of participants

Due to the observational nature of the study, the protocol does not define any withdrawal/discontinuation criteria. Patients electing to withdraw from the study may do so at any point. In this case, no further data will be collected, while already collected, encoded data will be pseudonymised and analysis may be performed up to the point of data collection. Withdrawing participants will not be replaced provided that their number does not exceed 5% of the projected sample size one month prior to the end of the planned recruitment period. Under such unlikely conditions, the SC will decide upon potential replacement by extension

of the recruitment period, under consideration (among other) of the number of events already registered in the database at the relevant time point.

6. PROJECT ASSESSMENTS

6.1 Project table of procedures and assessments: Figure 1.

PIs or designees will screen the elective surgical schedule for eligible patients. This may include screening patients attending the preoperative clinic if the surgery is planned within three months. The time window between answering the consent and surgery cannot exceed 90 days. Because of the minimal interference to normal clinical care which this study proposes, patients may also be invited to participate on the day of surgery, provided they receive this request on the ward before coming to theatre.

As it will also be particularly important to include diabetic patients undergoing emergency surgery, these patients will need to be screened and give informed consent on the day of surgery or up until to hospital discharge.

Intraoperative and postoperative management techniques of diabetes therapy will be documented, including capillary blood glucose levels before, during and <2hr after surgery. Also: Time to resumption of normal diabetes therapy (insulin or oral hypoglycaemics and diet); incidence of diabetic Ketoacidosis (defined as presence of the triad of: glucose > 12 mmol.L; ketonaemia > 3.0 mmol.L and lactaemia > 2.0 mmol.L; Incidence and duration of use of IV Insulin Infusion.

6.2 Assessments of primary endpoint outcome

The Primary Outcome is:

Days at Home at 30 days (DAH-30). [12,13].

Secondary Outcomes:

Comprehensive Complications Index [14,15]

The local Principal Investigators will determine the comprehensive complication index (CCI), based on the Clavien-Dindo scale based on review of in-hospital charts, other relevant documents, and questioning of patients. Appendix 11 gives the definitions of specific morbidity.[18]

How to calculate the CCI score for a patient is found in Appendix 14 ’How to calculate the CCI score’

How to manage QoR-15 scale at Day 1:[16]. This is explained in Appendix 13 ‘QoR-15 Patient Survey’.

Investigators are asked to simply put the 15-point patient well-being questionnaire to the patient, <u>if they remain in hospital on Day 1 only</u>. This should be possible to achieve in 5 minutes.

The 15 domains of response are graded 0 (worst recovery) to 10 (best possible outcome). Therefore, given 15 responses, the range of QoR-15 scores is 0 to 150. Typically, values are skewed towards the higher end, typical median QoR scores are 100-120.

6.3 Assessment of secondary endpoint/outcome(s)

Morbidity definitions are shown in Appendix 11, then applied to the Clavien Dindo score and CCI score (see Appendix 11 'Definitions of Outcomes' and Appendix 14 'How to calculate the CCI Score').

6.4 Other comments on endpoints:

The following data will be extracted from clinical charts: age, gender, weight, height, variables for CCI, variables for SORT calculation (see Appendix 12 'Surgical Outcome Risk Tool (SORT)'),
ASA classification, relevant medical history, preoperative diabetes medication (substance classes only), type of anesthesia, date, type, and location of surgery, procedure duration, type and date if ICU admission, date of discharge from ICU and from hospital. For details, please see the eCRF

Enrolled patients, whose surgery is unexpectedly delayed more than 90 days after the preoperative visit, may be asked to give informed consent again.

At the end of the study period each center will provide an "End of Study Reporting Form" (see Appendix 17) to report the number of patients meeting the inclusion criteria during the study period and the total number of screening failure patients. Furthermore, each center will provide a 'Screening Failure Tracking Form' (Appendix 6) giving the reasons for screening failures at the end of the study period. Using this form, it will be possible to analyse what are the reasons for exclusion from study (e.g. subject refused to sign informed consent, subject language, cognitive difficulties, etc.).

6.5 Assessment of safety and reporting

The only study-related procedure in MOPED is the follow up call at 30 days (10 minutes) and for those in hospital on Day 1 postoperatively, the QoR-15 questionnaire (3-5 min). As such, the potential for serious events appears too remote to require their definition, assessment, or documentation.

6.5.1 Definition of Serious Adverse Events (SAEs)

SAEs are not applicable, because this is an observational study and no interventions are performed.

6.5.2 Assessment and Documentation of SAEs

The assessment and documentation of SAEs is not required, because this is an observational study and no interventions are performed.

6.5.3 Reporting of SAEs, Safety and Protective Measures

Not applicable.

7. STATISTICAL METHODOLOGY

7.1 Sample size estimation

It is proposed to evaluate a pragmatic sample of 5,000 European diabetic patients across at least 50 centres in a minimum of 15 nations. It is expected that this should be sufficient for the main epidemiological aspects of this study. It is envisaged that this target number would be enrolled over a two-year period from initial roll-out, with up to a further 12 months needed for final data acquisition, data cleaning and analysis. A sample size of 5,000 should be sufficient to avoid over-fitting and variance inflation for 50 to 70 factors and interactions based on the conventional square root or 100 values per variable respectively. In addition, a sample size of 5,000 will have at least 90% power to find a small standardized difference of

0.15 as significant at *P*<0.05 (Bonferroni corrected at *P*<0.0007) for up to 70 independent hypotheses and in comparing subsets of interest.

7.2 Data processing

Data will be collected at each centre, pseudonymised, and entered into a bespoke electronic case report form (eCRF). Completed forms will be submitted to the sponsor, ESAIC Clinical Trials Network (ESAIC CTN), in Brussels, Belgium.

7.3 Planned analyses

7.3.1 Main analysis

The aim of this research is to describe and quantify the epidemiology of the perioperative management of diabetic patients in Europe. Descriptive statistics such as mean (SD), median [interquartiles, range] and frequencies (%) with be presented as appropriate. The precision of the estimates will be reported with 95% confidence intervals to show the prevalence and incidence rates of diabetic phenotypes and major adverse events and complications.

The primary outcome measure is Days at Home at 30 Days (DAH-30).
Secondary outcomes include: Comprehensive Complications Index (CCI) score, based on Clavien-Dindo scale and the QoR-15 instrument measuring quality of recovery, taken only in patients who remain in hospital for Day 1 postoperative.

Secondary outcomes also include 30-day mortality, length of hospital stay, incidences of specific major adverse events (MI, MINS, AKI, PPC, CVA, PE, DVT and surgical site infection (SSI).)

Univariate analyses will be used to help identify variables of potential interest for multivariable analyses, in addition to stepwise selections. Robust multivariable regressions using maximum likelihood estimation (MLE), including Poisson and negative binomial, will be used to identify significant associations. Specific factors, or subsets of interest, will be investigated further using linear mixed models with MLE. Binary and categorical outcomes, such as occurrence of a postoperative pulmonary complication (PPC) will be analysed using multivariable logistic regression, survival analysis and Cox proportional hazards regression as appropriate.

7.3.2 Datasets to be analysed

Data from all participants will be analysed with respect to completeness of data entry for all variables in an pseudonymised format. Patients will be nested within centre and stratified by country for relevant epidemiological purposes.

7.3.3 Handling of missing data

Analyses will be performed on the observed data. Data missing at random exceeding 10% may be imputed and models will be re-analysed as sensitivity analyses. Linear mixed models with MLE will be used as these are relatively robust with missing longitudinal data compared to least squares methods such as repeated measures analysis of variance (ANOVA). Exact multivariable logistic regression with Firth penalised MLE will be used for sparse and missing data as practical.

7.3.4 Ancillary analyses

In addition to the sensitivity analyses as described, the effects of pre-defined subsets will be investigated. These subsets will include: DM1, DM2, DM3, MODY and LADA diabetic patients; Strata of glycaemic control, HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol/mmol;

Anaesthetic techniques, inhalational (IA) versus total intravenous (TIVA), regional (RA) versus general (GA), combined GA and RA versus GA alone.

7.3.5 Deviations from the original statistical plan

Any deviations from the initial statistical analysis plan will be identified and explained in any reports. It is expected that such additional analyses will be reported in the Discussion only as *post hoc* and not in Results, as appropriate.

8. GDPR, DATA AND QUALITY MANAGEMENT

8.1 Data quality

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirements.

Quality control measures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly, including written SOP (in English for all countries) for data collection and entry, automated consistency checks, and training of National Coordinating Investigator and local PI. It will be responsibility of the National Coordinating Investigator, with support by the study coordinating office, to train local PI. Local PI will ensure that the data in the eCRF are carefully entered and verified regularly. It will be the responsibility of local PIs to conduct periodic and random checks to ensure data quality in her/his centre. The sponsor will make random assessments of centres in order to confirm that there are no improper and incorrect data entered into the eCRF. On-site monitoring visits by the sponsor are not planned.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities. Any agreements, made by the sponsor with the investigator/institution and any other parties involved with the study, will be in writing, as part of the protocol or in a separate agreement. No fee or financial compensation is given to PI and/or participating institution for patient recruitment.

8.2 Data handling and record keeping / archiving

Data will be entered into a secure on-line database protected by personalised and confidential usernames and passwords and documenting the time and individual entering the data. The language of the online database, eCRF, and the relative SOPs is English and will not be translated in the national languages. Data will be collected directly from source documents into the encoded paper CRF (Appendix 7 and Appendix 8 ‘CRF Completion Guidelines’). and secondarily entered into the eCRF. A copy of the original source documents will be stored within a locked cabinet/office accessible to authorised personnel only in accordance with local and national regulations.

An identifiable patient data page reporting the assigned patient identification code will be stored separately also in a locked cabinet/office (accessible to authorised personnel only) in order to record in-hospital outcomes, supply missing data points, and to allow potential monitoring visits by National Coordinating Investigators, Sponsor, IRB, or regulatory authorities. Signed Consent Forms to document that written informed consent was obtained prior to enrollment will be stored as described above. All study documents will be archived as

required by local legislation. Sponsor and centres will maintain and update their trial master files according to the recommendation of the ICH-GCP Guidelines E6(R2).

8.3 Confidentiality, Data Protection

To safeguard patients' confidentiality, a patient identification code will be assigned to encode data. The confidential log linking patient identification code and identifiable patient data will be stored separately in a locked cabinet accessible to authorised personnel only and corresponding electronic files will be protected by personalised and confidential usernames and passwords. eCRF are identified through the patient identification code and will not include any names, initials, date of birth or local hospital patient numbers; therefore, no patient identifiable data will be directly accessible from the eCRF. Data protection will be guaranteed through encoding and the use of a secured database with restricted access by individual log-in and gradated user rights. Further, only encrypted data will be stored centrally. The database will be hosted on servers physically located in the European Union and data can only be transferred to servers located in member States of the European Union or in other countries where the level of personal data protection has been determined as adequate by the European Commission on the basis of the General Data Protection Regulation (GDPR, Article 45).
Open direct access to all relevant study information as well as source data/documents will be permitted for purposes of monitoring, audits or inspections to the sponsor, national coordinators, IRB, or regulatory authorities. All handling of personal data will comply with the GCP Guidelines and follow strictly the legal and national requirements of GDPR. For any additional question please contact the ESAIC Data Protection Officer at privacy@esaic.org or 24, Rue des comédiens 1000 Brussels, Belgium.

Please see Appendix 15 - Data Protection Overview is destined to any person involved in the Squeeze study to have a better understanding of the data flow and data storage of the study.

Please see Appendix 16 – Lawfulness of processing of data – GDPR can be used to give an overview to the patients of the processing of the patient's data. The first part of the document details the information that can be given to the patient while the second part explains the situation to the Local Investigator.

9. PUBLICATION AND DISSEMINATION POLICY

9.1 Publication of results

The main results of MOPED and its sub-studies will be published in peer–reviewed international medical journals and presented at Euroanaesthesia and at international and national meetings. As recommended by the International Committee of Medical Journal Editors *(http://www.icmje.org/ recommendations/browse/roles-and-responsibilities/ defining-the-role-of-authors-and-contributors.html; accessed August 30th 2016),* authorship will be considered based on contributions to recruitment of patients, data acquisition and cleaning, analysis and interpretation of the data, manuscript writing, and submission of national/local grants AND final approval of the version to be published AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Steering Committee (SC) will also be the Writing Committee (WC).

All papers derived from the MOPED database will be published under the acronym "The MOPED Investigators". All authors will be specifically named, in order to give every investigator the same credit and the same responsibilities for successfully performing this study. All authors will be mentioned with their name and affiliation in the collaborators list which will be published in an appendix to the manuscript. The members of the Steering-

Writing committee will be specifically identified as required by most journals. Collaborators names will be listed in PubMed.

It is the responsibility of the local PIs to determine who is to be considered as investigator. The local PI will be asked to submit names of staff actively involved from their institution in the 'End of Study Reporting Form' (Appendix 17). If the number of recruited patients from a centre is too low to justify sufficient active involvement, the SC may decide on the legitimacy of the collaboration based on other contributions. The final decision will be left to the SC in consultation with the ESAIC.

The number of investigators allowed from each centre will be determined by the number of patients enrolled by that centre. This is described in Table 2 below.

Note that no more than 25% of a centre's enrolled patients should be day cases (ambulatory anaesthesia).

Table 2: Number of investigators named according to number of patients enrolled and followed to completion at 30 days:

Number of patients completed	Number of investigators at that centre
45	1
85	2
120	3
150	4

If more than 150 patients are enrolled from a single centre, the local PI may nominate up to six (6) investigators as co-authors if they meet the criteria for authorship. The maximum number of patients from one centre will be n=200. This is to avoid any one centre having an unduly large influence on the overall dataset. Note that no more than 25% of a centre's enrolled patients should be day cases (ambulatory anaesthesia).

Presentation at international meetings will be restricted to the members of the SC or their delegates. National Coordinators will qualify for presentation at national meetings after approval by the SC and the sponsor. ESAIC Clinical Trial Network will be acknowledged in all publications and presentations.

9.2 Secondary analyses, nested sub-studies, and data sharing

After publication of the pooled results, centres will be allowed to use their own pseudonymised data for local presentation and publication. Duplicate data publication is not permitted.

The pseudonymised pooled dataset may be available for secondary analyses upon specific request in the form of a detailed study proposal (including authorship rules) to the SC. The final approval of these potential secondary analyses rests with the SC. Prior to journal submission, any paper originating from the pooled data will be reviewed by the SC. Authorship of any secondary publication derived from the pooled data set will include the group name "MOPED Investigators" and the names of the SC who have worked on the particular manuscript, with a by-line clearly stating that the individual names are elsewhere in the paper. For transparency, the original paper has to be referenced to in all articles of secondary analyses.

Local or national nested cohorts addressing additional questions, i.e. question not addressed in MOPED, and collecting additional data while sharing part of the variables collected for

MOPED, are allowed under the following conditions: nomination of a separate sponsor (i.e., other than the ESAIC), separate ethical approval, separate informed consent, independent data management, and approval of a detailed study proposal by the SC.

The Sponsor and the SC have the right to veto the nesting of a study into MOPED. The publication of any study nested within MOPED will occur after publication of the main results of MOPED (main objectives 1 and 2). For transparency, the original paper should be referenced to in all articles of nested analyses. Authorship rules for potential publications derived from such nested cohort studies are to be submitted to the Sponsor and SC together with the study proposal.
Requests for data sharing for individual-level meta-analyses are to be addressed to the Sponsor and SC.
The sponsor of the study (ESAIC CTN) can use pseudonymised pooled data for internal analyses and educational purposes.

10. FUNDING AND SUPPORT

MOPED is sponsored by a grant from the ESAIC CTN. The submission for national or local peer-reviewed grants to fund national or local implementation of the study is allowed conditional on prior written authorization from the sponsor and the SC. The SC members declare not to have any conflicts of interest (a declaration of conflict of interest will be signed by each SC member and kept by the Sponsor).

11. INSURANCE

MOPED is a negligible-risk, observational study. Insurance might be required based upon individual agreement between local Principal Investigator and the relevant institutional legal department. The ESAIC has Public Liability insurance in place to cover the legal liability of the ESAIC as Sponsor in the eventuality of harm to a research participant arising from management of the research by the ESAIC. This does not in any way affect the responsibility of a Centre for any clinical negligence on the part of its staff.

12. REFERENCES

1. International diabetes federation, Cho NH, Kirigia J, Claude J et al. IDF diabetes atlas 8th ed. 2019: Visit: http://www.diabetesatlas.org/resources/2017-atlas.html. [accessed 22 Jan 2020]
2. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycaemia in the perioperative period in non-cardiac surgery. Diabetes Care 2010;33:1783-88.
3. Hulst A, Hermanides J, Hollmann MW, DeVries JH, Preckel B. Lack of Consensus on Peri-Operative Management of Patients with Diabetes Mellitus. Eur J Anaesthesiol 2019 Feb;36(2):168-169.
4. Plummer MP, Bellomo R, Cousins CE, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med. 2014 Jul;40(7):973-80. doi: 10.1007/s00134-014-3287-7. Epub 2014 Apr 24.
5. Umpierrex G, Smiley D, Jacobs S et al. Randomised study of basal-bolus insulin therapy in the management of patients with type 2diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 2011;34:256-61.
6. Emily T Martin 1, Keith S Kaye 2, Caitlin Knott. Diabetes and Risk of Surgical Site Infection: A Systematic Review and Meta-analysis Infect Control Hosp Epidemiol 2016 Jan;37(1):88-99. doi: 10.1017/ice.2015.249. Epub 2015 Oct 27.

7. Vascular events in non-cardiac surgery patients cohort evaluation (VISION investigators). Association between complications and death within 30 days after noncardiac surgery. CMAJ 2019;191:E830-37.
8. Kuzulugil D, Papeix G, Luu J, Kerridge R. Recent advances in diabetes treatments and their perioperative implications. Current Opinion in Anaesthesiology 2019:32:398-404.
9. National Confidential Enquiry into Patient Outcome and Death. Highs and Lows, London, 2018. Visit: https://www.ncepod.org.uk/2018pd/Highs%and%20Lows_Summary%20Report.pdf. Accessed 22 January 2020
10. Garg R, Schuman B, Bader A et al. Effect of preoperative diabetes management on glycaemic control and clinical outcomes after elective surgery. Ann Surg 2018;267:858-62.
11. Giuseppe Gatti 1, Andrea Perrotti, Daniel Reichart. Glycated Hemoglobin and Risk of Sternal Wound Infection After Isolated Coronary Surgery. Circ J 2016 Dec 22;81(1):36-43.doi: 10.1253/circj.CJ-16-0778.
12. Bell M, Erikson L, Svensson T et al. Days at home after surgery: an integrated and efficient outcome measure for clinical trials and quality assurance. E-Clinical Medicine 2019;11:18-26.
13. Myles PS, Shulman M, Heritier S et al. Validation of days at home as an outcome measure after surgery: A prospective cohort study. BMJ Open 2017;7:E015828
14. Slankamenac K, Nederlof N, Pessaux P, et al. The comprehensive complications index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Ann Surg 2014; 260(5):757-62; discussion 762-3.
15. Clavien PA, Vetter D, Staiger RD, et al. The Comprehensive Complication Index (CCI(R)): Added Value and Clinical Perspectives 3 Years "Down the Line". Ann Surg 2017; 265(6):1045-1050.
16. Stark PA, Myles PS, Burke JA. Development and Psychometric Evaluation of a Postoperative Quality of Recovery Score. The QoR-15. Anesthesiology 2013;118(6):1332-40.
17. Protopappa KL, Simpson JC, Smith N, Moonesinghe R. Development and validation of the surgical outcome risk tool (SORT). Br J Surg 2014;101:1774-83.
18. Jammer I et al. European Perioperative Clinical Outcomes (EPCO) Definitions. Eur J Anaesthesiol 2015;32:88-105

13. LIST OF APPENDICES

1. Protocol Synopsis
2. Patient Information Sheet
3. Patient Consent Form
4. Approval Documentation Coversheet
5. Patient Follow-Up Log
6. Screening Failure Tracking Form
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