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Title:

Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)

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Author Contributions:

DJB: Concept instigation, ESA funding applicant, study design, manuscript draft;

Malachy Colomb: : Study design, analysis plan draft;

Marc Coburn: Study design, manuscript draft;

JH: Study design, manuscript draft;

MWH: Study design, manuscript draft;

RN: Study design, manuscript draft;

AZ: Study design, manuscript draft;

Abstract:

Introduction - Diabetes is common (about 20m patients in Europe), and diabetic patients have more surgical interventions than the general population. There are plausible pathophysiology and clinical mechanisms that diabetic patients are at increased risk of postoperative complications. When postoperative complications occur in the general population, they increase major adverse events and subsequently increase one-year mortality. 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 different strata of preoperative glycaemic control affects outcome.

Methods and analysis - A prospective, observational, international, multicentre cohort study, recruiting 5,000 patients in at least n=50 centres with diabetes undergoing elective or emergency surgery (NCT04511312). Inclusion criteria are any diabetic patient undergoing surgery under any substantive anaesthetic technique. Exclusion criteria are not confirmed diabetic patients, and diabetic patients undergoing procedures under monitored sedation or local anaesthetic infiltration only. Follow up duration to 30 days after surgery. Primary outcome is Days At Home at 30 days (DAH-30). Secondary outcomes are Comprehensive Complications Index (CCI), Quality of Recovery (QoR-15) Day 1, 30 -day mortality, length of hospital stay and incidence of specific major adverse events (MI, MINS, AKI, PPC, CVA, PE, DVT, Surgical Site Infection (SSI), Postoperative pulmonary infection (PPI)). Tertiary outcomes include 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, and change in diabetic management at 30 days.

Ethics and dissemination – This study will adhere to the principles 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 requirements will be followed as applicable. The main results of MOPED and its sub-studies will be published in peer–reviewed international medical journals and presented at Euroanaesthesia congress and other international and national meetings.

ClinicalTrials.gov Identifier: NCT04511312

ARTICLE SUMMARY

Strengths and limitations of this study:

1. There is wide variation in the perioperative anaesthetic management of diabetic patients, internationally and between centres. This will be the largest prospective, observational study documenting the influence of perioperative management on 30-day outcomes.

2. The primary endpoint is Days at Home at 30 days (DAH-30). This recently validated standardised end-point for perioperative trials (range 0-30 days, higher number indicating better outcome) gives a patient-centred outcome reflecting mortality, postoperative complications and return to independent living.

3. Secondary outcomes include Comprehensive Complications Index (CCI), a scale 0-100, higher number indicating worse outcome), based on the Clavien-Dindo scale of postoperative complications.

4. Broad inclusion criteria includes confirmed diabetic patients undergoing any surgery under any substantive anaesthetic technique. Excluded are procedures where local anaesthetic infiltration alone with or without monitored sedation. A maximum of 25% of cases evaluated will be ambulatory. This will enhance the external validity of the trial results and render it generalisable on a global scale.

5. The power of this study is driven by the target number 5,000 patients, which will enable more than 60 variables to be evaluated and up to ten a priori hypotheses to be tested.

Keywords: Diabetes, perioperative, complications, glycaemic control

Word Count: 3,146

Introduction:

The incidence of diabetes is increasing globally, with an estimated 20 million 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].

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 centres.[3,8] 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] Whether this variability in practice affects postoperative outcome among diabetic patients in countries across Europe has not been investigated.

Further, although it is assumed 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[10], it is not known if this reduces postoperative morbidity overall. Moreover, whether certain anaesthetic techniques may be associated with better or worse outcomes after major non-cardiac surgery is unknown.

Sub-group analysis will provide novel data on how patients with different strata (levels) of preoperative glycaemic 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 the level of preoperative glycaemic control and postoperative outcome, 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.

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

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-centred 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

    a. Type 1, Type 2, and other diabetic patients;

    b. Patients with different strata (levels) of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mol;

    c. Patients who received different anaesthetic techniques: -Volatile versus total intravenous anaesthesia; regional versus general anaesthesia (GA);

    d. Diabetics of longer duration have higher risk of intraoperative hypotension due to autonomic neuropathy.

Methods and Analysis:

Overall study design - MOPED is a prospective, observational, international, multicentre cohort study, supported by the European Society of Anaesthesiology (ESA). It has been registered on clinicaltrials.gov, NCT04511312.

Setting - 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 Steering Committee. Centres will be asked to enroll a minimum of 45 patients to nominate one named co-investigator over a recruitment period of up to 18 months from the date of the centre's registration with ESA. No more than one quarter (25%) of a centre's patients can be day cases (ambulatory anaesthesia). Study centre registration will occur online via the dedicated "Call for Centres form" on the ESA 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 ESA, provided that there is prior Institutional Review Board (IRB) approval. It is envisaged that at least n=50 centres will be actively enrolling patients. It is hoped that patients from at least ten nations will be enrolled. Enrollment will continue until the planned sample size (n=5,000) has been reached.

National coordinating investigators are anaesthesiologists appointed by ESA and the Steering Committee to lead the project within individual countries and their responsibility includes:

Identifying participating centres in their country and recruiting local co-ordinators in participating hospitals; Ensuring all necessary national or regional regulatory approvals are in place prior to start of patient inclusion; and facilitating good communication with ESA

headquarters and the participating sites in his/her countries during all study steps including data cleaning. Local centre co-ordinators may be anesthesiologists, surgeons or diabetes physicians working in perioperative medicine who will ensure all relevant regulatory/ethical approvals are in place for their institution,

supervise enrollment, daily data collection, and adjudicate morbidity events.

Participants:

Inclusion criteria - Diabetic patients (all classes except gestational diabetes) undergoing surgery with a substantive anaesthetic technique. This 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 surgery without a substantive anaesthetic technique, i.e. surgery under local anaesthetic infiltration or topical anaesthesia alone with or without monitored sedation .

Criteria for withdrawal or 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 anonymised 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 at the end of the planned recruitment period.

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 the local IRB review and given approval.

Variables:

Primary end point - Days at Home at 30 days (DAH-30) [12,13]. DAH-30 has been validated as an outcome metric by numerous large scale cohort studies [13] as an end-point which is pragmatic and easily obtained. It is affected by both patient factors (poor function, co-morbidities) and surgical technique. DAH-30 is sensitive to surgical risk and impact of post-operative complications in that it accounts for both delayed discharge and re-admission.

Secondary end points - 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[17]. These and other outcomes are shown in Table 1.

Data sources: The following data will be extracted from clinical charts: age, gender, weight, height, variables for CCI, variables for SORT calculation (SORT score Appendix 3).

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 CRF. Patients' consent will be requested to allow documentation of their perioperative course and 30-day outcome as outlined in the outcome measures.

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 date of registration of their centre with ESA 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.

Study procedures:

Recruitment and screening -

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. Diabetic patients listed for both elective and emergency surgery will be approached by a member of the research team and invited to participate. They will be offered a Patient Information Leaflet and the investigator will withdraw to allow the patient to consider it by themselves. The team member will then obtain signed written consent if the patient agrees to proceed. 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. 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, 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 Surgical Outcome Risk Tool (SORT) will be used to indicate surgical risk [17]

If patients remain in hospital on the day after surgery, some data will be documented including QoR-15 quality of recovery score, taking 3-5 minutes. Some patient data will also be recorded on Day of Discharge, provided 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. See Figure 1: Study Flow Table

Data collection:

At the end of the study period each center will provide an “end of study reporting form” (see Appendix 8) 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 9) 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 is already participating in other clinical trial, subject language, cognitive difficulties, etc). Data will be collected at each centre, anonymised, and entered into a bespoke electronic case-report form

(eCRF). Completed forms will be submitted to the sponsor at the ESA Clinical Trials Network (ESA CTN) in Brussels, Belgium.

Statistical methodology:

Sample size estimation - Up to 5% of the population of Europe is thought to have diabetes. About 30 million surgeries are performed in Europe per annum, therefore perhaps 1.5 million diabetics have surgery in Europe each year. 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.

The aim of this research is the 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. A further publication of the Study analysis plan is in preparation.

GDPR, Data and Quality Management:

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 centre coordinators will ensure that the data in the eCRF are carefully entered and verified regularly. It will be the responsibility of local coordinators to conduct periodic and random checks to ensure data quality in her/his centre. The ESA, as sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents for the purpose of monitoring and auditing. No fee or financial compensation is given to any co-investigator or participating institution for patient recruitment.

Data Handling - 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 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. 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).

Confidentiality and 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. Open direct access to all relevant trial 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 for data protection.

Patient and Public Involvement – To maximise the benefit of this study to patients we prioritised using a patient-centric, holistic primary outcome; Days at Home at 30 days. Previous delphi process driven studies have shown this to be a sensitive index of postoperative complications and their impact on patients' lives. Ireland’s diabetes patient advocacy association, Diabetes Ireland, kindly reviewed the draft protocol and offered comment and suggestion which influenced the final draft.

Publication and dissemination 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 coordinators 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. 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 collaboratorship based on other contributions. The final decision will be left to the SC in consultation with the ESA. The number of investigators allowed from each centre will be determined by the number of patients enrolled by that centre. TNo 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. ESA Clinical Trial Network will be acknowledged in all publications and presentations.

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

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 (ESA CTN) can use anonymised pooled data for internal analyses and educational purposes.

Figure Legend:

Table 1: Study end-points

Figure 1: Study work flow

References:

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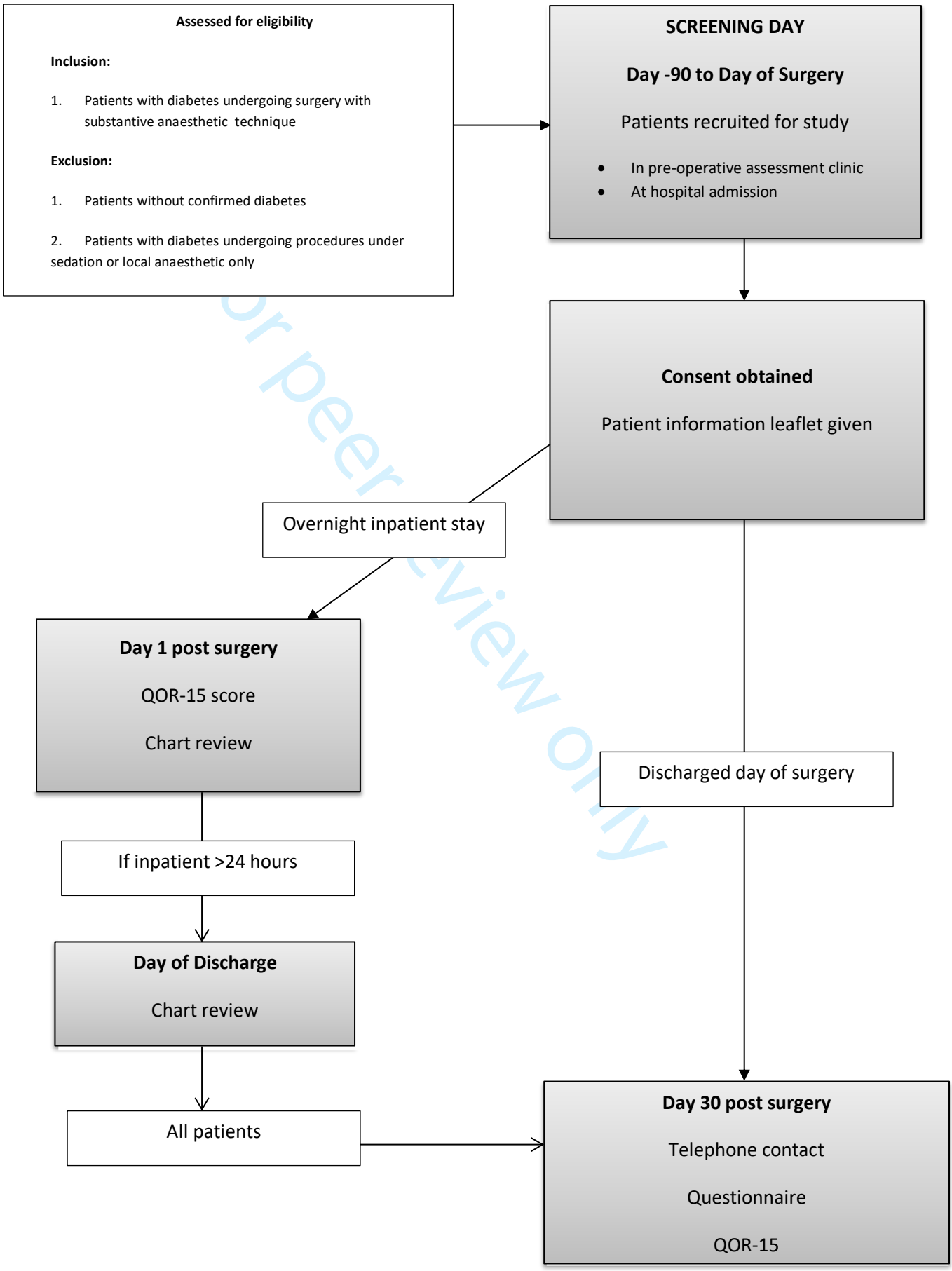
Table 1: Study End-Points

Primary	Secondary	Tertiary
Days at Home at 30 days	Comprehensive Complications Index	Time to resumption of normal diabetes therapy
	Quality of Recovery scale (QoR-15)	Incidence of diabetic ketoacidosis or hypoglycaemia
	30-day mortality	incidence and duration of use of IV insulin infusion therapy
	Length of Stay in Hospital	Incidence of diabetic ketoacidosis or hypoglycaemia
	Length of Stay in ICU (if applicable)	Change in diabetic management at 30 days
	Incidence of specific major adverse events	

Figure 1: Study Work Flow



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)

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Title:

Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)

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DJB: Concept instigation, ESA applicant, study design, manuscript draft;

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Abstract:

Introduction: Diabetes is common (about 20m patients in Europe), and diabetic patients have more surgical interventions than the general population. There are plausible pathophysiological and clinical mechanisms suggesting that diabetic patients are at increased risk of postoperative complications. When postoperative complications occur in the general population, they increase major adverse events and subsequently increase one-year mortality. 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 different strata of preoperative glycaemic control affects outcome.

Methods and analysis: A prospective, observational, international, multicentre cohort study, recruiting 5,000 diabetic patients undergoing elective or emergency surgery in at least n=50 centres (NCT04511312). Inclusion criteria are any diabetic patient undergoing surgery under any substantive anaesthetic technique. Exclusion criteria are not being a confirmed diabetic patient and diabetic patients undergoing procedures under monitored sedation or local anaesthetic infiltration only. Follow up duration is 30 days after surgery. Primary outcome is Days At Home at 30 days (DAH-30). Secondary outcomes are Comprehensive Complications Index (CCI), Quality of Recovery (QoR-15) Day 1, 30 -day mortality, length of hospital stay and incidence of specific major adverse events (MI, MINS, AKI, PPC, CVA, PE, DVT, Surgical Site Infection (SSI), Postoperative pulmonary infection (PPI)). Tertiary outcomes include time to resumption of normal diabetes therapy, incidence of diabetic

ketoacidosis or hypoglycaemia, incidence and duration of use of IV insulin infusion therapy, and change in diabetic management at 30 days.

Ethics and dissemination: This study will adhere to the principles 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 requirements will be followed as applicable. The main results of MOPED and its sub-studies will be published in peer–reviewed international medical journals and presented at Euroanaesthesia congress and other international and national meetings.

ClinicalTrials.gov Identifier: NCT04511312

ARTICLE SUMMARY

Strengths and limitations of this study:

1. There is wide variation in the perioperative anaesthetic management of diabetic patients, internationally and between centres. This will be the largest prospective, observational study documenting the influence of perioperative management on 30-day outcomes.

2. The primary endpoint is Days at Home at 30 days (DAH-30). This recently validated standardised end-point for perioperative trials (range 0-30 days, higher number indicating better outcome) gives a patient-centred outcome reflecting mortality, postoperative complications and return to independent living.

3. Secondary outcomes include Comprehensive Complications Index (CCI), a scale 0-100, higher number indicating worse outcome), based on the Clavien-Dindo scale of postoperative complications.

4. Broad inclusion criteria includes confirmed diabetic patients undergoing any surgery under any substantive anaesthetic technique. Excluded are procedures where local anaesthetic infiltration alone with or without monitored sedation. A maximum of 25% of cases evaluated will be ambulatory. This will enhance the external validity of the trial results and render it generalisable on a global scale.

5. The power of this study is driven by the target number 5,000 patients, which will enable more than 60 variables to be evaluated and up to eleven a priori hypotheses to be tested.

Keywords: Diabetes, perioperative, complications, glycaemic control

Word Count: 3,146

Introduction:

The incidence of diabetes is increasing globally, with an estimated 20 m diabetic patients in Europe. This is likely to increase, 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 pathophysiological and clinical mechanisms that diabetic patients are at increased risk of postoperative complications.[3,4] When postoperative complications occur in the general population, they increase mortality or 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].

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 centres.[3,8] Given the multiplicity of guidelines and differing recommendations, it is unsurprising that variability of 'real-world' clinical practice regarding perioperative management of oral antihyperglycemic medications and insulin therapy has been observed in audits such as the National Confidential Enquiry into Patient Outcome and Death (NCEPOD).[9] Whether this variability in practice affects postoperative outcome among diabetic patients in Europe or elsewhere has not been investigated.

Further, although it is assumed that diabetic patients are at increased risk of postoperative complications[5-8], this has not been evaluated recently, 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[10], it is not known if this reduces postoperative morbidity overall. Moreover, whether certain anaesthetic techniques may be associated with better or worse outcomes after major non-cardiac surgery is unknown.

Sub-group analysis will provide novel data on how patients with different strata (levels) of preoperative glycaemic control progress in the postoperative period. Poor pre-operative glycaemic control is associated with postoperative complications in retrospective studies[10,11]. If this prospective study confirms an association between the level of preoperative glycaemic control and postoperative outcome, then the beginning of personalised perioperative medicine for diabetic patients might 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].

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

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 nations?

2. What is the extent and patient-centred impact of postoperative complications among diabetic patients up to 30 days after surgery in Europe?

3. To undertake sub-group analysis comparing:

    a. Type 1, Type 2, and other diabetic patients;

    b. Patients with different strata (levels) of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mol;

    c. Patients who received different anaesthetic techniques: -Volatile versus total intravenous anaesthesia; regional versus general anaesthesia (GA);

    d. Whether diabetic patients of longer duration versus more recently diagnosed diabetic patients have higher risk of intraoperative hypotension due to autonomic neuropathy.

Methods and Analysis:

Overall study design - MOPED is a prospective, observational, international, multicentre cohort study, supported by the European Society of Anaesthesiology (ESA). It has been registered on clinicaltrials.gov, NCT04511312.

Setting - 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 Steering Committee. Centres will be asked to enroll a minimum of 45 patients, in order to nominate one named co-investigator. The recruitment period will be up to 18 months from the date of the centre's registration with ESA. No more than one quarter (25%) of a centre's patients can be day cases (ambulatory anaesthesia). Study centre registration will occur online via the dedicated "Call for Centres form" on the ESA website. The start of recruitment for individual centres should be soon as possible after centre registration with ESA, provided that there is prior Institutional Review Board (IRB) approval. It is envisaged that at least n=50 centres will actively enroll patients. It is hoped that patients from at least ten nations will be enrolled. Enrollment will continue until the planned sample size (n=5,000) has been reached.

National coordinating investigators are anaesthesiologists appointed by ESA and the Steering Committee to lead the project within individual countries. Their responsibility includes:

Identifying participating centres in their country and recruiting local co-ordinators in participating hospitals; Ensuring all necessary national or regional regulatory approvals are in place prior to start of patient inclusion; facilitating good communication between ESA headquarters and the participating sites in that nation. Local centre co-ordinators may be

anesthesiologists, surgeons or diabetes physician working in perioperative medicine who will ensure all relevant regulatory/ethical approvals are in place for their institution, and who will supervise enrollment, data collection and adjudicate morbidity events.

Participants:

Inclusion criteria - Diabetic patients (all classes except gestational diabetes) undergoing surgery with a substantive anaesthetic technique will be included. A substantive anaesthetic technique is defined as one requiring any general anaesthesia 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 surgery without a substantive anaesthetic technique, i.e. surgery under local anaesthetic infiltration or topical anaesthesia alone with or without monitored sedation .

Criteria for withdrawal or 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. Previously collected, encoded data will be anonymised 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 at the end of the planned recruitment period.

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. A Patient Information Leaflet (PIL) will be provided to patients, and must be subject to local IRB review and approval.

End-Points: (Table 1).

Primary end point - Days at Home at 30 days (DAH-30) [12,13]. DAH-30 has been validated as a patient-centric outcome metric by numerous large scale cohort studies [13] as an end-point which is pragmatic and easily obtained. It is affected by both patient factors (poor function, co-morbidities) and surgical technique. DAH-30 is sensitive to surgical risk and impact of post-operative complications in that it accounts for both delayed discharge and re-admission.

Secondary end points –

*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[17]. These and other outcomes are shown in Table 1.

Data sources: The following data will be extracted from clinical charts: age, gender, weight, height, variables for CCI, variables for SORT calculation (SORT score Appendix 3).
ASA classification, relevant medical history, preoperative diabetes medication (substance classes only), type of anesthesia, date, type, and location of surgery, procedure duration, date of ICU admission, date of discharge from ICU.
A continuous glucose/insulin infusion will be regarded as planned, any insulin boluses on top of this infusion will be deemed rescue (or "additional").

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 date of registration of their centre with ESA for up to 18 months. Once they start to enroll patients, centres are asked to do so consecutively, i.e. to take all eligible diabetic patients one after another. No other exclusion criteria apply, even emergency surgery patients are eligible. Therefore, we do not believe that significant risk of bias exists.

Study procedures:

Recruitment and screening -

At screening day ("day -90" to "day of surgery", i.e. within 3 months of planned day of surgery), patients may be screened and invited to participate. Diabetic patients listed for both elective and emergency surgery are eligible. They will be offered a Patient Information Leaflet and the investigator will withdraw to allow the patient to consider it by alone. The team member will obtain signed written consent if the patient agrees to proceed. 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. 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, 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 Surgical Outcome Risk Tool (SORT) will be used to indicate surgical risk [17]

If patients remain in hospital on the day after surgery, QoR-15 quality of recovery score will be documented. Patient data on insulin use, glucose levels and any complications observed will also be recorded on Day of Discharge, provided 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. See Figure 1: Study Flow Table

Data collection:

At the end of the study period, each center will provide an "end of study reporting form" 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 9) 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 is already participating in other clinical trial, subject language, cognitive difficulties, etc). Data will be collected at each centre, anonymised, and entered into a bespoke electronic case-report form (eCRF). Completed forms will be submitted to the sponsor at the ESA Clinical Trials Network (ESA CTN) in Brussels, Belgium.

Statistical Analysis Plan

Primary Outcome

Descriptive epidemiology of the perioperative management and postoperative morbidity of Diabetic patients across different countries in Europe. Morbidity and mortality will be assessed using Days at Home at 30 days (DAH-30) as the primary outcome.

Secondary Outcomes

Secondary outcomes will be morbidity as assessed by the Comprehensive Complications Index (CCI) score, based on Clavien-Dindo scale and additional hypotheses of interest as listed in Table 2.

Sample size estimation

Up to 5% of the population of Europe is thought to have diabetes. About 30 million surgeries are performed in Europe per annum, therefore perhaps 1.5 million diabetics have surgery in Europe each year. 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. It is expected that this should be sufficient for the main epidemiological aspects of this study. It is envisaged that this target

number will 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 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.

Primary Statistical Analysis

Descriptive statistics such as mean (SD), median [interquartile range] and frequencies (%) with be presented as appropriate. Gaussian distributions will be assessed using frequency histograms, normality plots and the Shapiro-Wilks statistic. The precision of the estimates will be reported as 95% confidence intervals to show the prevalence and incidence rates of diabetic phenotypes and major adverse events and complications.

Continuous data will be analysed using Student *t*-, Welch *t*-, Mann-Whitney *U*-, one-way analysis of variance (ANOVA) and Kruskal-Wallis *H*- statistics. Categorical data will be analysed using chi-square independence and expanded Fisher exact statistics. Multiple hypothesis or comparison testing will be addressed using Tukey-Kramer and Bonferroni corrections and overall statistical significance will be defined at $P<0.05$ (two-sided).

Repeated measurements in patients will be analysed using generalized linear mixed models (GLMM) with maximum likelihood estimation (MLE) using appropriate link functions: Gaussian, Poisson, Negative Binomial and Logit. Robust multivariable linear, logistic, proportional hazards and quantile regression models will be constructed to identify significant independent risk factors for adverse outcomes. Variables with $P<0.15$ on bivariate

analysis, or that are clinically relevant, will be entered. Multicollinearity will be assessed using variance inflation factors. Hierarchical nesting of patients in hospitals and countries will be entered as random effects in multilevel mixed-effects GLMM.

Secondary Statistical Analysis

Exploratory post-hoc analyses may be performed to gain further information about the cohort and to assess clinical outcomes with respect to participating countries and hospitals. Any post-hoc analyses will be identified as such in any reports. Participating institutions can request data extraction for further analysis and quality improvement, subject to approval of the Steering Committee. As the primary purpose of this project is epidemiological, missing data will not be replaced or imputed.

Software

Data will be analysed using Stata 16.1, StataCorp Inc., College Station, TX and Number Cruncher Statistical Systems 2020 (NCSS), NCSS Inc., Kaysville, UT.

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 (ESA CTN) can use anonymised pooled data for internal analyses and educational purposes.

GDPR, Data and Quality Management:

Quality control measures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. This will include 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 the responsibility of the National Coordinating Investigator, with support by the study coordinating office, to train local PIs. Local centre coordinators will ensure that the data in the eCRF are carefully entered and verified regularly. It will be the responsibility of local coordinators to conduct periodic and random checks to ensure data quality in that centre. The ESA as sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, and source documents for the purpose of monitoring and auditing. No fee or financial compensation is given to any co-investigator or participating institution for patient recruitment.

Data Handling - Data will be entered into a secure on-line database protected by personalised and confidential usernames and passwords, which document the time and the individual entering the data. The language of the online database, eCRF, and the relative SOPs is English and will not be translated into different languages. Data will be collected directly from source documents into the encoded paper CRF 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. 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).

Confidentiality and Data protection - To safeguard patients' confidentiality, a patient identification code will be assigned to encode data. The confidential log linking patient identification codes 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. Open direct access to all relevant trial information as well as source data/documents will be permitted for purposes of monitoring, audits or inspections by 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 for data protection.

Patient and Public Involvement – To maximise the benefit of this study to patients, we prioritised using a patient-centric, holistic primary outcome: Days at Home at 30 days. Previous Delphi process driven studies have shown this to be a sensitive index of postoperative complications and their impact on patients' lives. Ireland’s diabetes patient advocacy association, Diabetes Ireland, kindly reviewed the draft protocol and offered comment and suggestion which influenced the final draft.

Publication and dissemination 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 data, manuscript writing, and submission of national/local grants. Authors are required to give final approval of the version to be published and agree 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 coordinators 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. 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 collaboratorship based on other contributions. The final decision will be left to the SC in consultation with the ESA. The number of investigators allowed from each centre will be determined by the number of patients enrolled by that centre. No more than 25% of a centre's enrolled patients should be day cases (ambulatory anaesthesia).

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

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

Contributorship statement:

D.B., M.C., J.H., M.H., A.Z. devised the project, D.B., M.C., M.C., J.H., M.H., A.Z. contributed to the design of the study and developed the protocols for data collection and analysis. D.B., M.C., M.C., J.H., M.H., R.N., A.Z. were involved in drafting the manuscript. All authors gave final approval to the publishing of this work. All authors agree to be accountable for the integrity and veracity of this protocol and the data collected and analysed thereafter.

Competing interests:

None declared. No additional data available.

Funding:

The European Society of Anaesthesiology (ESA) as a study sponsor is providing administrative support for data collating. There is no other funding source for this study.

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Figure Legend:

Figure 1: Study work flow

Table 1: Study end-points

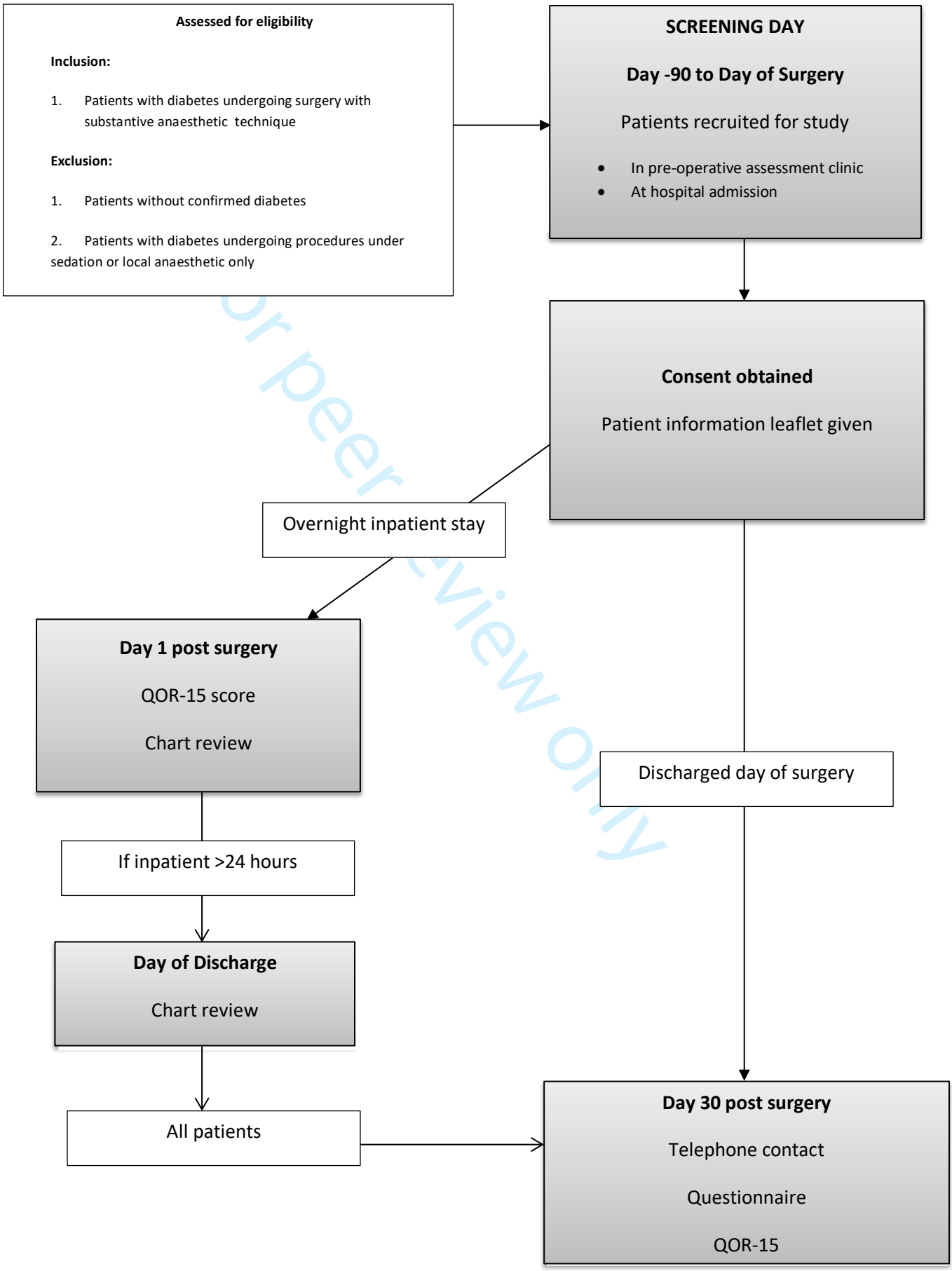
Primary	Secondary	Tertiary
Days at Home at 30 days	Comprehensive Complications Index	Time to resumption of normal diabetes therapy
	Quality of Recovery scale (QoR-15)	Incidence of diabetic ketoacidosis or hypoglycaemia
	30-day mortality	incidence and duration of use of IV insulin infusion therapy
	Length of Stay in Hospital	Incidence of diabetic ketoacidosis or hypoglycaemia
	Length of Stay in ICU (if applicable)	Change in diabetic management at 30 days
	Incidence of specific major adverse events	

Table 2. Secondary outcomes and hypotheses of interest

Hypothesis	Variables
There are major differences in perioperative management of diabetic patients in different nations in Europe	Insulin dose Methods of insulin admin Oral hypoglycaemic use
There are major differences in postoperative morbidity and outcomes among diabetic patients in different nations in Europe	DAH-30 CCI
Outcomes among patients with different strata of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mmol will be different;	Preop HbA1c and glucose DAH-30 CCI
Diabetic patient outcomes differ depending on anaesthetic technique: Volatile versus total intravenous anaesthesia; Regional versus general anaesthesia (GA) Combined GA and regional anaesthesia versus patients receiving GA alone.	DAH30 CCI All secondary outcomes
Diabetic Patients receiving liberal fluids perioperatively have better outcomes than patients receiving restrictive fluids, compared to their body weight	DAH-30, CCI crystalloid and colloid totals up to PACU
Type 2 DM patients have worse outcomes than Type 1	DAH-30, CCI
Patients where a consultant /senior surgeon and senior anaesthesiologist is present have better outcomes than when not present	Personnel tracking All Outcomes
Diabetic patients of longer duration experience more hypotension duration/episodes due to autonomic neuropathy and have worse outcomes than diabetic patients with shorter duration	Intraop and PACU hypotension and use vasopressors and outcomes; Duration of DM

NSAID use perioperatively worsens outcomes especially AKI	DAH30,CCI AKI
Risk factors for higher morbidity in diabetic patients undergoing surgery	All factors, All outcomes Multivariable analysis
Patients with preoperative GLP-1 use have better perioperative glucose control (and outcome) as compared to other oral hypoglycaemics	PreOp medication use DAH30 CCI
There is no association between metformin use and perioperative lactic acidosis	Preop medication use Incidence of DKA DAH-30 CCI
Patients with known preoperative susceptibility for hypoglycaemia/DKA are more prone for perioperative hypoglycaemia/DKA	PreOK hypoglycaemia/DKA PeriOK hypoglycaemia/DKA
Surgery in DM will lead to dysglycaemia up to 30 days	DM medication at 30 days

Figure 1: Study Work Flow



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)

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Primary Subject Heading:	Anaesthesia
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Title:

Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)

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Funding:

MOPED is sponsored by a grant from the European Society of Anaesthesiology Clinical Trial Network (ESA CTN).

Author Contributions:

DJB: Concept instigation, ESA funding applicant, study design, manuscript draft;

Malachy Colomb: : Study design, analysis plan draft;

Marc Coburn: Study design, manuscript draft;

JH: Study design, manuscript draft;

MWH: Study design, manuscript draft;

RN: Study design, manuscript draft;

AZ: Study design, manuscript draft;

Abstract:

Introduction: Diabetes is common (about 20m patients in Europe), and diabetic patients have more surgical interventions than the general population. There are plausible pathophysiological and clinical mechanisms suggesting that diabetic patients are at increased risk of postoperative complications. When postoperative complications occur in the general population, they increase major adverse events and subsequently increase one-year mortality. 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 different strata of preoperative glycaemic control affects outcome.

Methods and analysis: A prospective, observational, international, multicentre cohort study, recruiting 5,000 diabetic patients undergoing elective or emergency surgery in at least n=50 centres (NCT04511312). Inclusion criteria are any diabetic patient undergoing surgery under any substantive anaesthetic technique. Exclusion criteria are not being a confirmed diabetic patient and diabetic patients undergoing procedures under monitored sedation or local anaesthetic infiltration only. Follow up duration is 30 days after surgery. Primary outcome is Days At Home at 30 days (DAH-30). Secondary outcomes are Comprehensive Complications Index (CCI), Quality of Recovery (QoR-15) Day 1, 30 -day mortality, length of hospital stay and incidence of specific major adverse events (MI, MINS, AKI, PPC, CVA, PE, DVT, Surgical Site Infection (SSI), Postoperative pulmonary infection (PPI)). Tertiary outcomes include time to resumption of normal diabetes therapy, incidence of diabetic

ketoacidosis or hypoglycaemia, incidence and duration of use of IV insulin infusion therapy, and change in diabetic management at 30 days.

Ethics and dissemination: This study will adhere to the principles 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 requirements will be followed as applicable. The main results of MOPED and its sub-studies will be published in peer–reviewed international medical journals and presented at Euroanaesthesia congress and other international and national meetings.

ClinicalTrials.gov Identifier: NCT04511312

ARTICLE SUMMARY

Strengths and limitations of this study:

1. This will be the largest prospective, observational study of the perioperative anaesthetic management of diabetic patients, documenting the influence of perioperative management on 30-day outcomes.

2. The primary endpoint is Days at Home at 30 days (DAH-30), which is a recently validated standardised end-point for perioperative trials (range 0-30 days, higher number indicating better outcome) that gives a patient-centred outcome reflecting mortality, postoperative complications and return to independent living.

3. Secondary outcomes include Comprehensive Complications Index (CCI), a scale 0-100, higher number indicating worse outcome), based on the Clavien-Dindo scale of postoperative complications.

4. Broad inclusion criteria includes confirmed diabetic patients undergoing any surgery under any substantive anaesthetic technique, which will enhance the external validity of the trial results and render it generalisable on a global scale.

5. The power of this study is driven by the target number 5,000 patients, which will enable more than 60 variables to be evaluated and up to eleven a priori hypotheses to be tested.

Keywords: Diabetes, perioperative, complications, glycaemic control

Word Count: 3,146

Introduction:

The incidence of diabetes is increasing globally, with an estimated 20 m diabetic patients in Europe. This is likely to increase, 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 pathophysiological and clinical mechanisms that diabetic patients are at increased risk of postoperative complications.[3,4] When postoperative complications occur in the general population, they increase mortality or 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].

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 centres.[3,8] Given the multiplicity of guidelines and differing recommendations, it is unsurprising that variability of 'real-world' clinical practice regarding perioperative management of oral antihyperglycemic medications and insulin therapy has been observed in audits such as the National Confidential Enquiry into Patient Outcome and Death (NCEPOD).[9] Whether this variability in practice affects postoperative outcome among diabetic patients in Europe or elsewhere has not been investigated.

Further, although it is assumed that diabetic patients are at increased risk of postoperative complications[5-8], this has not been evaluated recently, 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[10], it is not known if this reduces postoperative morbidity overall. Moreover, whether certain anaesthetic techniques may be associated with better or worse outcomes after major non-cardiac surgery is unknown.

Sub-group analysis will provide novel data on how patients with different strata (levels) of preoperative glycaemic control progress in the postoperative period. Poor pre-operative glycaemic control is associated with postoperative complications in retrospective studies[10,11]. If this prospective study confirms an association between the level of preoperative glycaemic control and postoperative outcome, then the beginning of personalised perioperative medicine for diabetic patients might 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].

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

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 nations?

2. What is the extent and patient-centred impact of postoperative complications among diabetic patients up to 30 days after surgery in Europe?

3. To undertake sub-group analysis comparing:

    a. Type 1, Type 2, and other diabetic patients;

    b. Patients with different strata (levels) of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mol;

    c. Patients who received different anaesthetic techniques: -Volatile versus total intravenous anaesthesia; regional versus general anaesthesia (GA);

    d. Whether diabetic patients of longer duration versus more recently diagnosed diabetic patients have higher risk of intraoperative hypotension due to autonomic neuropathy.

Methods and Analysis:

Overall study design - MOPED is a prospective, observational, international, multicentre cohort study, supported by the European Society of Anaesthesiology (ESA). It has been registered on clinicaltrials.gov, NCT04511312.

Setting - 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 Steering Committee. Centres will be asked to enroll a minimum of 45 patients, in order to nominate one named co-investigator. The recruitment period will be up to 18 months from the date of the centre's registration with ESA. No more than one quarter (25%) of a centre's patients can be day cases (ambulatory anaesthesia). Study centre registration will occur online via the dedicated "Call for Centres form" on the ESA website. The start of recruitment for individual centres should be soon as possible after centre registration with ESA, provided that there is prior Institutional Review Board (IRB) approval. It is envisaged that at least n=50 centres will actively enroll patients. It is hoped that patients from at least ten nations will be enrolled. Enrollment will continue until the planned sample size (n=5,000) has been reached.

National coordinating investigators are anaesthesiologists appointed by ESA and the Steering Committee to lead the project within individual countries. Their responsibility includes:

Identifying participating centres in their country and recruiting local co-ordinators in participating hospitals; Ensuring all necessary national or regional regulatory approvals are in place prior to start of patient inclusion; facilitating good communication between ESA headquarters and the participating sites in that nation. Local centre co-ordinators may be

anesthesiologists, surgeons or diabetes physician working in perioperative medicine who will ensure all relevant regulatory/ethical approvals are in place for their institution, and who will supervise enrollment, data collection and adjudicate morbidity events.

Participants:

Inclusion criteria - Diabetic patients (all classes except gestational diabetes) undergoing surgery with a substantive anaesthetic technique will be included. A substantive anaesthetic technique is defined as one requiring any general anaesthesia 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 surgery without a substantive anaesthetic technique, i.e. surgery under local anaesthetic infiltration or topical anaesthesia alone with or without monitored sedation .

Criteria for withdrawal or 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. Previously collected, encoded data will be anonymised 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 at the end of the planned recruitment period.

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. A Patient Information Leaflet (PIL) will be provided to patients, and must be subject to local IRB review and approval.

End-Points: (Table 1).

Primary end point - Days at Home at 30 days (DAH-30) [12,13]. DAH-30 has been validated as a patient-centric outcome metric by numerous large scale cohort studies [13] as an end-point which is pragmatic and easily obtained. It is affected by both patient factors (poor function, co-morbidities) and surgical technique. DAH-30 is sensitive to surgical risk and impact of post-operative complications in that it accounts for both delayed discharge and re-admission.

Secondary end points –

*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[17]. These and other outcomes are shown in Table 1.

Data sources: The following data will be extracted from clinical charts: age, gender, weight, height, variables for CCI, variables for SORT calculation (SORT score Appendix 3).
ASA classification, relevant medical history, preoperative diabetes medication (substance classes only), type of anesthesia, date, type, and location of surgery, procedure duration, date of ICU admission, date of discharge from ICU.
A continuous glucose/insulin infusion will be regarded as planned, any insulin boluses on top of this infusion will be deemed rescue (or "additional").

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 date of registration of their centre with ESA for up to 18 months. Once they start to enroll patients, centres are asked to do so consecutively, i.e. to take all eligible diabetic patients one after another. No other exclusion criteria apply, even emergency surgery patients are eligible. Therefore, we do not believe that significant risk of bias exists.

Study procedures:

Recruitment and screening -

At screening day ("day -90" to "day of surgery", i.e. within 3 months of planned day of surgery), patients may be screened and invited to participate. Diabetic patients listed for both elective and emergency surgery are eligible. They will be offered a Patient Information Leaflet and the investigator will withdraw to allow the patient to consider it by alone. The team member will obtain signed written consent if the patient agrees to proceed. 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. 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, 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 Surgical Outcome Risk Tool (SORT) will be used to indicate surgical risk [17]

If patients remain in hospital on the day after surgery, QoR-15 quality of recovery score will be documented. Patient data on insulin use, glucose levels and any complications observed will also be recorded on Day of Discharge, provided 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. See Figure 1: Study Flow Table

Data collection:

At the end of the study period, each center will provide an "end of study reporting form" 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 9) 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 is already participating in other clinical trial, subject language, cognitive difficulties, etc). Data will be collected at each centre, anonymised, and entered into a bespoke electronic case-report form (eCRF). Completed forms will be submitted to the sponsor at the ESA Clinical Trials Network (ESA CTN) in Brussels, Belgium.

Statistical Analysis Plan

Primary Outcome

Descriptive epidemiology of the perioperative management and postoperative morbidity of Diabetic patients across different countries in Europe. Morbidity and mortality will be assessed using Days at Home at 30 days (DAH-30) as the primary outcome.

Secondary Outcomes

Secondary outcomes will be morbidity as assessed by the Comprehensive Complications Index (CCI) score, based on Clavien-Dindo scale and additional hypotheses of interest as listed in Table 2.

Sample size estimation

Up to 5% of the population of Europe is thought to have diabetes. About 30 million surgeries are performed in Europe per annum, therefore perhaps 1.5 million diabetics have surgery in Europe each year. 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. It is expected that this should be sufficient for the main epidemiological aspects of this study. It is envisaged that this target

number will 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 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.

Primary Statistical Analysis

Descriptive statistics such as mean (SD), median [interquartile range] and frequencies (%) with be presented as appropriate. Gaussian distributions will be assessed using frequency histograms, normality plots and the Shapiro-Wilks statistic. The precision of the estimates will be reported as 95% confidence intervals to show the prevalence and incidence rates of diabetic phenotypes and major adverse events and complications.

Continuous data will be analysed using Student *t*-, Welch *t*-, Mann-Whitney *U*-, one-way analysis of variance (ANOVA) and Kruskal-Wallis *H*- statistics. Categorical data will be analysed using chi-square independence and expanded Fisher exact statistics. Multiple hypothesis or comparison testing will be addressed using Tukey-Kramer and Bonferroni corrections and overall statistical significance will be defined at $P<0.05$ (two-sided).

Repeated measurements in patients will be analysed using generalized linear mixed models (GLMM) with maximum likelihood estimation (MLE) using appropriate link functions: Gaussian, Poisson, Negative Binomial and Logit. Robust multivariable linear, logistic, proportional hazards and quantile regression models will be constructed to identify significant independent risk factors for adverse outcomes. Variables with $P<0.15$ on bivariate

analysis, or that are clinically relevant, will be entered. Multicollinearity will be assessed using variance inflation factors. Hierarchical nesting of patients in hospitals and countries will be entered as random effects in multilevel mixed-effects GLMM.

Secondary Statistical Analysis

Exploratory post-hoc analyses may be performed to gain further information about the cohort and to assess clinical outcomes with respect to participating countries and hospitals. Any post-hoc analyses will be identified as such in any reports. Participating institutions can request data extraction for further analysis and quality improvement, subject to approval of the Steering Committee. As the primary purpose of this project is epidemiological, missing data will not be replaced or imputed.

Software

Data will be analysed using Stata 16.1, StataCorp Inc., College Station, TX and Number Cruncher Statistical Systems 2020 (NCSS), NCSS Inc., Kaysville, UT.

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 (ESA CTN) can use anonymised pooled data for internal analyses and educational purposes.

GDPR, Data and Quality Management:

Quality control measures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. This will include 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 the responsibility of the National Coordinating Investigator, with support by the study coordinating office, to train local PIs. Local centre coordinators will ensure that the data in the eCRF are carefully entered and verified regularly. It will be the responsibility of local coordinators to conduct periodic and random checks to ensure data quality in that centre. The ESA as sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, and source documents for the purpose of monitoring and auditing. No fee or financial compensation is given to any co-investigator or participating institution for patient recruitment.

Data Handling - Data will be entered into a secure on-line database protected by personalised and confidential usernames and passwords, which document the time and the individual entering the data. The language of the online database, eCRF, and the relative SOPs is English and will not be translated into different languages. Data will be collected directly from source documents into the encoded paper CRF 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. 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).

Confidentiality and Data protection - To safeguard patients' confidentiality, a patient identification code will be assigned to encode data. The confidential log linking patient identification codes 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. Open direct access to all relevant trial information as well as source data/documents will be permitted for purposes of monitoring, audits or inspections by 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 for data protection.

Patient and Public Involvement – To maximise the benefit of this study to patients, we prioritised using a patient-centric, holistic primary outcome: Days at Home at 30 days. Previous Delphi process driven studies have shown this to be a sensitive index of postoperative complications and their impact on patients' lives. Ireland’s diabetes patient advocacy association, Diabetes Ireland, kindly reviewed the draft protocol and offered comment and suggestion which influenced the final draft.

Publication and dissemination 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 data, manuscript writing, and submission of national/local grants. Authors are required to give final approval of the version to be published and agree 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 coordinators 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. 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 collaboratorship based on other contributions. The final decision will be left to the SC in consultation with the ESA. The number of investigators allowed from each centre will be determined by the number of patients enrolled by that centre. No more than 25% of a centre's enrolled patients should be day cases (ambulatory anaesthesia).

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

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

Data availability statement:

No additional data available. All relevant data will be uploaded in the published study results.

Contributorship statement:

D.B., M.C., M.C., J.H., M.H., A.Z. devised the project, D.B., M.C., M.C., J.H., M.H., A.Z. contributed to the design of the study and developed the protocols for data collection and analysis. D.B., R.N., M.C., M.C. were involved in the writing of the manuscript. All authors gave final approval to the publishing of this work. All authors agree to be accountable for the integrity and veracity of this protocol and the data collected and analysed thereafter.

Competing interests:

There are no competing interests for any author.

Funding:

European Society of Anaesthesia as study sponsor is providing administrative support for data collating. There is no other funding source for this study.

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Figure Legend:

Figure 1: Study work flow

Table 1: Study end-points

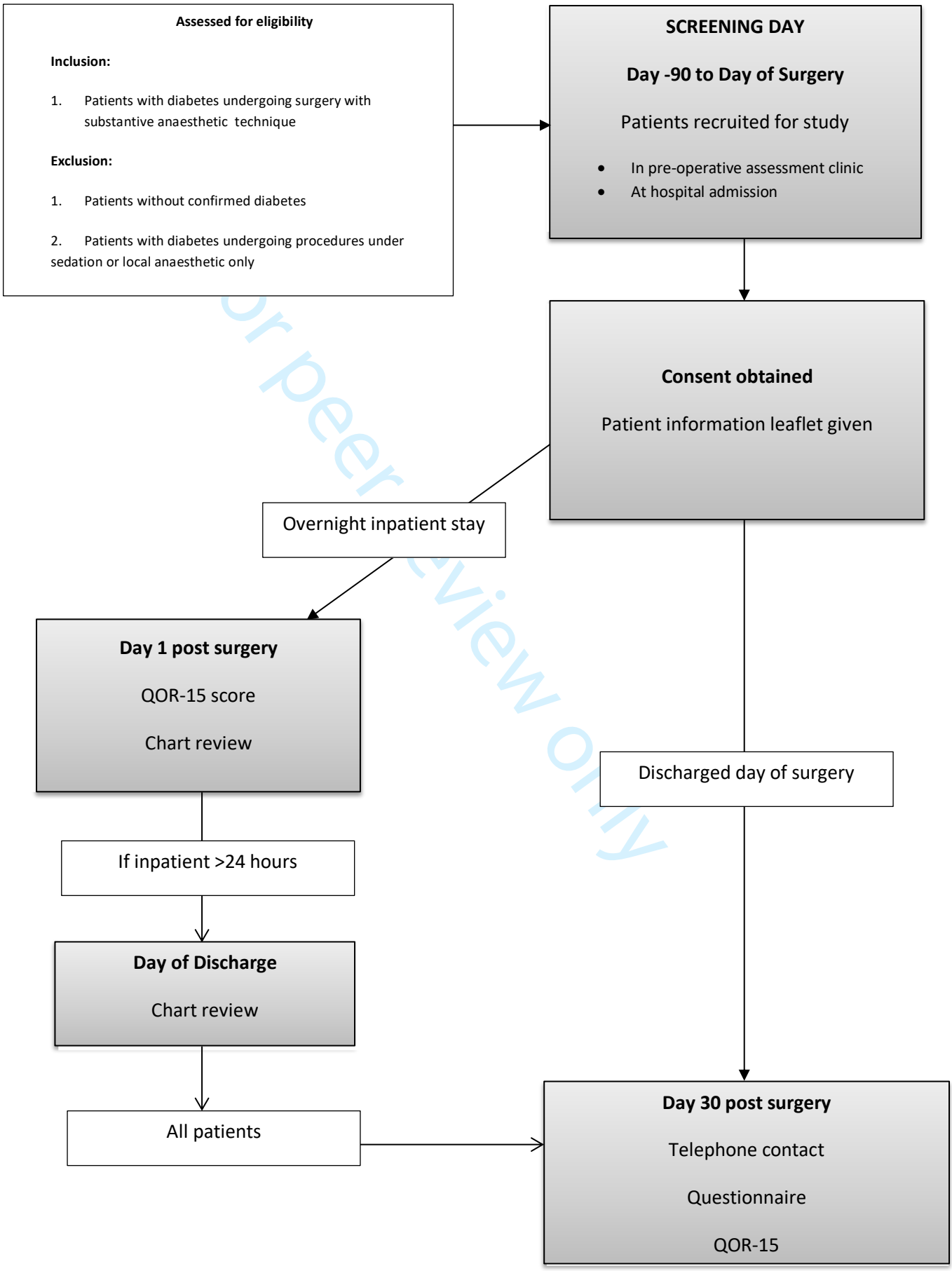
Primary	Secondary	Tertiary
Days at Home at 30 days	Comprehensive Complications Index	Time to resumption of normal diabetes therapy
	Quality of Recovery scale (QoR-15)	Incidence of diabetic ketoacidosis or hypoglycaemia
	30-day mortality	incidence and duration of use of IV insulin infusion therapy
	Length of Stay in Hospital	Incidence of diabetic ketoacidosis or hypoglycaemia
	Length of Stay in ICU (if applicable)	Change in diabetic management at 30 days
	Incidence of specific major adverse events	

Table 2. Secondary outcomes and hypotheses of interest

Hypothesis	Variables
There are major differences in perioperative management of diabetic patients in different nations in Europe	Insulin dose Methods of insulin admin Oral hypoglycaemic use
There are major differences in postoperative morbidity and outcomes among diabetic patients in different nations in Europe	DAH-30 CCI
Outcomes among patients with different strata of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mmol will be different;	Preop HbA1c and glucose DAH-30 CCI
Diabetic patient outcomes differ depending on anaesthetic technique: Volatile versus total intravenous anaesthesia; Regional versus general anaesthesia (GA) Combined GA and regional anaesthesia versus patients receiving GA alone.	DAH30 CCI All secondary outcomes
Diabetic Patients receiving liberal fluids perioperatively have better outcomes than patients receiving restrictive fluids, compared to their body weight	DAH-30, CCI crystalloid and colloid totals up to PACU
Type 2 DM patients have worse outcomes than Type 1	DAH-30, CCI
Patients where a consultant /senior surgeon and senior anaesthesiologist is present have better outcomes than when not present	Personnel tracking All Outcomes
Diabetic patients of longer duration experience more hypotension duration/episodes due to autonomic neuropathy and have worse outcomes than diabetic patients with shorter duration	Intraop and PACU hypotension and use vasopressors and outcomes; Duration of DM

NSAID use perioperatively worsens outcomes especially AKI	DAH30,CCI AKI
Risk factors for higher morbidity in diabetic patients undergoing surgery	All factors, All outcomes Multivariable analysis
Patients with preoperative GLP-1 use have better perioperative glucose control (and outcome) as compared to other oral hypoglycaemics	Preop medication use DAH30 CCI
There is no association between metformin use and perioperative lactic acidosis	Preop medication use Incidence of DKA DAH-30 CCI
Patients with known preoperative susceptibility for hypoglycaemia/DKA are more prone for perioperative hypoglycaemia/DKA	Preop hypoglycaemia/DKA Periop hypoglycaemia/DKA
Surgery in DM will lead to dysglycaemia up to 30 days	DM medication at 30 days

Figure 1: Study Work Flow



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Diabetes and endocrinology, Surgery
Keywords:	Adult anaesthesia < ANAESTHETICS, DIABETES & ENDOCRINOLOGY, SURGERY

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Title:

Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)

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Author Contributions:

D.B., M.C., M.C., J.H., M.H., A.Z. devised the project, D.B., M.C., M.C., J.H., M.H., A.Z. contributed to the design of the study and developed the protocols for data collection and analysis. D.B., R.N., M.C., M.C. were involved in the writing of the manuscript. All authors gave final approval to the publishing of this work. All authors agree to be accountable for the integrity and veracity of this protocol and the data collected and analysed thereafter.

Abstract:

Introduction: Diabetes is common (about 20m patients in Europe), and diabetic patients have more surgical interventions than the general population. There are plausible pathophysiological and clinical mechanisms suggesting that diabetic patients are at increased risk of postoperative complications. When postoperative complications occur in the general population, they increase major adverse events and subsequently increase one-year mortality. 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 different strata of preoperative glycaemic control affects outcome.

Methods and analysis: A prospective, observational, international, multicentre cohort study, recruiting 5,000 diabetic patients undergoing elective or emergency surgery in at least n=50 centres (NCT04511312). Inclusion criteria are any diabetic patient undergoing surgery under any substantive anaesthetic technique. Exclusion criteria are not being a confirmed diabetic patient and diabetic patients undergoing procedures under monitored sedation or local anaesthetic infiltration only. Follow up duration is 30 days after surgery. Primary outcome is Days At Home at 30 days (DAH-30). Secondary outcomes are Comprehensive Complications Index (CCI), Quality of Recovery (QoR-15) Day 1, 30 -day mortality, length of hospital stay and incidence of specific major adverse events (MI, MINS, AKI, PPC, CVA, PE, DVT, Surgical Site Infection (SSI), Postoperative pulmonary infection (PPI)). Tertiary outcomes include time to resumption of normal diabetes therapy, incidence of diabetic

ketoacidosis or hypoglycaemia, incidence and duration of use of IV insulin infusion therapy, and change in diabetic management at 30 days.

Ethics and dissemination: This study will adhere to the principles 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 requirements will be followed as applicable. Ethical approval has been granted by has been granted by the Institutional Review Board of the Mater Misericordiae University Hospital, Dublin, Ireland. As enrolment for this study is ongoing, ethical approval from additional centers is being added continuously. The main results of MOPED and its sub-studies will be published in peer–reviewed international medical journals and presented at Euroanaesthesia congress and other international and national meetings.

ClinicalTrials.gov Identifier: NCT04511312

ARTICLE SUMMARY

Strengths and limitations of this study:

1. This will be the largest prospective, observational study of the perioperative anaesthetic management of diabetic patients, documenting the influence of perioperative management on 30-day outcomes.

2. The primary endpoint is Days at Home at 30 days (DAH-30), which is a recently validated standardised end-point for perioperative trials (range 0-30 days, higher number indicating better outcome) that gives a patient-centred outcome reflecting mortality, postoperative complications and return to independent living.

3. Secondary outcomes include Comprehensive Complications Index (CCI), a scale 0-100, higher number indicating worse outcome), based on the Clavien-Dindo scale of postoperative complications.

4. Broad inclusion criteria includes confirmed diabetic patients undergoing any surgery under any substantive anaesthetic technique, which will enhance the external validity of the trial results and render it generalisable on a global scale.

5. The power of this study is driven by the target number 5,000 patients, which will enable more than 60 variables to be evaluated and up to eleven a priori hypotheses to be tested.

Keywords: Diabetes, perioperative, complications, glycaemic control

Word Count: 3,146

Introduction:

The incidence of diabetes is increasing globally, with an estimated 20 m diabetic patients in Europe. This is likely to increase, 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 pathophysiological and clinical mechanisms that diabetic patients are at increased risk of postoperative complications.[3,4] When postoperative complications occur in the general population, they increase mortality or 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].

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 centres.[3,8] Given the multiplicity of guidelines and differing recommendations, it is unsurprising that variability of 'real-world' clinical practice regarding perioperative management of oral antihyperglycemic medications and insulin therapy has been observed in audits such as the National Confidential Enquiry into Patient Outcome and Death (NCEPOD).[9] Whether this variability in practice affects postoperative outcome among diabetic patients in Europe or elsewhere has not been investigated.

Further, although it is assumed that diabetic patients are at increased risk of postoperative complications[5-8], this has not been evaluated recently, 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[10], it is not known if this reduces postoperative morbidity overall. Moreover, whether certain anaesthetic techniques may be associated with better or worse outcomes after major non-cardiac surgery is unknown.

Sub-group analysis will provide novel data on how patients with different strata (levels) of preoperative glycaemic control progress in the postoperative period. Poor pre-operative glycaemic control is associated with postoperative complications in retrospective studies[10,11]. If this prospective study confirms an association between the level of preoperative glycaemic control and postoperative outcome, then the beginning of personalised perioperative medicine for diabetic patients might 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].

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

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 nations?

2. What is the extent and patient-centred impact of postoperative complications among diabetic patients up to 30 days after surgery in Europe?

3. To undertake sub-group analysis comparing:

    a. Type 1, Type 2, and other diabetic patients;

    b. Patients with different strata (levels) of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mol;

    c. Patients who received different anaesthetic techniques: -Volatile versus total intravenous anaesthesia; regional versus general anaesthesia (GA);

    d. Whether diabetic patients of longer duration versus more recently diagnosed diabetic patients have higher risk of intraoperative hypotension due to autonomic neuropathy.

Methods and Analysis:

Overall study design - MOPED is a prospective, observational, international, multicentre cohort study, supported by the European Society of Anaesthesiology (ESA). It has been registered on clinicaltrials.gov, NCT04511312.

Setting - 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 Steering Committee. Centres will be asked to enroll a minimum of 45 patients, in order to nominate one named co-investigator. The recruitment period will be up to 18 months from the date of the centre's registration with ESA. No more than one quarter (25%) of a centre's patients can be day cases (ambulatory anaesthesia). Study centre registration will occur online via the dedicated "Call for Centres form" on the ESA website. The start of recruitment for individual centres should be soon as possible after centre registration with ESA, provided that there is prior Institutional Review Board (IRB) approval. It is envisaged that at least n=50 centres will actively enroll patients. It is hoped that patients from at least ten nations will be enrolled. Enrollment will continue until the planned sample size (n=5,000) has been reached.

National coordinating investigators are anaesthesiologists appointed by ESA and the Steering Committee to lead the project within individual countries. Their responsibility includes:

Identifying participating centres in their country and recruiting local co-ordinators in participating hospitals; Ensuring all necessary national or regional regulatory approvals are in place prior to start of patient inclusion; facilitating good communication between ESA headquarters and the participating sites in that nation. Local centre co-ordinators may be

anesthesiologists, surgeons or diabetes physician working in perioperative medicine who will ensure all relevant regulatory/ethical approvals are in place for their institution, and who will supervise enrollment, data collection and adjudicate morbidity events.

Participants:

Inclusion criteria - Diabetic patients (all classes except gestational diabetes) undergoing surgery with a substantive anaesthetic technique will be included. A substantive anaesthetic technique is defined as one requiring any general anaesthesia 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 surgery without a substantive anaesthetic technique, i.e. surgery under local anaesthetic infiltration or topical anaesthesia alone with or without monitored sedation .

Criteria for withdrawal or 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. Previously collected, encoded data will be anonymised 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 at the end of the planned recruitment period.

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. A Patient Information Leaflet (PIL) will be provided to patients, and must be subject to local IRB review and approval.

End-Points: (Table 1).

Primary end point - Days at Home at 30 days (DAH-30) [12,13]. DAH-30 has been validated as a patient-centric outcome metric by numerous large scale cohort studies [13] as an end-point which is pragmatic and easily obtained. It is affected by both patient factors (poor function, co-morbidities) and surgical technique. DAH-30 is sensitive to surgical risk and impact of post-operative complications in that it accounts for both delayed discharge and re-admission.

Secondary end points –

*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[17]. These and other outcomes are shown in Table 1.

Data sources: The following data will be extracted from clinical charts: age, gender, weight, height, variables for CCI, variables for SORT calculation (SORT score).

ASA classification, relevant medical history, preoperative diabetes medication (substance classes only), type of anesthesia, date, type, and location of surgery, procedure duration, date of ICU admission, date of discharge from ICU.

A continuous glucose/insulin infusion will be regarded as planned, any insulin boluses on top of this infusion will be deemed rescue (or “additional”).

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 date of registration of their centre with ESA for up to 18 months. Once they start to enroll patients, centres are asked to do so consecutively, i.e. to take all eligible diabetic patients one after another. No other exclusion criteria apply, even emergency surgery patients are eligible. Therefore, we do not believe that significant risk of bias exists.

Study procedures:

Recruitment and screening -

At screening day (“day -90” to “day of surgery”, i.e. within 3 months of planned day of surgery), patients may be screened and invited to participate. Diabetic patients listed for both elective and emergency surgery are eligible. They will be offered a Patient Information Leaflet and the investigator will withdraw to allow the patient to consider it by alone. The team member will obtain signed written consent if the patient agrees to proceed. 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. 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, 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 Surgical Outcome Risk Tool (SORT) will be used to indicate surgical risk [17]

If patients remain in hospital on the day after surgery, QoR-15 quality of recovery score will be documented. Patient data on insulin use, glucose levels and any complications observed will also be recorded on Day of Discharge, provided 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. See Figure 1: Study Flow Table

Data collection:

At the end of the study period, each center will provide an "end of study reporting form" 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 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 is already participating in other clinical trial, subject language, cognitive difficulties, etc). Data will be collected at each centre, anonymised, and entered into a bespoke electronic case-report form (eCRF). Completed forms will be submitted to the sponsor at the ESA Clinical Trials Network (ESA CTN) in Brussels, Belgium.

Statistical Analysis Plan

Primary Outcome

Descriptive epidemiology of the perioperative management and postoperative morbidity of Diabetic patients across different countries in Europe. Morbidity and mortality will be assessed using Days at Home at 30 days (DAH-30) as the primary outcome.

Secondary Outcomes

Secondary outcomes will be morbidity as assessed by the Comprehensive Complications Index (CCI) score, based on Clavien-Dindo scale and additional hypotheses of interest as listed in Table 2.

Sample size estimation

Up to 5% of the population of Europe is thought to have diabetes. About 30 million surgeries are performed in Europe per annum, therefore perhaps 1.5 million diabetics have surgery in Europe each year. 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. It is expected that this should be sufficient for the main epidemiological aspects of this study. It is envisaged that this target

number will 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 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.

Primary Statistical Analysis

Descriptive statistics such as mean (SD), median [interquartile range] and frequencies (%) with be presented as appropriate. Gaussian distributions will be assessed using frequency histograms, normality plots and the Shapiro-Wilks statistic. The precision of the estimates will be reported as 95% confidence intervals to show the prevalence and incidence rates of diabetic phenotypes and major adverse events and complications.

Continuous data will be analysed using Student *t*-, Welch *t*-, Mann-Whitney *U*-, one-way analysis of variance (ANOVA) and Kruskal-Wallis *H*- statistics. Categorical data will be analysed using chi-square independence and expanded Fisher exact statistics. Multiple hypothesis or comparison testing will be addressed using Tukey-Kramer and Bonferroni corrections and overall statistical significance will be defined at $P<0.05$ (two-sided).

Repeated measurements in patients will be analysed using generalized linear mixed models (GLMM) with maximum likelihood estimation (MLE) using appropriate link functions: Gaussian, Poisson, Negative Binomial and Logit. Robust multivariable linear, logistic, proportional hazards and quantile regression models will be constructed to identify significant independent risk factors for adverse outcomes. Variables with $P<0.15$ on bivariate

analysis, or that are clinically relevant, will be entered. Multicollinearity will be assessed using variance inflation factors. Hierarchical nesting of patients in hospitals and countries will be entered as random effects in multilevel mixed-effects GLMM.

Secondary Statistical Analysis

Exploratory post-hoc analyses may be performed to gain further information about the cohort and to assess clinical outcomes with respect to participating countries and hospitals. Any post-hoc analyses will be identified as such in any reports. Participating institutions can request data extraction for further analysis and quality improvement, subject to approval of the Steering Committee. As the primary purpose of this project is epidemiological, missing data will not be replaced or imputed.

Software

Data will be analysed using Stata 16.1, StataCorp Inc., College Station, TX and Number Cruncher Statistical Systems 2020 (NCSS), NCSS Inc., Kaysville, UT.

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 (ESA CTN) can use anonymised pooled data for internal analyses and educational purposes.

GDPR, Data and Quality Management:

Quality control measures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. This will include 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 the responsibility of the National Coordinating Investigator, with support by the study coordinating office, to train local PIs. Local centre coordinators will ensure that the data in the eCRF are carefully entered and verified regularly. It will be the responsibility of local coordinators to conduct periodic and random checks to ensure data quality in that centre. The ESA as sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, and source documents for the purpose of monitoring and auditing. No fee or financial compensation is given to any co-investigator or participating institution for patient recruitment.

Data Handling - Data will be entered into a secure on-line database protected by personalised and confidential usernames and passwords, which document the time and the individual entering the data. The language of the online database, eCRF, and the relative SOPs is English and will not be translated into different languages. Data will be collected directly from source documents into the encoded paper CRF 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. 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).

Confidentiality and Data protection - To safeguard patients' confidentiality, a patient identification code will be assigned to encode data. The confidential log linking patient identification codes 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. Open direct access to all relevant trial information as well as source data/documents will be permitted for purposes of monitoring, audits or inspections by 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 for data protection.

Patient and Public Involvement – To maximise the benefit of this study to patients, we prioritised using a patient-centric, holistic primary outcome: Days at Home at 30 days. Previous Delphi process driven studies have shown this to be a sensitive index of postoperative complications and their impact on patients' lives. Ireland’s diabetes patient advocacy association, Diabetes Ireland, kindly reviewed the draft protocol and offered comment and suggestion which influenced the final draft.

Publication and dissemination 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 data, manuscript writing, and submission of national/local grants. Authors are required to give final approval of the version to be published and agree 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 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 coordinators 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. 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 collaboratorship based on other contributions. The final decision will be left to the SC in consultation with the ESA. The number of investigators allowed from each centre will be determined by the number of patients enrolled by that centre. No more than 25% of a centre's enrolled patients should be day cases (ambulatory anaesthesia).

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

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

Data availability statement:

No additional data available. All relevant data will be uploaded in the published study results.

Contributorship statement:

D.B., M.C., M.C., J.H., M.H., A.Z. devised the project, D.B., M.C., M.C., J.H., M.H., A.Z. contributed to the design of the study and developed the protocols for data collection and analysis. D.B., R.N., M.C., M.C. were involved in the writing of the manuscript. All authors gave final approval to the publishing of this work. All authors agree to be accountable for the integrity and veracity of this protocol and the data collected and analysed thereafter.

Competing interests:

There are no competing interests for any author.

Funding:

European Society of Anaesthesia as study sponsor is providing administrative support for data collating. There is no other funding source for this study.

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Figure Legend:

Figure 1: Study work flow

Table 1: Study end-points

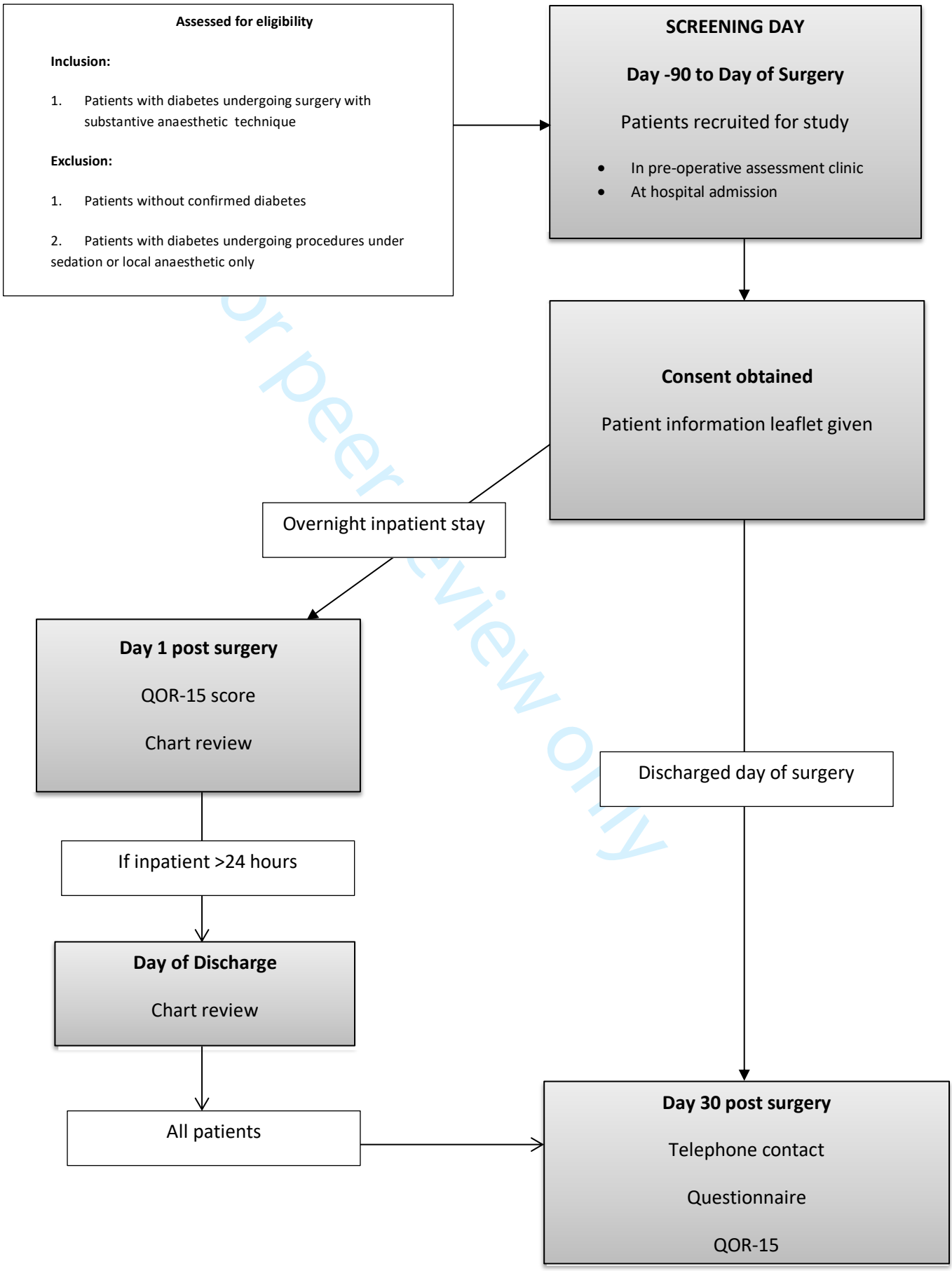
Primary	Secondary	Tertiary
Days at Home at 30 days	Comprehensive Complications Index	Time to resumption of normal diabetes therapy
	Quality of Recovery scale (QoR-15)	Incidence of diabetic ketoacidosis or hypoglycaemia
	30-day mortality	incidence and duration of use of IV insulin infusion therapy
	Length of Stay in Hospital	Incidence of diabetic ketoacidosis or hypoglycaemia
	Length of Stay in ICU (if applicable)	Change in diabetic management at 30 days
	Incidence of specific major adverse events	

Table 2. Secondary outcomes and hypotheses of interest

Hypothesis	Variables
There are major differences in perioperative management of diabetic patients in different nations in Europe	Insulin dose Methods of insulin admin Oral hypoglycaemic use
There are major differences in postoperative morbidity and outcomes among diabetic patients in different nations in Europe	DAH-30 CCI
Outcomes among patients with different strata of glycaemic control, i.e. HbA1c <53, HbA1c 53-69 and HbA1c >69 mmol.mmol will be different;	Preop HbA1c and glucose DAH-30 CCI
Diabetic patient outcomes differ depending on anaesthetic technique: Volatile versus total intravenous anaesthesia; Regional versus general anaesthesia (GA) Combined GA and regional anaesthesia versus patients receiving GA alone.	DAH30 CCI All secondary outcomes
Diabetic Patients receiving liberal fluids perioperatively have better outcomes than patients receiving restrictive fluids, compared to their body weight	DAH-30, CCI crystalloid and colloid totals up to PACU
Type 2 DM patients have worse outcomes than Type 1	DAH-30, CCI
Patients where a consultant /senior surgeon and senior anaesthesiologist is present have better outcomes than when not present	Personnel tracking All Outcomes
Diabetic patients of longer duration experience more hypotension duration/episodes due to autonomic neuropathy and have worse outcomes than diabetic patients with shorter duration	Intraop and PACU hypotension and use vasopressors and outcomes; Duration of DM

NSAID use perioperatively worsens outcomes especially AKI	DAH30,CCI AKI
Risk factors for higher morbidity in diabetic patients undergoing surgery	All factors, All outcomes Multivariable analysis
Patients with preoperative GLP-1 use have better perioperative glucose control (and outcome) as compared to other oral hypoglycaemics	Preop medication use DAH30 CCI
There is no association between metformin use and perioperative lactic acidosis	Preop medication use Incidence of DKA DAH-30 CCI
Patients with known preoperative susceptibility for hypoglycaemia/DKA are more prone for perioperative hypoglycaemia/DKA	Preop hypoglycaemia/DKA Periop hypoglycaemia/DKA
Surgery in DM will lead to dysglycaemia up to 30 days	DM medication at 30 days

Figure 1: Study Work Flow



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.