




BMJ Open Outcome in patients undergoing postponed elective surgery during the COVID-19 pandemic (TRACE II): study protocol for a multicentre prospective observational study

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ABSTRACT

Introduction During the COVID-19 pandemic many non-acute elective surgeries were cancelled or postponed around the world. This has created an opportunity to study the effect of delayed surgery on health conditions prior to surgery and postsurgical outcomes in patients with postponed elective surgery. The control group of the Routine Postsurgical Anesthesia Visit to Improve Patient Outcome (TRACE I) study, conducted between 2016 and 2019, will serve as a control cohort.

Methods and analysis TRACE II is an observational, multicentre, prospective cohort study among surgical patients with postponed surgery due to COVID-19 in academic and non-academic hospitals in the Netherlands. We aim to include 2500 adult patients. The primary outcome will be the 30-day incidence of major postoperative complications. Secondary outcome measures include the 30-day incidence of minor postoperative complications, 1 year mortality, length of stay (in hospital, medium care and intensive care), quality of recovery 30 days after surgery and postoperative quality of life up to 1 year following surgery. Multivariable logistic mixed-effects regression analysis with a random intercept for hospital will be used to test group differences on the primary outcome.

Ethics and dissemination Ethical approval was obtained from the Institutional Review Board of Maastricht University Medical Centre+ and Amsterdam UMC. Findings will be presented at national and international conferences, as well as published in peer-reviewed scientific journals, with a preference for open access journals. Data will be made publicly available after publication of the main results.

Trial registration number NL8841.

INTRODUCTION

The COVID-19 pandemic has had a massive impact on non-acute elective surgeries around the world. During the 12 weeks of peak disruption, approximately 28 000 000 routine

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ In this study we will be able to make use of a large pre-COVID-19 control group (~2500 subjects) of medium to high-risk surgical patients, including detailed information on clinical and patient-reported data.
- ⇒ Comparability between the postponed cohort and the control cohort may be biased because standard of care and hospital logistics may have been adapted during the COVID-19 pandemic.
- ⇒ As we are only including patients whose postponed surgery has been replanned, we will not be able to draw conclusions about patients whose surgery, for various reasons, was not replanned.

surgical procedures were cancelled or postponed worldwide.¹ The Dutch Healthcare Authority (Nederlandse Zorgautoriteit) estimated that in the Netherlands alone, approximately 340 000–380 000 elective surgeries were cancelled or postponed between March 2020 and May 2021.² The main reason for postponing these surgical procedures was the redistribution of personnel and equipment to the intensive care unit (ICU), to provide adequate care for large numbers of patients with COVID-19. Patients themselves also cancelled their scheduled procedures either due to fear of contracting COVID-19 in the hospital or to reduce the burden on the already overloaded health system. Additionally, referrals to hospitals decreased by an estimated 1 490 000 in the Netherlands,² either because patients were unable to get appointments at their general practitioners for referral or were unable to get appointments at the hospital. The Dutch population

screening programmes for breast, cervical and colon cancers came to a complete halt during the first COVID-19 wave,³ which also contributed to fewer referrals. The Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland) estimated that 4000 fewer new cancer diagnoses were made.^{4 5} Consequently, diagnostic procedures were delayed, resulting in postponement in surgical treatment.

Elective surgical care was decreased in the Netherlands for three periods, consistent with the three COVID-19 waves. In the first wave (March 2020 to June 2020),⁶ all elective surgeries were cancelled. In the second (July 2020 to January 2021) and third waves (February 2021),⁶ elective surgical care was resumed but with a decreased capacity. Due to this, hospital logistics, such as surgical planning, and presurgical and postsurgical patient pathways were sometimes also influenced. The gradual upscaling of non-COVID-19 care in 2020 and 2021 has created a unique window of opportunity to study the effect of delayed surgery on health conditions prior to surgery and postsurgical outcomes in patients with postponed elective surgery. These outcomes will be compared with those of the Routine Postsurgical Anesthesia Visit to Improve Patient Outcome (TRACE I)⁷ study population. This large-scale nationwide interventional study on perioperative care and patient outcomes was conducted in nine academic and non-academic hospitals in the Netherlands. The TRACE I database contains records of >5400 patients undergoing medium to high-risk surgery before COVID-19 in 2016–2018, with detailed information on preoperative patient characteristics, intraoperative conditions and events, postoperative recovery, complications (including mortality) and quality of life until 12 months after surgery. The control group of the TRACE study (n=~2500) will serve as a control cohort, when studying the effects of postponed surgery on minor and major postoperative complications, and postoperative quality of life.

Research questions

1. What is the effect of postponing elective surgery on 30-day postoperative mortality compared with the control cohort?
2. What is the effect of postponing elective surgery on the preoperative health status of surgical patients in the TRACE II cohort compared with the control cohort?
3. What effect does postponing surgery have on quality of life preoperatively, at 30 days and at 1 year postoperatively compared with the control cohort?
4. What is the effect of the COVID-19 pandemic on surgical patient pathways with regard to length of stay in specialised wards (medium care or ICU)?

METHODS AND ANALYSIS

TRACE II is an observational, multicentre, prospective cohort study among surgical patients with postponed surgery due to COVID-19 in academic and non-academic

hospitals in the Netherlands. We aim to include 2500 adult patients with postponed surgery and compare this new cohort with the historical control cohort from the TRACE I study.

Inclusion and exclusion criteria

Inclusion criteria

Patients undergoing elective surgery with an indication for postoperative hospital stay can be included in the study if they meet at least one of the following criteria:

- ▶ Sixty years and older.
- ▶ Forty-five years and older with a revised Cardiac Risk Index >2.
- ▶ Eighteen years and older with an indication for postoperative invasive pain therapy.
- ▶ Eighteen years and older with a postoperative surgical Apgar score <5.

Patients not fulfilling this or any other criterion will be excluded after surgery.

Exclusion criteria

- ▶ Patients who do not sign informed consent.
- ▶ Patients who are not able to complete the questionnaires in the Dutch language.
- ▶ Patients who are pregnant and patients undergoing caesarean section.
- ▶ Patients with surgery for fractures, appendectomy and organ transplant donors.
- ▶ Patients who had no delay in surgery.

We followed the same inclusion and exclusion criteria as the TRACE I study. Cardiac surgery and patients with an indication for postoperative stay in the ICU were excluded in TRACE I but included in this study. Delay is estimated by patients and the local study team in days, weeks or months. We aim to include all delays directly or indirectly related to COVID-19 by asking the patient about postponement or delay in the planning of their surgery and by having the local study team review the medical records.

Recruitment and consent

Patients will be recruited by a member of the local study team (anaesthesiologist or research assistant) preoperatively either during the preoperative screening or directly after hospital admission. Patients receive a patient information letter and are additionally verbally informed about the study aims. If they agree to participate, they will be asked to sign informed consent. This strategy is similar to the one used in the TRACE I study.

Participating centres

The study will be performed in seven Dutch hospitals, representing general hospitals, tertiary referral hospitals and academic centres. With the exception of two, all participated in the TRACE I study. All participating hospitals received approval from the ethical committee and the board of directors to participate in the TRACE II study.

Patient and public involvement

The Dutch Patient Federation (Patiëntenfederatie Nederland) and a patient panel from the Maastricht University Medical Centre (MUMC+) were involved in the design of the study protocol and the development of the questionnaires. We intend to ask the Dutch Patient Federation to help interpret the results of the questionnaires and for a plan to disseminate these results to the general public.

Data collection

Patient-reported and clinical data will be collected at inclusion (baseline), intraoperatively and postoperatively until 1 year after surgery. Data to be collected from patient record files include patient baseline characteristics, data on surgery and anaesthesia, intraoperative adverse events, the postoperative clinical course, postoperative in-hospital adverse events and postdischarge events measured at 30 days and at 12 months after surgery. Data will also be collected from patient questionnaires, completed at inclusion, 30 days and 12 months postoperatively. The questionnaires include questions on quality of life (EuroQol Dutch EQ-5D-5L), pain score (Numeric Rating Scale), functional recovery (Functional Recovery Index), and expected/perceived recovery (Global Surgery Recovery Index), delay in planning of the surgery, perioperative anxiety/fear (Surgical Fear Questionnaire), infection with the coronavirus and vaccination against the coronavirus. Patient questionnaires compare to the TRACE I study with the addition of anxiety/fear, delay in surgery and COVID-19-related questions.

Data management

Data will be recorded by local investigators into an internet-based electronic case record form in a Good Clinical Practice (GCP)-compliant database (Castor EDC). Data records are coded and the code key is kept securely in each participating centre. For data quality, we will do a 10% check by an independent monitor. Data will be standardised (SNOMED coding) and data sets and metadata will be made publicly available via a public repository after publication of the main results.

Outcome measures

The primary outcome will be the postoperative 30-day incidence of grade III, IV and V postoperative complications according to the modified Clavien-Dindo classification.⁸

Secondary outcome measures will be the 30-day incidence of grade I and II postoperative complications according to the modified Clavien-Dindo classification⁸: 1-year mortality, length of stay (in hospital, medium care and intensive care), quality of recovery 30 days after surgery and postoperative quality of life up to 1 year following surgery. Congruent with Meguid *et al*, postoperative complications will also be studied in eight domains: infectious, cardiac/transfusion, pulmonary, venous thromboembolic, renal, neurological, surgical and other.^{9,10}

Sample size calculation

We will recruit eligible patients from September 2020 onwards.

In the TRACE I study, we included a total of 2490 patients in the control arm. For this study, we will recruit ~2500 patients in seven hospitals to match the number of patients in the TRACE I control cohort. With a sample of this size, we will have over 80% power to detect an effect size on the primary outcome (the proportion of patients with at least one major complication) as small as 4%. The type I error rate is fixed at 5%.

Statistical analysis

Patient characteristics at baseline will be described using mean and SD for continuous variables, and count and percentage for categorical variables. We will use independent samples t-test or the Mann-Whitney U test to test for differences in continuous baseline measures that are normally and non-normally distributed, and Pearson's χ^2 test or Fisher's exact test to check for differences in categorical variables between the two cohorts. The primary outcome, 30-day incidence of major complications including mortality, will be compared between groups using logistic mixed-effects regression analysis, with a random intercept for hospital. Group differences will be adjusted for time effects and baseline characteristics that differed between groups to a clinically meaningful extent. Secondary outcomes will be tested between groups using either linear or logistic mixed-effects regression with a link function, depending on the distribution of the outcome, with a similar random-effects structure as for primary outcome measure. The length of surgical delay will also be a variable for adjustment to see if length of delay influences outcome. We also plan to do subgroup analyses on surgery types. Statistical analysis will be conducted using R, SPSS Version 28 and/or another compatible statistical software.

Ethics and dissemination

Ethical approval was obtained from the Institutional Review Board of MUMC+ (METC azM/UM 2020-2316) and Amsterdam UMC (Medical Ethics Review Committee AMC W20_384#20.429). The study was registered with the Netherlands Trial Registry (NL8841) on 17 August 2020, before the first patient was included. Findings will be presented at national and international conferences, as well as published in peer-reviewed scientific journals, with a preference for open access journals. Data will be made publicly available after publication of the main results. We followed the principles of the Declaration of Helsinki (Fortaleza) and GCP in the conduct of this study. We used the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines for our study protocol.¹¹

Protocol amendments

Protocol amendments have been added to the trial registration in the Netherlands Trial Registry and also noted and explained in the final published manuscript.

Trial status

Recruitment started in September 2020 but has not been completed at the time of submission of this manuscript. Current protocol version is 1.1 (13 October 2021).

DISCUSSION

The TRACE II study is currently the only prospective study assessing the effects of postponed elective surgery during the COVID-19 pandemic. In this study, we will make use of a large control group (~2500 subjects) of medium to high-risk surgical patients, including detailed information on clinical and patient-reported data from the TRACE I study. By employing the infrastructure of the TRACE I study, we were able to quickly activate the participating (TRACE consortium) hospitals to start the study, soon after the start of the COVID-19 pandemic. TRACE II is designed as a prospective study using a historical control cohort, reflecting an ethical manner to study the phenomenon of postponed surgery. As a result of the observational design, comparability between the postponed cohort and the control cohort may be biased because standard of care and hospital logistics may have been affected during the COVID-19 pandemic. Additionally, we decided to include cardiac surgery patients in the TRACE II study, although they are not represented in TRACE I. This may impact the comparability between groups, but nevertheless, it is important to include this group because of the potential high impact of postponing surgery in cardiac surgery patients. A sensitivity analysis excluding cardiac surgery patients will be performed. As we are only including patients whose postponed surgery has been replanned, we will not be able to draw conclusions about patients whose surgery was relocated to another hospital, whose indication for surgery was withdrawn, whose elective surgery turned into emergency surgery because of the delay or who died while waiting for their surgery. Findings from TRACE II will increase our knowledge on perioperative management and logistics in crisis situations where surgical care capacity is restricted, which could be useful in future calamities. This knowledge may impact future prioritisation of surgeries, making informed decisions and organising perioperative care in the most beneficial way.

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Contributors DdK-dB, MWH and WB initiated the study. DdK-dB, MWH, WB, SvK, JB, SK, GJS, PGN, BAI'tV and ACW designed the study and wrote the study protocol. DdK-dB, ACW, JB, CSEB, SK, GJS, PGN and ACW were responsible for study conduct, reporting and acquisition of data in all the participating centres. ACW and DdK-dB wrote the draft manuscript. WB, MWH, SvK, JB, SK, GJS, PGN, BAI'tV, ACW and CSEB critically reviewed the draft and read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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