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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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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 TRACE I study, conducted between 2016 and 2019, will serve as a control cohort.

Methods and analysis: TRACE II is an observational, multi-centre, 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, one-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 one 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 UMC+ 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.

Discussion: The TRACE II study is currently the only prospective study assessing the effects of postponed elective surgery during the COVID-19 pandemic. Findings from TRACE II will increase our knowledge on perioperative management and logistics in crisis situations where

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surgical care capacity is restricted, which could be useful in future calamities and may impact future prioritization of surgeries, making informed decisions, and organizing perioperative care in the most beneficial way.

Trial registration: NL8841 Netherlands Trial Registry. Registered on 2020-08-17 before the first patient was included. https://www.trialregister.nl/trial/8841

Keywords: COVID-19, elective surgery, postponed surgery, outcomes, postoperative complications, postoperative mortality

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Article Summary

Strengths and limitations of this study

- 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 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

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- Because 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

Introduction

The COVID-19 pandemic has had a massive impact on non-acute elective surgeries around the world. During the twelve weeks of peak disruption, approximately 28.000.000 routine surgical procedures were cancelled or postponed worldwide.(1) The Dutch Healthcare authority (Nederlandse Zorgautoriteit, NZa) estimated that in the Netherlands alone, approximately 340.000 to 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 COVID-19 patients. 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 programs for breast, cervical and colon cancer came to a complete halt during the first COVID-19 wave, (3) which also contributed to fewer referrals. The Netherlands Comprehensive Cancer Organization (Integraal Kankercentrum Nederland, IKNL) estimated that 4000 fewer new cancer diagnoses were made. (4)(5) Consequently, diagnostic procedures were delayed, resulting in postponement in surgical treatment.

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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 surgery was 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. Because of this, hospital logistics, such as surgical planning, and pre- and post-surgical patient pathways sometimes also changed.

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 to those of the TRACE I (Routine posTsuRgical Anaesthesia visit to improve patient outComE) (7) study population. . This large-scale nationwide interventional study on peri-operative 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 in 2016-2018, with detailed information on pre-operative patient characteristics, intra-operative conditions and events, post-operative recovery, complications (including mortality) and quality of life until twelve 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) Does postponing elective surgery have an effect on 30-day postoperative mortality, compared to the control cohort?

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(2) Do surgical patients in the TRACE II cohort have poorer health conditions prior to surgery?

(3) Does postponing surgery have an impact on quality of life preoperatively at 30-days, and one year postoperatively, compared to the control cohort?

(4) Did surgical patient pathways (length of stay in medium care or intensive care unit) change during the COVID-19 pandemic?

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Methods and analysis

TRACE II is an observational, multi-centre, 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.

We used the SPIRIT reporting guidelines for our study protocol.(8)

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:

- 60 years and older
- 45 years and older with a revised cardiac risk index (rCRI) > 2

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- 18 years and older with an indication for postoperative invasive pain therapy
- 18 years and older with a postoperative surgical APGAR-score (sAPGAR) < 5

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

Recruitment and consent

Patients will be recruited by a member of the local study team (anaesthesiologist or research assistant) pre-operatively, either during the pre-operative screening or directly after hospital admission. Patients receive a patient information letter and are additionally verbally informed about the study aims and the study phase they will enter. If they agree to participate, they will be asked to sign informed consent.

Participating centres

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The study will be performed in seven Dutch hospitals, representing general hospitals, tertiary referral hospitals and academic centres. 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 interpretate the results of the questionnaires and a plan for dissemination of these results to the general public.

Data collection

Patient-reported and clinical data will be collected at inclusion (baseline), intraoperatively, and postoperatively until one year after surgery. Data to be collected from patient record files include patient baseline characteristics, data on surgery and anaesthesia, intra-operative adverse events, the postoperative clinical course, postoperative in-hospital adverse events and post-discharge events measured at 30 days, and at twelve months after surgery. Data will also be collected from patient questionnaires, completed at inclusion, 30 days, and twelve months postoperatively. The questionnaires include questions on quality of life (EuroQol Dutch EQ-5D-5L), pain score (numeric rating scale, NRS), functional recovery (Functional Recovery Index), and expected/perceived recovery (Global Surgery Recovery index), delay in planning

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of the surgery, perioperative anxiety/fear (Surgical Fear Questionnaire, SFQ), infection with the coronavirus, vaccination against the coronavirus.

Data management

Data will be recorded by local investigators into an internet-based electronic case record form in a Good Clinical Practice 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 made publicly available 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. (9)

Secondary outcome measures will be the 30-day incidence of grade I and II postoperative complications according to the modified Clavien-Dindo classification (9): one-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 one 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. (10)(11)

Sample size calculation

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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 1 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 standard deviation (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 chi-squared 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. Statistical analysis will be conducted utilizing R, SPSS and/or another compatible statistical software.

Ethics and dissemination

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Ethical approval was obtained from the institutional review board of Maastricht UMC+ (METC azM/ UM 2020-2316) and Amsterdam UMC (Medical Ethics Review Committee AMC W20_384#20.429). 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 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 (13-10-2021).

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 be able to 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. 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 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

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in cardiac surgery patients. 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 in to 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 prioritization of surgeries, making informed decisions, and organizing perioperative care in the most beneficial way.

Authors' contributions

DDK, MH and WB initiated the study. ACW and DDK wrote the draft manuscript. All authors critically reviewed the draft manuscript and read and approved the final manuscript.

Consent for publication

not applicable

Availability of data and material

After the study, data will be standardized (SNOMED coding), and datasets and metadata will be made available via a public repository

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Conflict of interests

The authors declare that they have no competing interests

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,2,11

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1,2,3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See link page 3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	See link page 3, 11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

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Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6/7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Not applicable; observational study
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Not applicable; no intervention in observational study
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Not applicable; no intervention in observational study
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable; no intervention in observational study
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	8

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		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Not applicable; no intervention in observational study
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable; no intervention in observational study
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable; no intervention in observational study
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable; no intervention in observational study
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable; no intervention in observational study
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	7

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		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7

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Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable; no interim analyses or stopping guidelines due to observational study
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Not applicable; no intervention in observational study
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11

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Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9/11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable; observational study
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9/11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	9/11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See attached file
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable; observational study

None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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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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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 TRACE I study, conducted between 2016 and 2019, will serve as a control cohort.

Methods and analysis: TRACE II is an observational, multi-centre, 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, one-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 one 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 UMC+ 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: NL8841 Netherlands Trial Registry. Registered on 2020-08-17 before the first patient was included. https://www.trialregister.nl/trial/8841

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Keywords: COVID-19, elective surgery, postponed surgery, outcomes, postoperative complications, postoperative mortality

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Article Summary

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

Introduction

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The COVID-19 pandemic has had a massive impact on non-acute elective surgeries around the world. During the twelve weeks of peak disruption, approximately 28.000.000 routine surgical procedures were cancelled or postponed worldwide.(1) The Dutch Healthcare authority (Nederlandse Zorgautoriteit, NZa) estimated that in the Netherlands alone, approximately 340.000 to 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 COVID-19 patients. 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 programs for breast, cervical and colon cancer came to a complete halt during the first COVID-19 wave, (3) which also contributed to fewer referrals. The Netherlands Comprehensive Cancer Organization (Integraal Kankercentrum Nederland, IKNL) 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 surgery was 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 pre- and post-surgical patient pathways were sometimes also influenced. The gradual upscaling of non-COVID-19 care in 2020 and 2021 has created a

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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 to those of the TRACE I (Routine posTsuRgical Anaesthesia visit to improve patient outComE) (7) study population. This large-scale nationwide interventional study on peri-operative 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 pre COVID-19 in 2016-2018, with detailed information on pre-operative patient characteristics, intra-operative conditions and events, post-operative recovery, complications (including mortality) and quality of life until twelve 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 to 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 to the control cohort?

(3) What effect does postponing surgery have on quality of life preoperatively, at 30-days, and at one year postoperatively, compared to the control cohort?

(1) 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 intensive care unit)?

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Methods and analysis

TRACE II is an observational, multi-centre, 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:

- 60 years and older
- 45 years and older with a revised cardiac risk index (rCRI) > 2
- 18 years and older with an indication for postoperative invasive pain therapy
- 18 years and older with a postoperative surgical APGAR-score (sAPGAR) < 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

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We followed the same in- 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) pre-operatively, either during the pre-operative 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.

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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 dissemination these results to the general public.

Data collection

Patient-reported and clinical data will be collected at inclusion (baseline), intraoperatively, and postoperatively until one year after surgery. Data to be collected from patient record files include patient baseline characteristics, data on surgery and anaesthesia, intra-operative adverse events, the postoperative clinical course, postoperative in-hospital adverse events and post-discharge events measured at 30 days, and at twelve months after surgery. Data will also be collected from patient questionnaires, completed at inclusion, 30 days, and twelve months postoperatively. The questionnaires include questions on quality of life (EuroQol Dutch EQ-5D-5L), pain score (numeric rating scale, NRS), 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, SFQ), infection with the coronavirus, 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.

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Data management

Data will be recorded by local investigators into an internet-based electronic case record form in a Good Clinical Practice 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 standardized (SNOMED coding) and datasets 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 classification (8): one-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 one 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)

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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 1 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 standard deviation (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 chi-squared 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

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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 utilizing R, SPSS and/or another compatible statistical software.

Ethics and dissemination

Ethical approval was obtained from the institutional review board of Maastricht UMC+ (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 under number NL8841, on the 17th of 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 Good Clinical Practice (GCP) in the conduct of this study. We used the SPIRIT reporting guidelines for our study protocol.(11)

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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 (13-10-2021).

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 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

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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 in to 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 prioritization of surgeries, making informed decisions, and organizing perioperative care in the most beneficial way.

Authors' contributions

DDK, MH and WB initiated the study. DDK, MH, WB, SvK, JB, SK, GJS, PN, BitV, and AW designed the study and wrote the study protocol. DDK, ACW, JB, CB, SK, GJS, PN, AW are responsible for study conduct, reporting and acquisition of data in all the participating centres. ACW and DDK wrote the draft manuscript. WB, MH, SvK, JB, SK, GJS, PN, BitV, AW, CB critically reviewed the draft and read and approved the final manuscript.

Consent for publication

not applicable

Availability of data and material

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After the study, data will be standardized (SNOMED coding), and datasets and metadata will be made available via a public repository

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Conflict of interests

The authors declare that they have no competing interests

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Word Count

3467

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	9
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,2,11

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1,2,3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See link page 3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	See link page 3, 11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			

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Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6/7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Not applicable; observational study
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	Not applicable; no intervention in observational study
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Not applicable; no intervention in observational study
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable; no intervention in observational study
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	8

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		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Not applicable; no intervention in observational study
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Not applicable; no intervention in observational study
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Not applicable; no intervention in observational study
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable; no intervention in observational study
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable; no intervention in observational study
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	7

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		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7

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Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable; no interim analyses or stopping guidelines due to observational study
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Not applicable; no intervention in observational study
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	9
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11

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Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9/11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable; observational study
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9/11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	9/11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See attached file
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable; observational study

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