Supplementary material

Individualised perioperative blood pressure and fluid therapy in oesophagectomy - Study protocol for a prospective randomised controlled trial

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Supplementary Material 1: Anaesthesia protocol for both groups

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Anaesthesia protocol for both groups

All patients are monitored with a left-sided radial arterial pressure and a three-lumen central venous catheter. Two large bore peripheral vein catheters are inserted.

In the active group a FloTrac sensor is used coupled to a Hemosphere monitor.

A thoracic epidural catheter is inserted at the level of Th6-Th9 according to the individual patient anatomy. After insertion, a test dose of lidocaine (2%) with adrenaline (5‰) 3-4 mL is given. During surgery, epidural analgesia is maintained with bupivacaine 2.5-5% 5-10 mL $hour^{-1}$ following a bolus dose of 5-7 mL. After surgery, epidural analgesia is switched to Dr. Breivik's mixture[1] (bupivacaine 0.1 mg mL^{-1}, fentanyl 2 ug mL^{-1}, adrenaline 2 ug mL^{-1}) and titrated to adequate pain relief.

Anaesthesia is induced with propofol, fentanyl and rocuronium and maintained with propofol and fentanyl.

Tidal volume during two-lung ventilation is 8 mL kg^{-1} ideal body weight (IBW) (defined as 22 × actual $height^2$ (m) regardless of sex). During one lung ventilation (OLV) tidal volume is 5 ml kg^{-1} IBW. Positive end-expiratory pressure (PEEP) is 5 cmH_2O.

The anaesthesia start sequence is

1. Arterial line & first peripheral venous line
2. Epidural catheter insertion & test dose
3. General anaesthesia induced & intubation
4. Central venous catheter inserted
5. Bolus dose of epidural analgesia (bupivacaine 2.5-5%) 5-7mL

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Supplementary Material 2: Outcomes (full list)

The primary endpoint is overall morbidity using the comprehensive complication index (CCI) calculated from www.assessurgery.com 30 days after surgery.

Secondary endpoints are:

- CCI day 90 after surgery
- Length of hospital stay (days)
- Reoperation defined as any intervention under general anesthesia within 90 days (n)
- Fluid balance during the intervention (mL)
- Norepinephrine requirement during the intervention (µg/kg/min)
- Quality of life difference from before surgery and 90 days after surgery

Explorative endpoints are:

- Anaesthesia time (minutes)
- Surgery time (minutes)
- Use of vasoactive medicine and fluids the first until 07:00 AM on the first post operative day
- Surgical complications as defined by European Perioperative Clinical Outcome
- Time in the ICU (actual time from admission to discharge, minutes)

At the pre-anaesthetic evaluation

- Resting blood pressure (after at least 25 min. rest)
- 24-hour ambulatory blood pressure

Within anaesthesia time

- Anaesthetics used (propofol (mg), fentanyl (µg), remifentanil (µg), rocuronium (mg), morphine (mg), methadone (mg), bupivacaine (epidural – mg), epidurals used (no))
- Vasoactive medication (norepinephrine (mg), phenylephrine (mg), ephedrine (mg), dopamine (mg), dobutamine (mg), epinephrine (µg),

- Systemic blood pressure (systolic- and diastolic blood pressure every 20 minutes – mmHg)
- Fluids: colloids (mL), crystalloids (mL)
- Estimated blood loss (mL)
- Blood transfusion (type and mL)
- Urine output (mL)
- Net fluid balance from the start of anaesthesia until the end of anaesthesia (mL)
- Net fluid balance from the start of anaesthesia until 24 hours after start of anaesthesia
- One-lung ventilation time and volume (mins and mL)
- Laparoscopic inflation time (no & min)
- Open thorax (open surgery only) (no & min)
- Thoracoscopic surgery time (only scopic surgery in thorax) (no & min)
    - CO (continuous – L/min) (including COs in recorded during PLR)
    - SVV (continuous - %)
    - PPV (continuous - %)
    - HPI (continuous – 1-100)
    - Mean, systolic and diastolic blood pressures (continuous – mmHg)
- Peritoneal pressure (from the laparoscopy inflation device) is recorded manually during surgery

In the ICU

- Opioids used (morphine (mg), fentanyl (ug), alfentanil (mg), oxycodone (mg).
- Epidural dose of. Breivik's mixture[1] (bupivacaine 0.1 mg/mL, fentanyl 2 ug/mL, adrenaline 2 ug/mL) mL
- Systemic blood pressure (systolic- and diastolic blood pressure every 2 minutes – mmHg)
    - CO (continuous – L/min)
    - PPV (continuous - %)
    - HPI (continuous – 1-100)
    - Mean, systolic and diastolic blood pressures (continuous – mmHg)
- Colloids (mL)

- Crystalloids (mL)
- Sum of colloids & crystalloids (mL)
- Blood transfusion (type and mL)
- Urine output (mL)
- New onset arrhythmia (atrial fibrillation/atrial flutter (no), ventricular tachycardia (no)
- Troponin I (day 1 morning)

Ultrasonographic muscle mass assessment will be compared to CCI at 30 and 90 days.

- With the curved array transducer on the patient's right leg at the 60% length mark measured from the anterior superior iliac spine to the superior border of patella:
    - Quadriceps depth (cm) day 1
    - Rectus femoris cross sectional area (cm^2) day 1

Variables from preoperative CT-scans

- Average of left and right psoas muscle area at the level of L4 (cm^2)

Complications: temporally defined as occurring within 30 and 90 days of surgery (date minus surgical date)

- Anastomotic leak (no and divided into mild, moderate and severe as defined by European Perioperative Clinical Outcome EPCO [3]
- Delirium (no of days): As defined by attending physician
- Pneumothorax (Drain in situ 8 days for (If no anastomotic leakage on day 8)) (no)
- Pneumothorax (requiring renewed drainage) (no)
- Pneumonia as defined by EPCO[3]
- Pleural Effusion (Chest X-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemi-thorax with preserved vascular shadows - OR Ultrasonographic confirmation of pleural effusion > 1 cm)

- Cardiogenic pulmonary oedema (no and divided into mild, moderate, and severe) (EPCO)
- Acute Lung Injury (ALI) (yes/no) definition:
    1. acute onset within a few days from the insult
    2. non-cardiogenic pulmonary oedema, as defined by attending physician
    3. diffuse bilateral infiltrates
    4. PaO2/FiO2 < 300 mmHg
- Acute Respiratory Distress Syndrome (ARDS) (yes/no) definition:
    1. acute, meaning onset over 1 week or less
    2. bilateral opacities consistent with pulmonary oedema must be present and may be detected on CT or chest radiograph
    3. PaO2/FiO2 < 200mmHg
    4. "Must not be fully explained by cardiac failure or fluid overload," in the physician's best estimation using available information — an "objective assessment" (e.g. echocardiogram) should be performed in most cases if there is no clear cause such as trauma or sepsis
- Overhydration defined as the clinician opting to treat weight gain with or without respiratory symptoms with diuretics
- Pulmonary embolism (no) as defined by radiology
- Non-fatal cardiac arrest as defined by EPCO
- Acute myocardial infarction (no) as defined by EPCO
- New onset arrythmia (no and divided into mild, moderate, and severe) (EPCO)
- Major Adverse Cardiac Events (MACE) (no) as defined by EPCO
- Acute kidney injury within 7 days of surgery (no total and divided in categories) – as defined with Kidney Disease Improving Global Outcomes (KDIGO) criteria (only changes in creatinine) (EPCO)
- Paralytic ileus as defined by EPCO
- Infection, superficial (no) as defined by EPCO
- Infection, deep (no) as defined by EPCO
- Urinary tract infection (no) as defined by EPCO

- Infection with unknown focus (no and divided into mild, moderate, and severe) (EPCO)
- Chyle leak, conservative treatment (no)
    1. The following diagnostic criteria must be met for chyle leakage to be diagnosed: triglycerides >110 mg/dL, cholesterol <200 mg/dL, and presence of chylomicrons. However, the above criteria may not be met when the patient is fasting, and the drainage colour can be serous with a normal level of triglycerides
- Chyle leak, operative treatment (no)
- Oesophageal stricture, conservative treatment (no)
- Oesophageal stricture, operative treatment (no)
- Deep vein thrombosis as diagnosed by ultrasound (no)
- Central venous line infection (no)
- Jejunostomy infection (no)
- Vocal cord palsy (no)
- All-cause mortality (90 days from date of surgery. Defined as date of death minus date of surgery)
- Postoperative intubation (no and hours)
- Creatinine before surgery and on day 1, 3 and 7

Miscellaneous

- Admission time (days – defined as the date of discharge minus the date of surgery)
- Admission time within 90 days from surgery - defined as discharge date minus surgery date/admission dates respectively (days)
- Admission days to the ICU (defined as readmissions or days spent in the postoperative ward exceeding one day)

Supplementary Material 3: Clavien-Dindo Classification

Table: Complications are graded according to the Clavien-Dindo Classification:

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU-management
- IVa	Single organ dysfunction (including dialysis)
- IVb	Multiorgandysfunction
Grade V	Death of a patient

Supplementary Material 4: Quality of life questionnaire

The following questionnaire (EORTC QLQ-C30) is sent out before surgery and 90 days after surgery.

Livskvalitet i forbindelse med operation for spiserørskræft

Introduktion
Spørgeskemaet tager 5-15 minutter at udfylde, jeg vil bede dig læse alle spørgsmål grundigt. Sådan udfyldes skemaet
Hvert spørgsmål udfyldes ved at afkrydse det mest passende svar i din situation her og nu. Af hensyn til undersøgelsens værdi er det vigtigt, at alle spørgsmål besvares.

1) Dato udfyldt spørgeskema

2) Har du nogen vanskeligheder med at udføre anstrengende aktiviteter, som f.eks. at bære en tung indkøbstaske eller en kuffert?

3) Har du nogen vanskeligheder ved at gå en lang tur?

4) Har du nogen vanskeligheder ved at gå en kort tur udendørs?

5) Er du nødt til at ligge i sengen eller sidde i en stol om dagen?

6) Har du brug for hjælp til at spise, tage tøj på eller gå på toilettet?

I den forløbne uge:

7) Var du begrænset i udførelsen af enten dit arbejde eller andre daglige aktiviteter?

8) Var du begrænset i at dyrke dine hobbyer eller andre fritidsaktiviteter?

9) Havde du åndenød?

10) Har du haft smerter?

11) Havde du brug for at hvile dig?

12) Har du haft søvnbesvær?

13) _____

Vi er interesserede i at vide noget om dig og dit helbred. Vær venlig at besvare alle spørgsmålene selv ved at markere det svar, som passer bedst på dig. Der er ingen 'rigtige' eller 'forkerte' svar. De oplysninger, som du giver os, vil forblive strengt fortrolige.

Slet ikke 1

Lidt 2

En del 3

Meget 4

Slet ikke 1

Lidt 2

En del 3

Meget 4

14) Har du savnet appetit?

15) Har du haft kvalme?

16) Har du kastet op?

17) Har du haft forstoppelse?

18) Har du haft diarré (tynd mave)?

19) Var du træt?

20) Vanskeliggjorde smerter dine daglige gøremål?

21) Har du haft svært ved at koncentrere dig om ting som f.eks. at læse avis eller se fjernsyn?

22) Følte du dig anspændt?

23) Var du bekymret?

24) Følte du dig irritabel?

25) Følte du dig deprimeret?

26) Har du haft svært ved at huske?

27) Har din fysiske tilstand eller medicinske behandling vanskeliggjort dit familieliv?

28) Har din fysiske tilstand eller medicinske behandling vanskeliggjort din omgang med andre mennesker?

29) Har din fysiske tilstand eller medicinske behandling medført økonomiske vanskeligheder?

Ved de næste 2 spørgsmål bedes du markere det tal mellem 1 og 7, som passer bedst på dig

30) Hvordan vil du vurdere dit samlede helbred i den forløbne uge?

31) Hvordan vil du vurdere din samlede livskvalitet i den forløbne uge?

Meget 2 3 4 5 6 Særdeles dårligt 1 godt 7

Meget 1 2 3 4 5 6 7 Særdeles

32) Kunne du indtage fast føde?

33) Kunne du indtage flydende eller "blød"/moset kost?

34) Kunne du indtage væske?

35) Har du haft problemer med at synke dit spyt?

36) Har du fået det galt i halsen, når du har sunket noget?

37) Har du haft svært ved at nyde dine måltider?

38) Er du blevet for hurtig mæt?

39) Har du haft svært ved at spise?

40) Har du haft svært ved at spise, mens andre var tilstede?

41) Har du været tør i munden?

42) Har mad og drikke smagt anderledes end normalt?

43) Har du haft besvær med at hoste?

44) Har du haft talebesvær?

45) Har du haft sure opstød eller halsbrand?

46) Har du haft problemer med mavesyre eller galde i munden?

47) Har du haft smerter, når du spiser?

48) Har du haft smerter i brystet?

49) Har du haft smerter i maven?

Page 3

Patienter fortæller undertiden, at de har følgende symptomer eller problemer. Anfør venligst, i hvilket
omfang du har haft disse symptomer eller problemer inden for den forløbne uge. Besvar spørgsmålene ved at sætte en ring omkring det tal, som passer bedst til dig.

I den forløbne uge:

Slet ikke 1

Lidt 2

En del 3

Meget 4

50) Skriv her hvis du har noget du ønsker at tilføje din besvarelse af spørgeskemaet

_____

Supplementary Material 5: SPIRIT Checklist

Individualised perioperative blood pressure and fluid therapy in oesophagectomy (UFL-10-22-0640)

Section/item	Item	Description	Addressed on page
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	Footer of all pages
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	N/A Reason: Due to journal limitations this field is omitted, however all authors have signed an author declaration which is handed to the journal editor.
	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)	Page 6 and 7 provide details on endpoint adjudication. Further specifications are not applicable in this single-center trail
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished)	3

		examining benefits and harms for each intervention	
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	4
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, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
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	4
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)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4-6
	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)	4
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A Reason: As all handling personnel is already trained in delivering the intervention as part of their clinical work and the primary investigator is present during the intervention, adherence to the protocol is not considered an issue
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4-6
Outcomes	12	Primary, secondary, and other outcomes, including the specific	7 and

		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	Supplementary Materials
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)	Page 7 and figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7-8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
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	6
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	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate 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	6
	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	Page 7 describes how we ensure replies to the QOL questionnaire. After the intervention all other follow-up is performed through electronic databases and we do not expect any lack of participant retention
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
Statistical methods	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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	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	21a	Composition of data monitoring committee (DMC); summary of its role	N/A

		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	Reason: according to Danish law all medical research is subject to monitoring from the Good Clinical Practice (GCP) unit. This trial of course adheres the national jurisdictions
	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	8
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	N/A Reason: Adverse Events are 1) Reported as part of the primary endpoint 2) In case of a serious event it is reported to the Danish Medicines Agency in accordance with Danish law
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A Reason: The trial is subject to the audits performed by the GCP-unit in accordance with Danish law
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
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)	N/A Reason: No further protocol amendments are applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data	N/A

		and biological specimens in ancillary studies, if applicable	Reason: no handling of biological specimens is planned for this trial
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	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	N/A Reason: all participating authors have filed a declaration of competing interests as is journal policy
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
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	N/A Reason: all patients are covered by the Danish Health Care insurance
Dissemination policy	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	8
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A Reason: all authors have filed in author declaration as is policy of the scientific journal
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A Reason: The informed consent material (in Danish) is approved by The Central Denmark Region Committees on Health Research

			Ethics (record number: 2021-002816-30)
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	N/A Reason: No biological sampling is planned

Supplementary Material 6: Defining target mean arterial pressure

All patients regardless of group will undergo a 24-hour non-invasive ambulatory blood pressure (OnTrak®, Spacelabs Healthcare, Washington, US) assessment prior to surgery. Daily readings are performed every 20 minutes. Night-time blood pressure is measured from 22:00 PM-07:00 AM with hourly readings.

Criteria for discarding measurements are as follows:

- Values of mean arterial pressure (MAP) < 40 mmHg and > 140 mmHg are discarded as artefactual
- Diastolic arterial pressure outside the range 40-140 mmHg
- Diastolic arterial pressure exceeding the preceding or subsequent systolic arterial pressure
- Pulse pressure less than 20 or more than 100 mmHg
- Heart rate less than 40 or more than 125 bpm
- Systolic arterial pressure less than 50 or more than 240 mmHg.
- We exclude measurements that the ambulatory blood pressure device considers erroneous, such as absent or non-analysable oscillations, zero point adjustment not possible, cuff leak present, and measurement cancelled by user[4]

Target MAP is defined as the average of the three lowest night-time MAPs.

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References

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3. Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol*. 2015;32(2):88-105. doi:10.1097/EJA.0000000000000118

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