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SUPRAMAX-study: supramaximal resection versus maximal resection for glioblastoma patients: study protocol for an international multicentre prospective cohort study (ENCRAM 2201)

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ABSTRACT

Introduction A greater extent of resection of the contrast-enhancing (CE) tumour part has been associated with improved outcomes in glioblastoma. Recent results suggest that resection of the non-contrast-enhancing (NCE) part might yield even better survival outcomes (supramaximal resection, SMR). Therefore, this study evaluates the efficacy and safety of SMR with and without mapping techniques in high-grade glioma (HGG) patients in terms of survival, functional, neurological, cognitive and quality of life outcomes. Furthermore, it evaluates which patients benefit the most from SMR, and how they could be identified preoperatively.

Methods and analysis This study is an international, multicentre, prospective, two-arm cohort study of observational nature. Consecutive glioblastoma patients will be operated with SMR or maximal resection at a 1:1 ratio. Primary endpoints are (1) overall survival and (2) proportion of patients with National Institute of Health Stroke Scale deterioration at 6 weeks, 3 months and 6 months postoperatively. Secondary endpoints are (1) residual CE and NCE tumour volume on postoperative T1-contrast and FLAIR (Fluid-attenuated inversion recovery) MRI scans; (2) progression-free survival; (3) receipt of adjuvant therapy with chemotherapy and radiotherapy; and (4) quality of life at 6 weeks, 3 months and 6 months postoperatively. The total duration of the study is 5 years. Patient inclusion is 4 years, follow-up is 1 year.

Ethics and dissemination The study has been approved by the Medical Ethics Committee (METC Zuid-West Holland/Erasmus Medical Center; MEC-2020-0812). The results will be published in peer-reviewed academic journals and disseminated to patient organisations and media.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ First multicentre prospective study directly comparing supramaximal resection (SMR) versus maximal resection in glioblastoma surgery.
- ⇒ International, multicentre design on a large scale, which will be of substantial benefit regarding subgroup analyses and external generalizability of the results.
- ⇒ SMR might not be feasible for all patients or all tumour resections.

INTRODUCTION

Glioblastoma is the most aggressive, invasive and most common primary brain malignancy.[1] Typically, it is treated by surgery followed by adjuvant chemotherapy and radiotherapy.[2] The tumour mass often grows in a nodular pattern that is visible on T1-contrast MRI (the contrast-enhancing (CE) lesion) and infiltrates the surrounding brain parenchyma (the non-contrast-enhancing (NCE) lesion) that is most frequently assessed on the FLAIR sequence as a peritumoral hyperintense signal. Previous scientific evidence has shown that in general, resection has a survival benefit over biopsy in these patients,[3 4] as does a higher extent of resection.[5–7] The goal of surgery is 'maximal safe resection', defined as resecting as much CE tumour as safely possible minimising the risk of postoperative deficits. This is particularly important if the tumour is located in or near functional tissue, in which awake or asleep mapping methods may be used to achieve maximal safe resection.[8–10] In recent years, there has been debate about whether resecting the surrounding the FLAIR hyperintense areas would yield additional survival benefit over resections

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targeting the CE.[11–15] Such a resection that includes the CE and the NCE is described as 'supramaximal resection' (SMR), or 'FLAIR-ectomy'. The amount of resected NCE corresponding with survival benefit has been reported in the literature to lay between 20% and 55%.[11–15] These developments raise questions, for example, which patients would benefit the most from SMR, which outcomes have SMR the potential to improve, should SMR be combined with mapping techniques or surgical adjuncts such as 5-ALA and what are the postoperative effects of SMR in terms of cognitive defects and quality of life. Currently, there is no literature to guide neurosurgeons in navigating these dilemmas. As colleagues De Leeuw and Vogelbaum stated, as of today there is insufficient evidence for the *carte blanche* application of SMR, and while recent results from small studies were promising, these claims require validation in prospective studies involving larger patient populations with clearly defined appropriate outcome metrics in order to reduce potential bias.[12] We, therefore, propose an international, multicentre, prospective cohort study in which the effect of SMR in glioblastoma patients will be evaluated. The primary study's objectives are to evaluate (1) the efficacy and safety of SMR with and without mapping techniques in glioblastoma patients in terms of survival, functional, neurological, cognitive and quality of life outcomes and (2) which patients benefit the most from SMR, for which outcomes and how they could be identified preoperatively. The study will be carried out by the centres affiliated with the European and North American Consortium and Registry for Intraoperative Mapping (ENCRAM).[16]

METHODS AND ANALYSIS

Study design

This is an international, multicentre, prospective, observational, two-arm cohort study (registration: clinicaltrials.gov ID number NCT06118723). Eligible patients are operated with SMR versus maximal resection with a 1:1 ratio with a sequential computer-generated number as subject ID by the decision of the neurosurgeon. The decision of which study arm a patient gets assigned to is part of standard care without any influence by the study's researchers (observational nature). Intraoperative mapping techniques and/or surgical adjuncts can be used in both treatment arms to ensure the safety of the resection (to minimise the risk of postoperative deficits). SMR is defined as 0 cm^3 CE tumour and 5 cm^3 or less NCE tumour, whereas maximal resection is defined as 0 cm^3 CE tumour and >5 cm^3 NCE tumour (in line with the updated RANO (Response Assessment in Neuro Oncology) criteria).

Study objectives

The primary study objective is to evaluate the safety and efficacy of SMR versus maximal resection in glioblastoma patients as measured by overall survival (OS) and postoperative National Institute of Health Stroke Scale (NIHSS) deterioration. Secondary study objectives are to evaluate the extent of resection of CE and NCE tumour, quality of life, progression-free survival (PFS), receipt of adjuvant chemoradiation and serious adverse events (SAEs) after SMR or maximal resections as measured by volumetric analyses of contrast-enhanced MRI images with gadolinium combined with FLAIR images, tumour progression on MRI scans, quality of life questionnaires (EORTC QLQ C30, EORTC QLQ BN20, EQ 5D), assessing the adjuvant treatment regimen and recording SAEs, respectively.

Study setting and participants

Patients will be recruited from the neurosurgical or neurological outpatient clinic or through referral from general hospitals of the participating neurosurgical hospitals, located in Europe and the United States. The study is carried out by centres from the ENCRAM Consortium.

Patient and public involvement statement

Patients enrolled in the SAFE-trial (awake craniotomy vs craniotomy under general anaesthesia for glioblastoma patients, NCT03861299) were consulted for this study to include patient experiences with the shared decision-making process regarding the surgical treatment options.

Ethics and dissemination

The study has been approved by the Medical Ethics Committee and will be conducted in compliance with the European Union Clinical Trials Directive (2001/20/EC) and the principles of the Declaration of Helsinki (2013). The results of the study will be published in peer-reviewed academic journals and disseminated to patient organisations and media.

Inclusion criteria

To be eligible to participate in this study, a participant must meet all the following criteria:

1. Age ≥18 years and ≤90 years.
2. Suspected glioblastoma on MRI as assessed by the neurosurgeon.
3. SMR is theoretically feasible as assessed by the neurosurgeon.
4. Written informed consent.

Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

1. Tumours of the cerebellum, brainstem or midline.
2. Multifocal CE lesions.
3. Medical reasons precluding MRI (eg, pacemaker).
4. Inability to give written informed consent.
5. Secondary high-grade glioma due to malignant transformation from low-grade glioma.
6. Second primary malignancy within the past 5 years with the exception of adequately treated in situ carcinoma of any organ or basal cell carcinoma of the skin.

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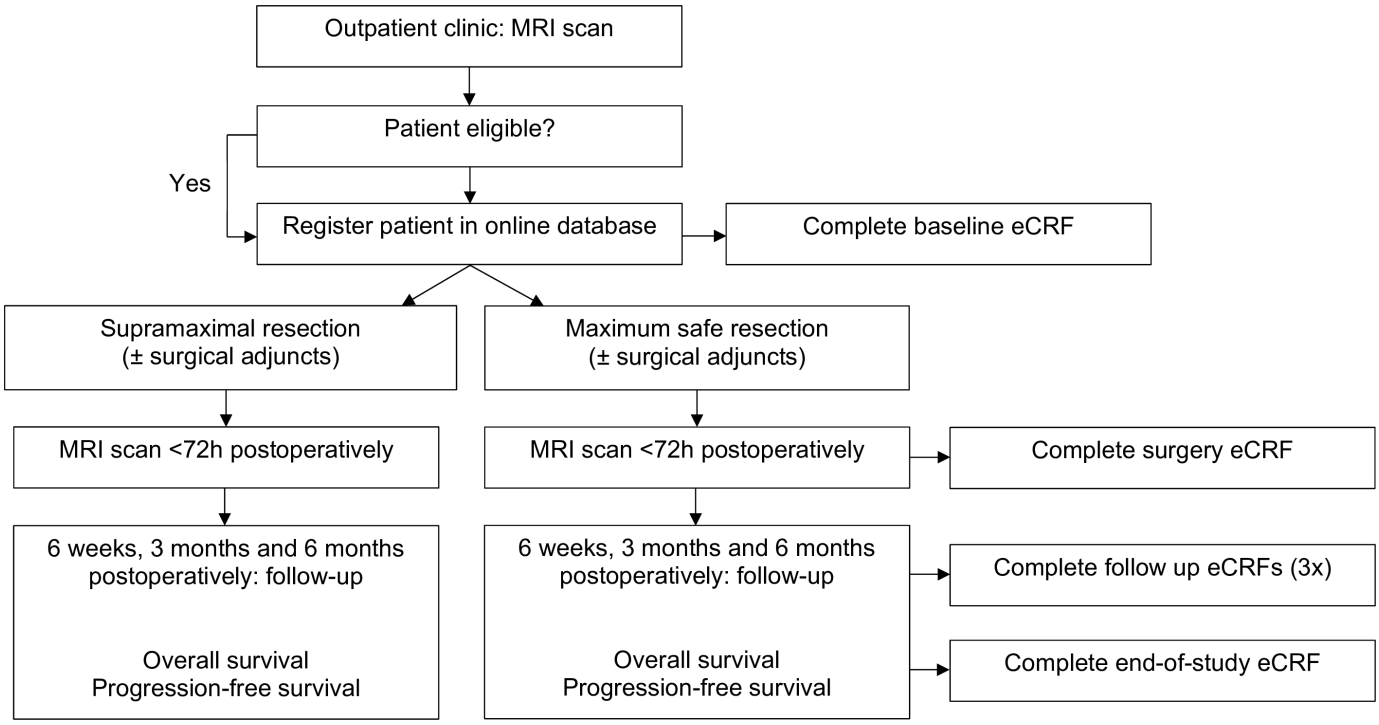

Figure 1 Study flowchart.

Interventions

The surgical procedures regarding SMR and maximal tumour resection with or without mapping techniques are described in the online supplemental appendix.

Participant timeline

The flow diagram illustrates the main study procedures, including follow-up evaluations (figure 1). In summary, eligible glioblastoma patients undergo tumour resection and are postoperatively included in either the supramaximal or maximal resection group. They will undergo evaluation at presentation (baseline) and during the follow-up period at 6 weeks, 3 months and 6 months postoperatively. Tumour location will be assessed with the parameters hemisphere, lobe, eloquent area and growing pattern (superficial vs deep-seated). Motor function will be evaluated using the NIHSS scale. Language function will be evaluated using a standard neurolinguistic test-battery consisting of the Aphasia Bedside Check, Shortened Token test, Verbal fluency, Picture description and Object naming. Cognitive function will be assessed using the Montreal Cognitive Assessment and Frontal Assessment Battery. Patient functioning with be assessed with the Karnofsky Performance Scale (KPS) and the American Society of Anesthesiologists physical status classification system. Moreover, length-of-stay after surgery and disposition of discharge are recorded. Health-related quality of life will be assessed with the EORTC QLQ C30, EORTC QLQ BN20 and EQ 5D questionnaires. Volumetric tumour measurements are performed preoperatively and <72 hours after surgery. Receipt of adjuvant treatment is assessed with the factors time-to-treatment, adjuvant treatment started and/or completed, number of TMZ cycles, number of radiotherapy fractions given, total dose of radiotherapy in Gy and other adjuvant treatments are assessed. OS and PFS will be assessed. We expect to complete patient inclusion in 4 years. The estimated duration of the study (including follow-up) will be 5 years.

Outcomes

Primary outcome measures

The primary outcomes are (1) OS, which is defined as time from diagnosis to death from any cause, and (2) neurological morbidity, which is defined as NIHSS deterioration of 1 point or more at 6 weeks, 3 months and/or 6 months after surgery.

Secondary outcome measures

The secondary outcomes are (1) PFS defined as time from diagnosis to disease progression (occurrence of new tumour lesions with a volume greater than 0.175 cm^3, or an increase in residual tumour volume of more than 25%) or death, whichever comes first; (2) residual tumour volume of the CE and NCE part, as assessed by a neuroradiologist on postoperative MRI scan (T1 with contrast and FLAIR sequences) using manual or semi-automatic volumetric analyses (Brainlab Elements iPlan CMF Segmentation, Brainlab AG, Munich, Germany; or similar software); (3) receipt of adjuvant chemoradiation; (4) quality of life as assessed by the EORTC QLQ C30, EORTC QLQ BN20 and EQ 5D questionnaires at 6 weeks, 3 months and 6 months after surgery; and (5) frequency and severity of SAEs within 6 weeks in each arm.

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Data collection

All patient data are collected in the electronic data software Castor EDC. This software allows built-in logical checks and validations to promote data quality. Data entry and group allocation are performed by the study coordinator or locally by trained physicians and research nurses under the supervision of the local investigator.

Sample size

This study has two primary endpoints: OS and postoperative NIHSS deterioration at 6 weeks. Furthermore, this study will have three predefined subgroup analyses based on MGMT (O6-methylguanine-DNA methyltransferase) promotor methylation status (methylated vs unmethylated), age (younger than 70 years vs 70 years and older) and preoperative Karnofsky Performance Status (90–100 vs 80 and lower). We hypothesise that SMR is associated with longer median OS in MGMT-methylated tumours, patients younger than 70 years old and/or with a preoperative KPS of 90–100. To ensure that the overall type I error rate does not exceed 5%, we apply a weighted Bonferroni correction for multiple testings. For the first primary endpoint, OS, we assume a median survival of 20 months in the control group (maximal resection), and 29 months in the experimental groups (SMR) (HR 0.62). A two-sample test for proportions with continuity correction requires 356 patients (178 per arm) in total to detect the above-mentioned difference of 9 months with 95% power at a 1% significance level. For the second primary endpoint, proportion of patients with postoperative NIHSS deterioration at 6 weeks, we assume a deterioration rate of 20% in the control group (maximal resection), and 30% in the experimental groups (SMR). A two-sample test for proportions with continuity correction requires 288 patients (145 per arm) in total to detect the above-mentioned difference of 10% with 95% power at a 1% significance level. In order to power the study for both primary endpoints, we should include the larger required number of patients, that is, 356. A total of 356 eligible and evaluable patients in two arms allow the difference of 10% in proportion of patients without postoperative NIHSS deterioration at 3 months to be detected with 99% power. Considering possible ineligibility and withdrawal of consent (we estimate this at 10%), a total of 392 patients should be included (196 patients per arm). Since propensity-score matching with a 1:1 ratio will be performed, 392 patients should be included after matching: 196 patients in the SMR arm and 196 patients in the maximal resection arm. Since we estimate the distribution of MGMT-methylated and MGMT unmethylated tumours at a ratio of 1:1 in our study population, we will include a total of 784 patients: 392 patients in the SMR arm and 392 patients in the maximal resection arm after matching.

promotor methylation status (methylated vs unmethylated), age (younger than 70 years vs 70 years and older) and preoperative Karnofsky Performance Status (90–100 vs 80 and lower). We hypothesise that SMR is associated with longer median OS in MGMT-methylated tumours, patients younger than 70 years old and/or with a preoperative KPS of 90–100. To ensure that the overall type I error rate does not exceed 5%, we apply a weighted Bonferroni correction for multiple testings. For the first primary endpoint, OS, we assume a median survival of 20 months in the control group (maximal resection), and 29 months in the experimental groups (SMR) (HR 0.62). A two-sample test for proportions with continuity correction requires 356 patients (178 per arm) in total to detect the above-mentioned difference of 9 months with 95% power at a 1% significance level. For the second primary endpoint, proportion of patients with postoperative NIHSS deterioration at 6 weeks, we assume a deterioration rate of 20% in the control group (maximal resection), and 30% in the experimental groups (SMR). A two-sample test for proportions with continuity correction requires 288 patients (145 per arm) in total to detect the above-mentioned difference of 10% with 95% power at a 1% significance level. In order to power the study for both primary endpoints, we should include the larger required number of patients, that is, 356. A total of 356 eligible and evaluable patients in two arms allow the difference of 10% in proportion of patients without postoperative NIHSS deterioration at 3 months to be detected with 99% power. Considering possible ineligibility and withdrawal of consent (we estimate this at 10%), a total of 392 patients should be included (196 patients per arm). Since propensity-score matching with a 1:1 ratio will be performed, 392 patients should be included after matching: 196 patients in the SMR arm and 196 patients in the maximal resection arm. Since we estimate the distribution of MGMT-methylated and MGMT unmethylated tumours at a ratio of 1:1 in our study population, we will include a total of 784 patients: 392 patients in the SMR arm and 392 patients in the maximal resection arm after matching.

Baseline characteristics, primary and secondary outcomes and SAEs will be summarised for the two treatment arms using descriptive statistics. Proportions of missing values will be reported.

Matching procedure

Propensity-score matching will be performed based on various factors including gender (male vs female), age (continuous), preoperative KPS (continuous), preoperative NIHSS score (continuous), preoperative tumour volume (continuous), tumour location by lobe (frontal vs parietal vs temporal vs occipital vs insula), tumour location by hemisphere (right vs left), intraoperative fluorescence (yes vs no), centre (categorical) and adjuvant

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therapy with chemotherapy and radiotherapy (yes vs no). The potential confounders that will be entered in the propensity-score matching were based on subject matter knowledge.

Primary study outcomes (OS, postoperative NIHSS deterioration)

OS will be analysed using the Kaplan-Meier method and log-rank test to estimate OS proportions per treatment group. Postoperative NIHSS deterioration will be compared between treatment arms using the χ^2 test.

Intervention effect estimates for the two primary outcomes will be derived from multivariable Cox proportional hazards and logistic regression models, adjusted for potential imbalances between treatment arms in the following major prognostic variables: age (continuous), preoperative KPS (continuous), preoperative NIHSS (continuous), molecular status (MGMT methylated vs MGMT unmethylated), intraoperative mapping (yes vs no), preoperative tumour volume (continuous) and tumour hemisphere (left vs right). Treatment-effect modification will be evaluated in prespecified relevant subgroups of patients based on MGMT methylation status, age and preoperative KPS.

Secondary study outcomes (PFS, extent of resection, residual CE and NCE tumour volume, Onco-functional outcome, Quality of life)

Comparison between treatment arms will be performed for secondary outcomes using appropriate hypothesis tests (the Kaplan-Meier method and the log-rank test, *t*-tests for independent means and χ^2 tests). Multivariable Cox proportional-hazards, linear and ordinal models will be built accordingly to estimate treatment group effects on the secondary outcomes, adjusted for potential imbalances in the following major prognostic variables: age (continuous), preoperative KPS (continuous), preoperative NIHSS (continuous), molecular status (MGMT methylated vs MGMT unmethylated), intraoperative mapping (yes vs no), intraoperative mapping (yes vs no), preoperative tumour volume (continuous) and tumour hemisphere (left vs right).

Statistical uncertainty in all the above-mentioned analyses will be quantified with 95% CIs derived from SE estimates. Missing outcomes will not be imputed. In case of missing values in the adjustment variables, these will be analysed for randomness and imputed.

Study monitoring

No scheduled on-site monitoring visits will be performed. Local investigators will remain responsible for the fact that the rights and well-being of patients are protected, the reported trial data are accurate, complete and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with good clinical practice and with the applicable regulatory requirement(s). Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF (Case Report Form) are consistent with the original source data. No Data Safety Monitoring Board will be installed: all treatment arms are care-as-usual and patients are allocated without randomisation.

An interim analysis will be performed at 50% of the number of projected inclusions. The study will be halted if the investigators observe between study arms (1) an absolute difference in the proportion of patients with NIHSS deterioration at 6 months of 20% or more (200% of the estimate used in the power analysis) or alternatively (2) an absolute OS difference of 12 months or more (133% of the estimate used in the power analysis).

DISCUSSION

Maximal safe resection is the current mainstay for glioblastoma treatment. Maximising the extent of resection, or alternatively, minimising residual tumour volume, has been demonstrated to have clear benefits in terms of survival outcomes in these patients. Ideally, gross-total resection (GTR) is achieved, although there is currently no consensus on the exact volumetric or percent-based threshold for GTR. However, the RANO resect group published their proposed new categories for extent of resection in glioblastoma recently, which underlines a few important issues.[11] First, for the first time, residual tumour volume is the preferred definition of extent of resection rather than a percentage of the amount of tumour resection. This is in line with recent studies that found that residual volume proved to be a stronger predictor for survival outcomes than percentual extent of resection.[5 8 17–19] Second, SMR ('class 1') is defined by the RANO as 0 cm^3 CE tumour and 5 cm^3 or less NCE tumour. Complete removal of the CE tumour in combination of a >5 cm^3 NCE tumour remnant is defined as complete CE resection ('class 2A'), whereas a remnant of 1 cm^3 or less of CE tumour classifies a resection as 2B (near-total resection). The categories regarding complete and near-total CE resection are somewhat different from our own findings, in which we found that <0.2 cm^3 yields significant survival benefits.[8] These findings need to be validated in prospective cohorts with appropriate patient selection. There are a few issues that need to be addressed when evaluating the effects of SMR and NCE tumour removal. First, there might be larger inter-rater variability for NCE tumour volumetric analysis compared with CE tumour.[20] To mitigate this risk, volumetric analyses should be coordinated between participating centres, performed by semi-automatic or fully automatic segmentation software, double-checked by independent neuro-radiologists and accompanied by inter-rater variability measurements for full disclosure. Second, the AANS/CNS Section on Tumors published in 2022 the results of their survey investigating a consensus definition of supratotal resection.[21] Approximately three-quarters of the respondents agreed that the right anterior temporal and right frontal would be the most suitable candidate locations for SMR. In order to evaluate this issue further, we will analyse the effect of tumour hemisphere, lobe and functional tissue

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('eloquent location') on the safety and efficacy of SMR as part of the broader question of which patient or patient subgroup would benefit the most from SMR and how we could predict this preoperatively. Third, the role of intraoperative mapping techniques in conjunction with SMR has to be elucidated, especially regarding neurological outcomes for tumours near functional tissue; and cognitive and quality of life outcomes for tumours in less functional areas. Therefore, we will include both awake mapping and asleep mapping patients to receive SMR and monitor cognition and quality of life as part of the study follow-up at three timepoints.

In conclusion, prospective evidence is necessary to warrant the use of these SMR in HGG patients, since it may have the potential to improve the survival of selected patients, thereby taking the next step in optimising treatment paradigms. The presented international neurosurgical research consortium will provide the needed infrastructure to perform ongoing large-scale data collection. This study aims to evaluate whether the use of SMR is the appropriate answer to the surgeon's striving to *safely* improve survival outcomes in *selected* high-grade glioma patients. It will be the first study to directly compare SMR versus maximal safe resection in their ability to improve patient outcomes for neurological morbidity, quality of life and survival. There will be a specific focus on identifying and predicting patient subgroups for whom SMR might benefit their outcomes.

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Contributors JKWG designed the study, wrote the study protocol and is end-responsible for the implementation and organization of the study in all participating centres as well as the conduct of the database. JSY, SMC and MSB contributed to the design of the study and are responsible for the local conduct of the study in San Francisco. SMK and CJ contributed to the design of the study and are responsible for the local conduct of the study in Heidelberg. MJvdB and DDS contributed to the design of the study. SI contributed to the design of the study and is responsible for the local conduct of the study in Munich. PS contributed to the design of the study and is responsible for the local conduct of the study in Bern. BVN contributed to the design of the study and is responsible for the local conduct of the study in Boston. MLDB contributed to the design of the study and is responsible for the local conduct of the study in The Hague. SDV contributed to the design of the study and is responsible for the local conduct of the study in Leuven. AJPEV contributed to the design of the study and is responsible for the local conduct of the study in Rotterdam. All authors read and approved the final version of the manuscript.

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