Participant Information and Informed Consent Form for participation in a research experiment

This Information for the potential Research Participant and the Informed Consent Form for participation in the Study is addressed to men and women who are patients of the Department of Neurosurgery and Neurooncology of the Copernicus Memorial Hospital Comprehensive Cancer Center and Traumatology in Łódź, diagnosed with glioblastoma multiforme, who are invited to participate in a study on the use of FET-PET in fusion with MRI in surgical treatment and postoperative radiotherapy of glioblastoma multiforme.

Title of the research experiment:: "The use of FET-PET in fusion with MRI in surgical treatment and postoperative radiotherapy of glioblastoma multiforme – randomized, blinded, prospective"

Principal Investigator: Kamil Krystkiewicz, MD, PhD

Site Data: Copernicus Memorial Hospital Comprehensive Cancer Center and Traumatology in Łódź, Pabianicka 62, 93-513 Łódź, PL

Sponsor Name: Copernicus Memorial Hospital Comprehensive Cancer Center and Traumatology in Łódź, Pabianicka 62, 93-513 Łódź, PL

Participant's Name and Surname:

This Informed Consent Form consists of two parts::

- **Participant Information (containing information about the research experiment);**
- **Declaration of Consent to participate in the Study (to be signed if you agree to participate) along with appendices.**

You will receive a full copy of the Informed Consent Form.

PART I: Information for the Research Experiment Participant

Introduction

Dear Madam / Dear Sir,

Whenever this document refers to the "Study", it shall be understood as the research experiment.

Please read the detailed information provided below regarding the goals and principles of conducting the Study in which we would like to propose your participation. Your participation in this Study is entirely voluntary. The decision to participate is yours. Regardless of the decision made, the hospital will continue to provide you with services; nothing in this regard will change. At any stage, you have the right to withdraw from participation in the experiment without any consequences. Withdrawal from the experiment does not affect the level or scope of healthcare services provided to you.

This form consists of two parts:

- Participant Information (containing information about the research experiment),
- Declaration of Consent to participate in the Study (to be signed if you agree to participate in the Study) along with an appendix in the form of consent for the processing of the research experiment Participant's personal data.

If this document contains any terms that are unclear to you, the physician will explain all such terms. If any questions arise at a later time, you will be able to ask the Investigator or a member of the research team. Confidentiality of personal data will be maintained; personal identifying data will be excluded from any Study report or scientific publication. Each Study Participant is covered by insurance for damages arising in connection with participation in the Study. The insurance policy number covering the experiment will be provided by the Investigator upon request at any time.

Biobanking

Each Study Participant will have the opportunity to join a scientific program conducted by the Medical Research Agency (MRA), which involves the collection and biobanking of biological material. For this purpose, you will receive an additional informed consent form containing all necessary information, developed by the MRA. The entity responsible for the biobanking of biological material is the MRA.

Purpose of the research experiment

Glioblastoma multiforme is the most common primary brain tumor in adults. At the same time, it is the most aggressive of all primary brain tumors, and the prognosis, despite the treatment applied, is not as good as we would like it to be. It has been proven that the extent of tumor excision translates into progression-free survival and overall survival. Despite extensive surgical procedures, however, local recurrence often occurs at the operated site. This is explained by the fact that glioblastoma stem cells remain in the nervous tissue surrounding the focus, and these are responsible for early tumor regrowth, while routine contrast-enhanced MRI does not demonstrate resection boundaries with sufficient sensitivity to maximize survival time. Tracers based on amino acids, particularly 18F-fluoroethyl-L-tyrosine (18F-FET), show greater specificity and sensitivity. Glial tumors show a significantly higher uptake of this amino acid than healthy nervous tissue. We are conducting this study because we want to find out whether the fusion of MRI and FET-PET using the 18F-FET tracer would allow for surgical planning such that the resection covers the largest possible area of abnormally increased radiopharmaceutical uptake.

As part of the Study, you will be randomly assigned to one of the Study arms (groups):

- Arm I - surgical treatment and radiotherapy planned based on FET-PET and MRI+T1C fusion;
- Arm II - surgical treatment planned based on MRI+T1C; radiotherapy planned based on FET-PET and MRI+T1C fusion;
- Arm III - surgical treatment and radiotherapy planned based on MRI+T1C.

Responsibilities related to participation in the research experiment

The Participant is obliged to: attend visits according to the planned visit schedule and undergo all procedures specified in the Study protocol. All medical procedures in the conducted Study will be performed with the Participant's consent. The Participant's refusal to undergo a medical procedure specified in the Study protocol will be equivalent to exclusion from further participation in the Study. The Participant is obliged to inform the research team about their well-being and any observed symptoms. During the Study, the Participant may not participate in any other research experiment.

It is important that when deciding to participate in the Study, you accept its course and purpose and are ready to participate in it until its completion or until you withdraw your consent to participate. Until you complete and sign the following informed consent form, none of the Study procedures can be performed on you.

Selection and number of Participants and conditions for participation in the research experiment

We invite adult patients of the Department of Neurosurgery and Neurooncology of the Copernicus Memorial Hospital Comprehensive Cancer Center and Traumatology in Łódź with a diagnosed disease to participate in the Study on the use of MRI and FET-PET fusion in patients with glioblastoma multiforme. 189 participants will take part in the Study. If, during the course of the Study, it turns out that events/factors occur in a potential Study participant that prevent further participation or if the risk to the participant associated with participation in the Study increases, the Principal Investigator may exclude the participant from the Study despite prior qualification.

Voluntary participation in the research experiment

Your participation in this Study is entirely voluntary. The decision to participate is yours. At any stage, you have the right to withdraw from participation in the experiment without any consequences. Withdrawal from participation in the experiment does not affect the level and scope of healthcare services provided to you.

Types of research interventions

The Study will involve randomly assigning you to one of three Study arms (Participant groups) and implementing a radiotherapy and surgical treatment strategy. Before the Study begins, a number of medical procedures listed below will be performed, which are necessary to conduct the research experiment.

The Study will involve performing an additional diagnostic procedure – FET-PET – which consists of intravenous administration of a drug followed by a PET imaging scan. The Participant will be required to report to the PET Laboratory for this diagnostic procedure before the start of the actual treatment. Prior to the examination, a detailed medical history will be taken, and blood and cerebrospinal fluid samples will be collected for laboratory testing.

Information about the study drug

Fluorotyrosine (18F-FET) is a special substance used in PET (positron emission tomography) scans, which allows for a very precise view of how brain cells function – especially those that may be cancerous, as in the case of gliomas. 18F-FET resembles a natural amino acid (a building block of protein), allowing it to easily penetrate tumor cells, which are metabolically more active than healthy tissues. This enables doctors to see the location of the tumor and its level of activity.

Although 18F-FET does not treat glioma, a PET scan using this tracer is highly helpful in planning and evaluating treatment. This agent accumulates in tumor cells and "lights up" during the PET scan. The drug is administered intravenously as an injection. This is a safe form of diagnostics, and the examination is usually well-tolerated. Allergic reactions may occur, but they have been rarely observed in studies regarding this diagnostic method.

It should be noted that this method is not available within the public health system. FET-PET is not funded by the National Health Fund (NFZ) for the diagnosis of brain tumors, which means that after the Study concludes, there will be no possibility of further use of this method.

Alternative treatment options

The Study includes treatment methods recognized as standard in glioma therapy – surgical treatment, chemotherapy, and radiotherapy. The only difference between the study groups is the use of a different, experimental imaging method – FET-PET – for planning surgical treatment and radiotherapy.

Procedures and research experiment protocol

Description of the process and duration of the research experiment

After meeting the inclusion criteria for the research experiment, you will be randomly assigned to one of the three groups described in the previous section of the information brochure. The term "randomly assigned" means that the treatment regimen will be assigned to you by chance, similar to a coin toss or drawing lots from a hat. You have an equal chance of being assigned to each of the three possible Study arms (groups of Study Participants). After being assigned to one of the groups, a physician will discuss the treatment options and its continuation with you.

Your treatment process will follow the current standards for the treatment of glioblastoma multiforme established by EANO (European Association of Neuro-Oncology). Upon your admission to the Department of Neurosurgery and Neurooncology at the Copernicus Memorial Hospital Comprehensive Cancer Center and Traumatology in Łódź, further procedures and care will follow the plan below:

a. A nursing interview will be conducted with you, and you will be familiarized with the structure and topography of the Department.

b. Blood will be drawn for routine laboratory tests (complete blood count, coagulogram, ionogram, urea, creatinine, ESR, inflammatory markers, total protein, albumin, HBs antigen, anti-HCV antibodies, blood group, hormonal tests depending on underlying diseases). The amount of blood drawn depends on the number of tests and is usually a few milliliters.

c. After determining the blood group, blood will be drawn from you again to secure and cross-match blood products for the procedure.

d. Depending on the needs, an imaging study will be performed – CT or contrast-enhanced MRI. The purpose and interpretation of each study, if ordered, will be discussed with you by a neurosurgeon.

e. The physician will discuss the management, treatment method, possible complications, their treatment, and prevention with you.

f. Subject to additional consent, cerebrospinal fluid will be collected via lumbar puncture before the surgical treatment. This is a routine medical procedure involving the insertion of a puncture needle under local anesthesia between the 4th and 5th lumbar vertebrae. The procedure is performed while lying on your side, after thorough washing and disinfection of the lower back. Then, the doctor locally anesthetizes the skin at the puncture site and inserts the puncture needle into the spinal canal between the vertebral arches. After the needle enters the subarachnoid space, 10 mL of cerebrospinal fluid is collected for testing. Upon completion, the needle is removed, and the site is secured with a dressing. After the procedure, you

must remain lying down for one hour, after which you may return to activity. A similar procedure will be performed after the surgical treatment.

g. In the following days, surgical treatment is scheduled – surgery under general anesthesia. After the procedure, you will be monitored by the anesthesiology team in the Postoperative Room. Following observation and in the absence of concerning symptoms, you will be transported back to the Department of Neurosurgery and Neurooncology, where you will continue to be monitored by the Department staff.

h. If, due to the lack of availability of the MRI laboratory, it is necessary to postpone the scan by more than 24 hours, the patient will have a non-contrast head CT scan performed to assess early postoperative changes (bleeding, stroke), and an MRI scan after 48 or 72 hours. In the case of normal results, inpatient rehabilitation will be planned for you, aimed at improving and initiating function one day after the procedure.

i. In the subsequent postoperative days, your blood count will be routinely assessed for the need for blood product transfusion. The schedule of other postoperative tests depends on the clinical course of your case.

j. A dressing change and an assessment of the wound and pain will be performed daily.

On the day of discharge, the attending physician will discuss recommendations and further postoperative management with you. The standard of care includes postoperative radiotherapy and chemotherapy, conducted by the Department of Radiotherapy after the histopathological report is prepared.

This study will be conducted for a total of 5 years. After completing hospital treatment, a follow-up visit will take place at the Center's Neurosurgical Clinic within one month. During this visit, your health status and the condition of the postoperative wound will be assessed. Additionally, your neurological status will be evaluated through a neurological examination. A follow-up contrast-enhanced head MRI will be scheduled. Thereafter, visits and examinations will take place regularly every 3 months.

At each visit, the investigator will inform you of the current test results and the further planned treatment. If information is obtained that could influence your decision to continue participating in the study, you will have the opportunity to provide consent to continue participation or to withdraw from the Study.

Unknown procedures

Due to the fact that it is not clear whether a PET scan with an amino acid tracer carries a direct benefit compared to the classic diagnostic method — contrast-enhanced MRI — these diagnostic regimens must be compared.

Recognized scientific methods that allow for a reliable comparison of treatment outcomes in both patient groups involve the assignment of subjects to different groups. This is done randomly, and the process is called randomization. As a result, the patient is assigned to the appropriate group in the Study without the possibility of the Investigator or the Participant influencing this decision. At this stage, it should be stated that each group receives the best possible therapy recognized in the treatment of glioblastoma multiforme, and the Participant may withdraw from the Study at any stage. The purpose of randomization is to exclude any phenomenon that would assign patients to groups in a non-random, preferential manner. Such a phenomenon is unfavorable and may distort the results of the scientific study. The remaining procedures used in the Study are standard for the treatment process. After the completion of the hospital treatment process, your further treatment will be conducted on an outpatient basis through visits to the Center's Neurosurgical Clinic. The study plan assumes visits every 3 months, during which your condition will be clinically and radiologically assessed by a specialist neurosurgeon.

In the event of health problems after discharge from the hospital, you will be able to receive medical assistance at the Center's Emergency Room or telephone advice at the number 42 689 53 44 or 42 689 53 45 (the number of the doctors' room of the Neurosurgery Department at the Center). If a need to contact the Investigators arises, the staff will discuss your clinical problem over the phone and arrange a follow-up visit within the outpatient clinic or the Department, should a physical examination be necessary. If re-hospitalization is required, you will be treated in the Center's Neurosurgery Department in accordance with the best available knowledge. In the event of side effects from medications that are routinely used in treatment, medical and nursing actions consistent with current medical knowledge will be applied.

In the event that further surgical treatment is necessary in the future, you have the right to be and will be treated in accordance with the results of the study.

Risks

Neuro-oncological procedures within the brain are high-risk procedures. Performing them involves the possibility of complications related to the surgical activity — neurological deficits (weakness of muscle strength, sensory disturbances of touch or temperature, gait disturbances), wound healing problems, or complications of hospital care — pneumonia, thrombosis, pulmonary embolism.

All applied procedures (surgical treatment, chemotherapy, radiotherapy) are standard and typical for the treatment process of brain cancer.

Participation in the Study does not involve additional risk for you. The only difference between the evaluated groups is the use of an additional diagnostic method — a

PET-CT scan with an amino acid tracer. This is a commercially available preparation, although it is not used as a standard of care in brain gliomas.

If anything raises your concerns, you should inform the doctor and ask questions at any stage of the study.

A team of trained doctors and nurses will oversee the entire course of the Study as well as your health and safety. In the event of a sudden, serious deterioration of your health or well-being related to participation in the Study, appropriate treatment will be implemented. The Center is equipped with the necessary equipment needed to provide assistance in emergencies, if necessary.

It is important that any previously unexperienced, disturbing symptoms, should they occur, be reported by you immediately to a doctor or nurse.

Note:

Concealing or providing false information about your health during the qualification procedures may cause serious health complications during the Study. All adverse events (any unforeseen medical event) will be recorded, and medical personnel will take the necessary actions aimed at reducing their negative consequences.

Benefits

The primary benefit of participating in the Study for you is the regular outpatient visits scheduled by the Staff. The program includes visits to the Neurosurgical Clinic every 3 months, including a clinical and radiological assessment of your brain.

Compensation / Reimbursement of costs

You will not incur any additional costs for participating in this Study. You are not expected to pay for procedures, the study drug, or tests required as part of this Study. You will be responsible for the costs of your standard medical care, including procedures and medications not related to the Study, which your Study physician or primary care physician requires as part of standard medical care. You will not receive any compensation for participating in this Study.

Data confidentiality

Your personal data collected for the purposes of the conducted experiment and processed by the Research Team will be secured and protected against unauthorized access. Information collected as part of the Study will be confidential and accessible only to the Investigators and the Research Team. Data enabling the identification of Participants will not be published anywhere.

Sharing Study results, including the provision of a summary of the research experiment results

After the completion of the Study, the results will be scientifically and statistically analyzed. The results of the experiment, including conclusions and statistical summaries (without the Participants' personal data), will be published in medical journals and at scientific conferences. Data enabling the identification of the Participant's identity will not be published. Participants will not be informed of the Study results.

Right to refuse or withdraw participation in the research experiment

You do not have to participate in the Study if you do not wish to. Refusal to participate will not affect your current treatment at the Research Center in any way. You will still be able to use the services provided at this Research Center. You may discontinue your participation in the Study at any time, and you will not lose the benefits you are entitled to as a patient. Such a decision will not affect the treatment received at the Center in any way.

Source of Study funding

The Study will be funded by a grant from the Medical Research Agency.

Contact options

If you have any questions, you may ask them now or later, even after the Study has started and at any point during its duration. If you wish to ask something later, you can contact::

Investigatorconducting the study at the Site:	Kamil Krystkiewicz, MD, PhD
Phone number:	42 689 53 44, 42 689 53 45

You may also contact the aforementioned persons if you wish to withdraw from the Study. In the event of any additional information regarding the research experiment that may affect your willingness to continue participating in the Study, the Investigator (Study physician) is obliged to provide it to the Participant immediately.

The design of this research experiment has been reviewed by the Bioethics Committee at the Medical University of Łódź and has received a positive opinion. The Bioethics Committee is a group of people whose task is to protect Study Participants from harm/injury that may be associated with the Study. If you wish to obtain further information about the Bioethics Committee, please contact the Secretariat of the Bioethics Committee at tel. (42) 271 11 23 or email: komisja.bioetyczna@iczmp.edu.pl.

In the event of any adverse symptoms, depending on the occurring clinical symptoms, you should contact the Emergency Notification Center (CPR) at tel. 112 or report to the nearest Emergency Department (SOR).

PART II: Declaration of voluntary consent to participate in the Study

Statement of the person consenting to participate in the Study

I have read the above information, or it has been read to me. I have had the opportunity to ask questions regarding this information and have received satisfactory answers to all my questions. I voluntarily consent / do not consent (cross out as appropriate) to participate in this Study as a Participant.

I give my consent: **YES** **NO** *(cross out as appropriate)*

Full Name of the Participant (in block letters)

_____

Participant's signature _____

Date of signature _____

INFORMATION CLAUSE ON THE PROCESSING OF PERSONAL DATA
of the research experiment Participant

Information clause regarding the processing of personal data of the research experiment Participant (hereinafter referred to as the Study)

In order to ensure transparency in the processing of personal data in connection with participation in a scientific Study, we would like to inform you that:

Data of the Personal Data Controller

- The controller of the Study Participant's personal data is the Copernicus Memorial Hospital Comprehensive Cancer Center and Traumatology in Łódź, hereinafter referred to as the Hospital.
- Hospital contact details: 62 Pabianicka St., 93-513 Łódź, tel.: +48 42 689 5000, e-mail: szpital@kopernik.lodz.pl.
- If you have any questions regarding data processing, please send them by mail to the Hospital's address or by email to the Data Protection Officer, Mr. Tomasz Zdzienicki (iod@kopernik.lodz.pl).

Purpose of data processing

The Study Participant's data will be processed for the purpose of:

- conducting the scientific Study titled: "The use of FET-PET in fusion with MRI in surgical treatment and postoperative radiotherapy of glioblastoma multiforme – randomized, blinded, prospective study."

Legal basis for data processing

The Study Participant's personal data are processed based on the Participant's consent and in accordance with:

- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), hereinafter referred to as GDPR;
- The Act of 5 December 1996 on the Professions of Physician and Dentist;
- The Act of 14 July 1983 on the National Archival Resources and Archives.

Sources of data collection

The Hospital may obtain the Study Participant's personal data:

- directly from the Participant;
- from other medical entities that obtain appropriate consent from the Participant to participate in the Study.

Data recipients

Recipients of the Participant's data may include:

- entities authorized to obtain them under the law (courts, police, bodies conducting proceedings and audits);
- entities providing services to the Hospital:
- legal services,
- support for IT systems used by the Controller.

Retention period

The Study Participant's personal data contained in the Study records will be processed for a period of 20 years from the end of the calendar year in which the final resolution regarding the opinion on the Study was issued by the Bioethics Committee.
Data contained in the scientific Study records cannot be deleted before the expiry of the above-mentioned period. Study documentation will be archived in accordance with Art. 5 of the Act of 14 July 1983 on the National Archival Resources and Archives.

Rights of individuals

In connection with the processing of personal data, the Participant may:

- gain access to the content of their data;
- request their rectification;
- request restriction of processing or deletion of certain data if the Study documentation retention period has expired;
- object to the processing;
- request any information regarding the processing of the Participant's data.

If you believe that the processing of personal data violates the provisions of the GDPR, you have the right to lodge a complaint with the supervisory authority, i.e., the President of the Personal Data Protection Office, 2 Stawki St., 00-193 Warsaw.

Consequences of failure to provide data

Participation in a scientific Study is voluntary. If the Participant consents to participate in the Study, it is necessary to obtain their personal data contained, among others, in medical records. Refusal to provide the Study Participant's personal data will result in the Participant's exclusion from the Study.
Refusal to participate in the scientific Study does not affect the process of providing medical assistance to the patient.

Automated decision-making

The Participant's data will not be processed in an automated manner, including in the form of profiling.

Transfer of data to a third country

We do not plan to transfer the Participant's data to third countries that do not guarantee an adequate level of data protection.

Consent to provide medical records for scientific purposes

If the Participant consents to participate in the scientific Study, they thereby consent to making their medical documentation available to the Research Team to the extent necessary to conduct the Study.

Below is the detailed legal basis for the processing of the Study Participant's data:

Activity / Scope of data	**Additional information**
Scope of processed data:	Scope of data: - identification data contained in medical records; - special categories of data: health information contained in the medical documentation used for the Study. Scope of medical documentation used in the scientific Study: - descriptions from diagnostic imaging (CT, MRI, PET); - histopathology results.
Obtaining and processing personal data for the Study	Art. 6(1)(c) and Art. 9(2)(c) and (j) of the GDPR in connection with: - Art. 25 of the Act of 5 December 1996 on the Professions of Physician and Dentist.
Defense against claims	Art. 6(1)(f) and Art. 9(2)(f) of the GDPR.
Archiving Study records	Art. 6(1)(f) and Art. 9(2)(j) of the GDPR in connection with: - Art. 29 point 21 of the Act of 5 December 1996 on the Professions of Physician and Dentist; - Art. 5 of the Act of 14 July 1983 on the National Archival Resources and Archives.
Entrusting data processing operations	Art. 6(1)(f) and Art. 9(2)(j) in connection with Art. 28 of the GDPR.

Full Name of the Participant (in block letters)

_____

Participant’s signature _____

Date of signature _____

Statement of the Investigator / Person Obtaining Consent

I hereby declare that I have discussed the presented Study with the potential Study Participant using clear, as simple as possible terminology, and I have provided explanations regarding the nature and significance of the Study.

I confirm that the Participant had the opportunity to ask questions about the Study, and I have answered the questions asked by the Participant truthfully and to the best of my ability.

I confirm that the Participant was not coerced into giving consent, and the consent was given freely and voluntarily.

A copy of this informed consent form has been provided to the Participant.

Full Name of the Investigator / Person Obtaining Consent (in block letters)
_____

Signature of the Investigator / Person Obtaining Consent _____

Date of Signature _____