Masarykův onkologický ústav

Health service provider accredited by the Organisation of European Cancer Institutes (OECI) and the Czech Society for Accreditation in Healthcare.

Žlutý kopec 7, 656 53 Brno Czech Republic
www.mou.cz

Conducting clinical trials at the MMCI Information for CROs and Sponsors

Dear representatives of sponsors and CROs,

we appreciate our cooperation in the conducting of clinical trials at the Masaryk Memorial Cancer Institute (MMCI).
Clinical trials have been a tradition at MMCI since the end of the 20th century and since 2000 we have conducted several hundred studies in the field of solid tumors.

As the only Czech "comprehensive cancer center" within the Organisation of European Cancer Institutes (OECI), we are also a top center with a long-established organization of clinical trials, which are carried out according to more than 40 SOPs and regularly audited and inspected. Our focus is on Phase I-III clinical trials for solid tumors, and we are also certified for first-in human clinical trials within the Phase I Unit. Our point of contact is the Department of Clinical Trials.
In order to improve and facilitate cooperation, we would like to inform you about the most important areas in the conduct of clinical trials.

CONTENT:

1. Site overview

We are the unique and largest cancer center in the Czech Republic, where highly specialized medical services, excellent research and education in the field of prevention, diagnosis and treatment of solid tumors are concentrated in one place.

The Institute is a directly managed organization of the Ministry of Health of the Czech Republic, it plays the role of the main coordinator of oncological care for adults with solid tumors for the South Moravian Region and in cooperation with the University Hospital Brno and St. Anna University Hospital it creates a joint Comprehensive Oncology Centre, which has the status of the National Oncology Centre in the network of Czech comprehensive oncology centers.

We are an internationally recognized institution, an accredited member of the Organisation of European Cancer Institutes (OECI), a member of the European Reference Networks for Rare Adult Solid Tumours (EURACAN) and Hereditary Cancer Syndromes (GENTURIS). Our international status gives patients the assurance of receiving care in the same way as other major European cancer centers.

MOÚ workplace: https://www.mou.cz/kontakty/t1320

We are conducting phases I (including first-in human) - III clinical trials for all types of solid tumors in adult patients (i.e., excluding hematooncology).
Each year, we initiate 15-25 oncology clinical trials.

The most often involved departments in clinical trials are:

Department of Comprehensive Cancer Care (incl. Phase I Study Unit)
Department of Clinical Trials
Hospital Pharmacy
Department of Radiology
Department of Nuclear Medicine
Department of Laboratory Medicine
Department of Oncological Pathology

Procedures and examinations that we are unable to provide on site and must be provided by an external facility:

- Ophthalmic examination
- DEXA
- Audiometry
- Specific laboratory tests: HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody, HBcAb, HBV DNA test, HCV RNA test, Imunoglubiliny IgE, tryptáza, Anti-nuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid (dsDNA), circulating anti-

neutrophil cytoplasmic antibody (cANCA), perinuclear anti-neutrophil cytoplasmic antiobdy (pANCA), Troponin I, CK-M

The feasibility of the clinical trial is verified within the feasibility questionnaire and pre-study visit.

2. QA/QC

Clinical trials at the MMCI are governed by Directive 2/2018 (Conducting Clinical Research at the MMCI) and the Standard Operating Procedures (SOPs).
Documents are available upon request.

List of SOPs for clinical trials:

I-A1	Creating and updating SOPs
I-A2	Staff training on SOPs
I-A3	KH staff training
I-A4	Setting up and quality control
I-A5	Controlled documentation
I-A6	Legislation for clinical trials and GCP
I-A7	Storing and managing documents on CTU
I-B2	CTU Personnel Management
I-B3	Project Manager
I-B4	Start-up coordinator
I-B5	Study Coordinator
I-B6	Data manager
I-B7	Payments
I-B9	Study nurse
II-C1	Clinical trial selection
II-C2	Procedures prior to the start of a clinical trial
II-D1	Communication and education in clinical trials
II-D2	Initiation visit
II-D3	Monitoring visit
II-D4	Screening
II-D5	Randomization
II-D6	Blinding and unblinding study subjects
II-D7	Investigational medicinal product
II-D8	In patient clinic for clinical trials
II-D9	Clinical trials and hospital information system
II-D10	Protocol Deviations
II-D11	Delegation of activities
II-D12	PI overview
II-E1	Patient selection and enrolment in clinical trials
II-E2	Informed consent

II-E3	Patient participation in a clinical trial
II-E4	Compensation for patients in clinical trials
II-E5	Adverse and serious adverse event
II-E6	Biological samples
II-E7	ECG
II-E8	Measurement of vital signs
II-F2	Clinical Trial Data Management and eCRFs
II-F4	Clinical Trials Note in EMR
II-F5	Source documentation
II-F6	Quality assurance of the devices
II-F7	Evaluation of laboratory results and deviations
II-G1	Completion of the clinical trial and archiving
J1	Management of early phase clinical trials
J2	Facilities and equipment in the early phase clinical trials
J3	Ensuring the safety of subjects in early phase clinical trials
N-1	Involvement of not delegated nurses (Memo to File)

Quality control is carried out according to the Quality Manual (SOP I-A4 Quality Setup and Control). Every year 2-5 sponsors audits are conducted and as of 30 SEP 2023 we have passed 1 FDA inspection (2012) and 4 SÚKL (Czech Regulatory Agency) inspections (2020-2023). No audit or inspection has recorded a critical finding.

3. Feasibility

The only recipient of the clinical trial proposal and feasibility is the Department of Clinical Trials:

Contact:
Mgr. Hana Blahynková
Start-up Coordinator
hana.blahynkova@mou.cz, studie@mou.cz
tel. 543 136 233

If it is necessary to sign a **Confidentiality Agreement (CDA) to** send more information about the study**,** we accept only the PI-only version, issued in the name of: **Assoc. Prof. Regina Demlová, MD, Ph.D.** (Head of the Department of Clinical Trials). We prefer a "wet-ink" signature as a faster option. The final Principal Investigator will be nominated only if the selection meeting is held.
The feasibility of the clinical trial is discussed with the clinical team for the diagnosis and the following is taken into account: the medical and scientific merit of the study, the nature of the IMP, the size of the patient population, the length of recruitment, the competitive ongoing or planned trials and previous experience with the sponsor/CRO. At a minimum, we need a

synopsis to competently assess the study. Feasibility with a blinded IMP, where the mechanism of action is not known, cannot be competently assessed.

We consider your subsequent feedback, even if negative (e.g., the study was not allocated to the Czech Republic), to every positively answered study offer as a sign of respect towards our site, which will facilitate the management of clinical trials and their effective planning.

Each year, we respond positively to around 60 study offers for solid tumors.

4. Pre-study visit (PSSV)

Always contact the Department of Clinical Trials to schedule a pre-study visit (PSSV):

Contact
Mgr. Hana Blahynková
Start-up Coordinator
hana.blahynkova@mou.cz, studie@mou.cz
tel. 543 136 233

The Principal Investigator (PI) will be nominated for the purposes of the PSSV. Within the framework of the internal rules of the MMCI, the nomination is decided by the management of the clinic. For the role of PI we guarantee an experienced board certified physician, with experience in clinical studies and trained in GCP.

The PSSV may be conducted in person or by teleconference. We prefer a personal visit.
The PSSV is always attended by the start-up coordinator of the Department of Clinical Trials and the Principal Investigator.

Prior to the PSSV, we require 2 printed A4 protocols to be sent to the start-up coordinator (see contact above) and an electronic protocol. We only accept the PSSV without a final or draft protocol in exceptional cases.

If the PSSV requires a CRA to visit any MMCI department (not standard), the start-up coordinator must be informed in advance.

Only the PI´s CV and GCP certificate will be provided as part of the PSSV, other members of the study team will be named later, as will the required documents.

Within the PSSV, we expect the CRO/sponsor representative to have a basic understanding of the protocol, IMP, study timelines (FPFV, LPFV), vendors involved, and organizational aspects of the study. We also expect that information passed from our side (contract requirements, etc.) will be further communicated towards the CRO/sponsor team.

5. Start-up phase

The start-up phase covers the period from the site selection to the site initiation visit (SIV).

Main contact (all requirements):
Mgr. Hana Blahynková
Start-up Coordinator
hana.blahynkova@mou.cz, studie@mou.cz
tel. 543 136 233

Please provide adequate contacts on your side as well.

For our site, this phase already means the involvement of many staff positions in the preparation (start-up coordinator, lawyer, economist, study coordinator, etc.), and therefore we ask for timely information on any change in the study (time shifts, cancelation, etc.), submitted always also to the start-up coordinator (hana.blahynkova@mou.cz). For us, study preparation means allocation of staff and inclusion of the study in the study plan, any information is essential.

During the start-up phase, a **study team** will be appointed. This will be **arranged and delivered by the start-up coordinator.**

- ✓ Principal Investigator (nominated by clinic management)
- ✓ Sub-investigators (designated by the PI)
- ✓ Study Coordinator (designated by the Department of Clinical Studies) - Medical Education
- ✓ Study nurse (appointed by the Department of Clinical Studies + station nurses at MOU)
- ✓ 2 radiologists (appointed by the Head of Radiology)
- ✓ Pharmacist and pharmaceutical assistant (designated by the Head of the Pharmacy)
- ✓ Laboratory technician for samples to the central laboratory
- ✓ According to the requirements of the study, the following may also be needed: data manager, pathologist, cardiologist, etc.

Documents for the study team (CV, GCP, etc.) are ideally provided in a single summary for the whole team (not just PI+SI). All documents must be requested and sent before the SIV.

Document **Suitability of the study site**
The Site Suitability document, which is a new requirement within CTIS, is ideally completed by the CRO/Sponsor based on information from the pre-study visit and submitted to the site (Start-up Coordinator) for review and signature.
In exceptional cases, the opposite procedure is possible, i.e. the MMCI delivers a partially completed document and sends it to the CRO/sponsor for completion of the information on the study.
The document is signed by the Head of the clinic or the PI.

As part of the final start-up phase, you will be requested by the MMCI start-up coordinator for:

- ✓ **Completed start-up questionnaires** (https://www.mou.cz/klinicke-studie/t1520, section For study sponsors)
- ✓ **Printed protocols in A4 format, ring-bound**
- ✓ **Color printed laboratory manual**
- ✓ **Protocol, Czech synopsis, manuals and sample ICFs in electronic form**
- ✓ **Access to vendor systems for specific persons**
- ✓ **Laboratory kits and other equipment**
- ✓ **Co-completing and approving the Delegation Log - site template**

Why do we ask for the above in advance? We are always well prepared for SIV, we have self-trained in the protocol, prepared workflows, arranged collaboration within the site departments, done training and obtained accesses, we often have pre-selected the patients. We really work with the printed materials. SIV is the moment for us to start the study and we expect our site to be activated in a few days. This is crucial for successful patient recruitment, which is in everyone's interest.

6. Contract and budget

Contact for contract and budget proposal:
Mgr. Michaela Hanáková
michaela.hanakova@mou.cz
tel. 543 136 226 (Mon-Thurs)

Only 1 trilateral contract is concluded in the MOU. Separate contracts are not allowed.
Information on the contract requirements is given at the pre-study visit.

If the selection meeting reveals that you need to enter into a separate contract with another provider (e.g. ophthalmology or laboratory tests), we will inform you.

The contract and the budget are negotiated in parallel, and the internal procedure always includes comments on both parts from: the PI, the lawyer, the economist, the Head of the pharmacy and a representative of the Department of Clinical Trials.

Please direct the draft contract and budget to the contact listed above.
To speed up the study preparation process**, we only accept the following contract templates for clinical trials of medicines**:

1. Framework agreement with the sponsor or CRO
2. Long-term used and mutually accepted template with the sponsor or CRO
3. National template of the Agreement (CTA), recommended by the Ministry of Health (downloadable here: https://www.mou.cz/klinicke-studie/t1520, section For sponsors), without further modifications from both sides
4. For non interventional clinical trials and for clinical trials of medical devices, special conditions apply

You will receive the initial comments within 8 weeks. Acceptance of the above model agreements, without further modifications, will allow for a quick start of the study due to minimized comments.

Budget information:
The only recipient of the payments (100%) is the institution, which distributes the funds (including remuneration for the study team) according to internal regulations. Therefore, the budget also includes the personal costs of the study team (e.g. for central labs, this includes the activities of the coordinator, the nurse and the laboratory technician).

We do not accept changes in payment terms beyond the above model contracts. Only the budget itself should be inserted in the contract.

We ask that the budget be provided in as simple form as possible - maximum procedures must be directly included in the amounts for study visits, with the exception of imaging.

As part of the comments, we follow a non-public internal price list for clinical trials.

Selection from the price list - start-up fees:

- ✓ **Start-up fee** - payable after signing the contract without any other conditions - 40.000 CZK
- ✓ **Pharmacy Start-up** - payable after signing the contract without further conditions - 8-10.000 CZK
- ✓ **Archiving fee (25 years)** - 35.000 CZK
- ✓ **Fee for contract amendment** - 5.000 CZK
- ✓ **Fee for the use of complex systems requested by the CRO/contractor** - e.g. SIP

Screening failures
In oncology, we are not able to predict the progress of screening in a patient. Therefore, we demand payment for all screened patients - **all screen failures**, in **the form of a flat fee of** 8-10.000 CZK + imaging tests or biopsies. In case the CRA reveals during the source data verification that the patient had not met the initial study criteria, the fee would not be reimbursed.

Patient compensation
The ways in which patients can be compensated vary. Due to the specifics of cancer patients (age, worsened condition, often living out of town), we prefer to pay in cash. Payment to a card provided by the sponsor through a payment vendor is also acceptable. In any case, we ask for lump sums for visits, or lump sums according to distance from residence. If **a payment vendor is used**, information and training must be provided during the start-up phase – this agenda will be fully handled by the study coordinator.

In case of cash payment, **we require a lump sum payment in advance in the amount of** CZK 30-50,000, the use of which is described in the contract. This is an amount that we will invoice after it is used up and we are entitled to invoice again before it is used up. The unpaid amount is refunded at the end of the study.

Please note that patient compensation invoices are often paid late or not at all. This is a threat to the rights of patients who, according to the ICF, are entitled to compensation after the visit has taken place and our site does not withhold these payments for ethical reasons. Therefore, please check the processes on your side to ensure that these invoices are paid on time, according to the contractual terms.

Paid travel compensations are documented in the patient's study file and available to the CRA during the monitoring visit. With respect to privacy and data protection, we do not scan these documents or send them by email or as an attachment to an invoice.

7. Site initiation visit (SIV)

The date of the site initiation visit (SIV) **is scheduled by the study coordinator**, in consultation with the PI and the CRA. We do set up this date until the **study is expected to start in approximately 4-6 weeks, depending on the status of contract negotiations and study approval**. This information will be confirmed by the site start-up coordinator.
The SIV takes place during 1 day, from approximately 8 am to 3 pm. The study coordinator will prepare a **schedule** for the individual study team members according to the site management rules and will brief the CRA on this schedule. The meeting takes place in the CTU conference room where the study team members come. The study coordinator is present during the whole SIV.

<u>The SIV can be performed under the following conditions:</u>

- ✓ Clinical trial has regulatory approval
- ✓ The CTA is either signed or approved and signatures are in progress (we accept SIVs without a signed contract)
- ✓ Laboratory kits, printed protocols and other documents requested by the site and described in the Start-up chapter were delivered to the site in advance.
- ✓ Members of the study team received the accesses that were requested for them.

From the moment of the SIV, the **primary contact of the site becomes the study coordinator of** the respective study.

<u>What do we expect from the CRA/CRO/sponsor representatives on the day and during the SIV?</u>

- ✓ Delivery of complete Investigator Site Files (but ideally in advance) - including sufficient **printed** Informed consents forms and Patient cards in appropriate format and size (legibility, durability, ability to add information)
- ✓ Perfect knowledge of the protocol as well as good knowledge of the study diagnosis
- ✓ Leadership and moderation of SIV, targeted information for individual team members (investigators/nurses/pharmacy/lab/radiology etc.)
- ✓ Resolving any missing documents
- ✓ Training and providing signatures on the Delegation Log and other documents.

Informed Consent Forms (ICF)

We require the delivery of (double-sided) printed Informed consents forms, both at the start of the study in sufficient numbers and afterwards (additional copies, new versions, etc.). The CRO/Sponsor is responsible for ensuring that fully approved ICFs are delivered to the site.

We strongly prefer if generally valid and known information (site name and address, name of the PI, contact to the EC, GDPR contact, etc.) is already pre-printed in the ICF by the CRO/sponsor. This prevents serious mistakes and compromises of patients' rights.

If this is not possible for the CRO/sponsor, then the forms must be printed in such a way that it is effectively possible to add this information manually and the spaces to be added must be visibly marked.

Delegation Log – site template

Please be advised that **we only accept the Delegation Log on the site form**, which is required in accordance with SOP II-D11 and the SUKL recommendation (inspection findings). This is a document of the Principal Investigator and the site.

The Delegation Log is completed before the SIV, during the SIV it is only completed with the signatures and initials of the study team, the signature and dates of the PI.

Other DL templates are not accepted.

Site Signature and Delegation of Responsibilities Log

Study Sponsor:	Click or tap here to enter text.	Principal Investigator:	Click or tap here to enter text.
Protocol Study Number:	Click or tap here to enter text.	Study Site Number:	Click or tap here to enter text.
Country:	Click or tap here to enter text.		

STUDY TASKS:

Medically Qualified/Trained/Licensed Staff	*Trained/Qualified Staff*	*Trained/Qualified Staff Continued*
1. Conduct the process and obtain Informed Consent	15. Discuss non-medical content of Informed Consent Form	29. Receive safety notifications
2. Determine eligibility criteria (inclusion/exclusion)	16. Manage IRB/EC Communication	30. Manage IMP receipt/storage/temperature monitoring
3. Perform physical exam	17. Maintain essential documents (ISF)	31. Prepare/Dispense IMP
4. Make study-related medical decisions	18. Collect biological samples	32. Perform IMP Accountability
5. Evaluate and interpret study-related test results	19. Process biological samples	33. Maintain Pharmacy File
6. Assess AE/SAE	20. Ship biological samples	34. Administer IMP
7. Sign off (e)CRF	21. Make (e)CRF entries, corrections and queries	35. Administer non-IMP
8. Unblind/unmask decision	22. Use IWRS/IRT	36. Perform radiology procedures
9. Assess safety notifications	23. Collect demographic data	37. Upload/submit radiology scans
10. Review and interpret radiology procedures (RECIST etc.)	24. Measure vital signs	38. Perform tumor biopsy
11. Evaluate central lab results	25. Perform ECG	39. Archival tumor and pathology report
12. Interpret ECG	26. Administer/manage QoL and Patient Diaries/Tools	40. Train staff
13. Perform and interpret ECHO	27. Submit SAE	41.
14. Collect medical/medication history	28. Receive central lab and vendors results	42.

8. Monitoring

The main contact for the CRA´s and monitoring visits is always the study coordinator.

We strive for the utmost helpful and respectful cooperation: we offer an experienced study team, we fulfil our obligations and we contact CRA´s when justified. On the other hand, we expect CRA´s to be available on mobile phones and email during normal working hours and working days. Inquiries concerning our patients usually do not tolerate long delays so as not to jeopardize treatment or patients' rights.

Monitoring of clinical trials at the MMCI takes place on the 5th floor of the Švejdův Pavilon. The **maximum capacity is 4 CRA´s per day. In accordance with the CTA, the monitoring of clinical trials takes place during normal working hours, from Monday to Friday from 7 a.m. to 3:30 p.m. After these hours, no one is allowed to remain in the area without a site staff member present, due to the need to secure the area as well as stricter access control to personal data. Please take this into account when planning your visits.**

Date of monitoring visit (MV)

The date of the MV must be arranged with the study coordinator or the data manager of the well in advance (at least 3 weeks). It is necessary to notify the number of people who will attend the MV. In the event that more than one person is absolutely necessary to attend - e.g. at study handover, 2 monitoring places must be booked. Please use this option only in justified cases.

In the case of a monitoring visit that is arranged only in the pharmacy (e.g. a blinded monitor), the MV appointment must be arranged in the same way as described above. The pharmacy does not have its own monitoring facilities, the appointment must be arranged with the main study coordinator.

Access to monitoring areas

Access to the 5th floor is possible only by two new lifts. To enter the 5th floor, you must use a chip card, which will be issued to you upon signature by the Student Coordinator at the Department of Clinical Studies **on the 3rd floor**. The card is returned at the end of the monitoring day, even during multi-day monitoring.

Course of the monitoring visit

The list of patients to be monitored must be sent by email to the study coordinator at least 1 day in advance (by 15:30) in order to secure source documentation. All required documentation (medical records, patient files, ISF, etc.) is ready at the monitoring site.

The CRA works independently and arranges a meeting with the study coordinator, data manager, or other team members at a convenient time (usually in the afternoon) to complete the necessary paperwork and corrections.

Visiting the pharmacy is usually possible after 1 pm - by appointment with the study pharmacist.

It may be that a patient's medical record is currently being used acutely in the context of healthcare delivery. In this case, it is possible that it will only be loaned for monitoring for a limited period of time.

The course of the MV, including meetings with the study team, must be planned taking into account that the monitoring site can only be used during the presence of the study coordinator. Documentation and chip card must be returned by 3:30pm and the space is secured.
Thank you for respecting these rules.

Working hours
Monday - Friday from 7:00 am - 3:30 pm.

Working with medical documentation
It is strictly forbidden to permanently interfere with medical records in any way, please use removable adhesives to communicate with the study team. Medical records must always be returned to their original condition (do not leave sheets loose outside the files).

Record of access to medical records
The monitor or auditor has the full right to inspect the medical records for the purpose of checking the implementation of the study. However, in accordance with Act 372/2011 Coll. on Health Services, § 66, point 6, there is an obligation to make a record of each inspection (who inspected and for what purpose) and to file it in the patient's medical record. Forms are available for each patient.

Equipment of monitoring areas
The monitor has a desk, chair and telephone for communication within the site.
Internet connection is possible via cable (network socket) or wi-fi (registration is required).
The photocopier, printer and fax machine are still available by prior arrangement with the study coordinator. Please use the copier on a limited basis only if it cannot be handled outside of site. The copier in the monitoring area is not freely available.
The kitchen is for site staff only – please don´t enter without previous permission.
1 Coffee/water/tea per MV will also be offered by the study coordinator.
Please note that smoking is prohibited in the entire area, including the terrace!

9. Payments

We expect compliance with the payment terms agreed in the contract. As a state-run hospital, we are obliged to penalize late payment of invoices; non-compliance with payment terms will be escalated to the legal department. We will also notify the study sponsor in the event of non-compliance by the CRO. Difficulties of an ongoing nature may negatively affect future cooperation with the CRO or sponsor.
Please communicate as much as possible in case of any deficiencies with the invoices received.

Please let us know who is responsible for payments on the CRO/sponsor side (grant specialist, project manager, etc.) - we require a specific contact. If we do not have this contact, we will contact the study monitor.

What is particularly important to us:

- To send statements of work/RFI´s to the site within the agreed timeframe and to the agreed contacts (fakturace-studie@mou.cz)
- Report any discrepancies in the invoice immediately to the site
- Payments made to the site account must be endorsed with the site invoice number
- Do not accumulate payment of multiple invoices into one payment.
- Actively collaborate on the creation and approval of invoiceable items (we have long been calling for the generation of these items from the eCRF and the replacement of manual processing of documents, which may be subject to a fee from the site)

Contact for payments at the MOU:

Michaela Hanáková
michaela.hanakova@mou.cz, fakturace-studie@mou.cz
tel. 543 136 226 (Mon-Thurs)

Kateřina Benešová
Clinical Trials Finance Officer
katerina.benesova@mou.cz, fakturace-studie@mou.cz

10. Contacts and links

www of the site: www.mou.cz
www Department of Clinical Trials: https://www.mou.cz/klinicke-studie/t1520

Contact for feasibility and organization of pre-study visits and start-up activities:

Hana Blahynková
Start-up Coordinator
hana.blahynkova@mou.cz
tel. 543 136 233

Contact for contract and budget proposal, Quality Manager, payments*:*

Michaela Hanáková
Head of the Clinical Trials Unit
michaela.hanakova@mou.cz
tel. 543 136 226 (Mon-Thurs)

Thank you for your cooperation in the clinical trials.