Policy for Clinical Researches and Trials

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Contents

1. GENERAL PROVISIONS

1.1. Basic principles for the organization of clinical researches and trials

(1) Principles for the conduct of clinical researches and trials:

a) Principle of freedom of research:
Article X of the Fundamental Law of Hungary expresses that Hungary ensures the freedom of scientific research. Under the Fundamental Law, Semmelweis University (hereinafter: "University" or "SE") shall ensure the freedom necessary for the smooth and efficient performance of scientific duties for the persons subject to these Clinical Research and Trials Policy (hereinafter: "Policy").

b) Principle of decentralization:
The University ensures that persons covered by these Regulations have the necessary supporting central organization (as the Central Coordination Office for Clinical Research of the Directorate for Health Management and Development of the Clinical Research Directorate of the Clinical Centre for Medicine, hereinafter referred to as the Bureau) for the independent performance of scientific duties. They shall also have professional and methodological conditions for supporting and promoting research activities in decentralized departments.

c) The principle of synergy between theoretical research and clinical practice:
The University shall ensure, through the organizational system of clinical research and clinical trials, that theoretical research and clinical practice are carried out in a coordinated way, and that innovative results are put into practice as soon as possible.

d) Transparency principle:
The University shall ensure and confirm in these Regulations that the processes of clinical research trials, including professional, financial, and legal compliance, and the activities of all parties involved in clinical research trials are designed and regulated clearly and transparently, following the principle of transparency.

(2) Principles for the organization of research trials:

a) the principle of supporting local (departmental) initiatives:
The University shall actively contribute to and support the preparation, conduct, legal, administrative and economic management of research studies within its remit and competence, and shall provide support to all the departments involved in the study and to its authorized Principal Investigators.

b) the principle of providing services complementary to research and trials:
The University shall provide research-related services at all stages of clinical trials in an incentive-based manner in the interest of clinical trials, the University, and the trial sites. The University shall also support the implementation of this principle by allowing the participation of the 100% University-owned Semmelweis Egészségügyi Kft. Through this, a more efficient provision of services, more transparent processes, and simplified administration can be provided, thus facilitating the use of the primary contract, mainly imaging and some pathology tests, within the University.

c) the principle of a staggered organizational structure:
The Rector manages the organization of research and studies and the participation in the development of the professional content, assisted by the President of the Clinical Centre. For the registration of clinical trials and non-interventional research initiated

by a researcher employed by the University, without the need for independent contracting, the bureau works closely with the unit managed by the Vice-Rector for Science and Innovation. The primary arena for the organization of research trials is the organizational unit and may also involve the collaboration of several organizational units. The Bureau supports the coordination, management, and legal tasks of the research and study, the Directorate-General for Finance (hereinafter referred to as: GFI) and the Directorate-General for Legal Affairs and Administration (hereinafter referred to as: JIF) as well as by the central unit(s) under these Regulations, which ensure that the professional objective is achieved in an external and internal regulatory environment and that financial and economic aspects are taken into account.

d) the principle of unity of research and trials:
In the preparation, conduct, and conclusion of clinical research trials, the University shall not assess the individual elements or sub-tasks in the medical, legal, administrative, and economic evaluation, but rather the interrelationship of the parts and the adequacy of the clinical research trial as a whole.

e) The principle of freedom to organize research and trials:
The University encourages and supports the use of optimal research-trial organization arrangements related to the professional requirements of clinical research trials, subject to the possibilities set out in these Regulations.

f) Responsibility Principle
The clinical trial may only be conducted without prejudice to the healthcare provider's continuing patient care responsibilities.

1.2. Scope

(1) The scope of these Rules covers the following:
   a) classic clinical trials involving patient recruitment,
   b) the transfer of patient data for the purpose of assessing clinical feasibility without patient admission.

(2) The scope of the Rules does not cover
   a) non-clinical trials
   b) for not involving patient admission, typically investigator-initiated, non-sponsored studies.

(3) Its personal scope shall apply to the organizational units and persons carrying out the research and study (in particular: researchers, medical specialists, residents, students, Ph.D. students, and research assistants), to the organizational units and persons carrying out its coordination and administration, and to the organizational units and persons carrying out the legal and economic tasks related to the study.

1.3. Definitions

Definition of the different forms of clinical research and trials

Clinical research:	As defined in Article 2(2)(1) of Regulation No 536/2014/EU of the European Parliament and the Council, any study involving human subjects, the purpose of which is: to establish and demonstrate the clinical, pharmacological, and/or other pharmacodynamic effects of one or more medicinal products; the identification of adverse reactions to one or more medicinal products; or the study of the absorption, distribution, metabolism, and excretion of one or more medicinal products to demonstrate the safety and/or efficacy of those medicinal products, subjects are subjected to diagnostic or monitoring procedures in addition to standard clinical practice.
Clinical trial:	A clinical trial meeting one of the following criteria as defined in Article 2 Section (2) point (2) of Regulation No 536/2014/EU of the European Parliament and of the Council (hereinafter referred to as a clinical trial): the inclusion of the subject in a given therapeutic strategy is based on a prior decision that is not in line with standard clinical practice in the Member State concerned; the decision to prescribe the trial medicinal products is taken at the same time as the inclusion of the subject in the clinical trial; or subjects are subject to additional diagnostic or monitoring procedures and standard clinical practice.
Medical device clinical trial:	Any planned and scheduled study conducted in humans at one or more study sites, defined as a systematic medical research study designed to collect clinical data on the safety and performance of one or more medical devices intended for clinical trials.
Non-interventional trial:	Any trial that is not a clinical trial of trial medicinal products or medical devices. The procedure followed does not deviate from usual healthcare practice.
Investigator-initiated study:	An investigator-initiated research study may be: a trial conducted as part of a grant application; monocentric or multicentric, funded entirely or partly by self-funding and/or external support, based on an investigator-designed protocol. The sponsor is typically an investigator, a group of investigators, a scientific society, a university, a research institute, or a foundation entitled to support research activities.

Pre- and post-marketing clinical trials:	Phase I study: Trial of the tolerability, safety, pharmacokinetics, and pharmacodynamic effects of the trial medicinal product in healthy volunteers or specific patient groups. The Phase I study may have the additional objective of determining the therapeutic dose range; Phase II study: A study of the IMP in an indication selected based on pharmacological activity to confirm the efficacy of the IMP, establish the dose-effect relationship, determine the optimum therapeutic dose, and assess safety and tolerability; Phase III study: A controlled, randomized, comparative study design with a more significant number of patients to demonstrate the efficacy, safety, and tolerability of the IMP; Phase IV study: A study using an IMP with a marketing authorization following the summary of product characteristics to further assess the benefit/risk ratio, safety, and tolerability.

Concepts related to contracting

Non-disclosure agreement:	An agreement, including a confidentiality agreement made by an individual before a clinical trial, is a legal statement to protect information about the data and procedures of a clinical trial.
Sponsor:	Any natural or legal person who initiates, conducts, and funds a clinical trial.
Contract Research Organization (hereinafter: CRO):	The sponsor contractually authorizes a person or organization (economic, scientific, or other) to carry out one or more of the sponsor's tasks and/or obligations concerning the research trial.
Study protocol:	A document describing the subject(s), design, methodology, statistical design, and study organization. The protocol usually includes the background to the study and the rationale for conducting the study but may also include other documents to which the protocol refers.
Trial fee:	The fee for the protocol activities performed at the site, excluding fees for clinical trial services provided by other University health care services, in a particular laboratory, imaging, and pathology services, except when the services are provided in the same department as the baseline study.
Pharmacy registration fee:	A separate register of trial medicinal products received for clinicaltrial and used in the patient's treatment must be kept in the institutional pharmacy. The head pharmacist of the institution shall be responsible for keeping the register. The pharmacy registration

	fee is allocated to this task and is financed by the trial site from the clinical part of the trial fee.
Cost per patient:	The total direct costs incurred under the primary study contract.
Institutional Contract:	A legal statement between the Sponsor and the University containing the essential medical, legal, economic, and other provisions, duties, rights, and obligations relating to the clinical trial. An institutional clinical trial contract may be an individual, institutional contract, a framework contract, or a case-by-case contract based on a framework agreement. Where a framework contract is used, the term 'institutional contract' shall be understood to mean both the framework contract and the legal declaration containing the provisions for the case study. In case upon the Client's agreement, the institutional contract does not include or fully include provisions for other health services in a particular laboratory, pathology, and imaging services, as set out in the clinical trial protocol. In that case, the Parties shall conclude a separate Service Contract(s) for these services.
Service Contract:	A legal agreement between the University and the Sponsor relating to clinical trials at the University and off-campus (external) trial sites, in a particular laboratory, pathology and imaging services, which is not covered by the Institutional Agreement, and which contains medical, legal, economic and other provisions, tasks, rights and obligations for the Sponsor and the University's service provider(s) relating to the clinical trial as defined in the protocol of the trial contract.
Single-contract model:	An exclusive contractual relationship between the parties to a clinical trial (University, Sponsor) (whether single or multiple contracts) that is not linked to any other legal relationship with a third party, such as an investigator's remuneration, entered into by the Sponsor.
Multi-contractual model:	A set of contractual relationships between the Sponsor and other parties involved in the clinical trial (University, Principal Investigator/team members, other legal entities), whereby, following acceptance of the overall clinical trial budget by the University and the Sponsor, the Sponsor enters into a separate contract with the Principal Investigator and the investigators for the share of the Principal Investigator’s/team members' fees, as set out in these Regulations, in respect of the task performed. In the case of a multi-contract model, the income received by the University covers the

	cost of the test centre and the central contribution (it cannot be used to pay staff directly at the test centre).
Hybrid model:	The special multi-contracting model is designed for high-cost clinical trials. In this model, certain participants, such as the Principal Investigator and/or team members, do not individually contract with the Sponsor. Instead, one or more of these participants receive their remuneration through the University.
Emergency fee	The fee, upon payment of which the University undertakes to carry out the contracting process within 25 working days of receipt of the draft contract.

Definitions relating to the staffing and facilities of the trial site

Standard Operating Procedures (SOPs):	Detailed written instructions for the consistent performance of a specified activity.
Recruitment:	A public invitation by a healthcare provider conducting a clinical trial, authorized by the National Centre for Public Health and Pharmacy (hereinafter: NNGYK), to recruit volunteers other than patients treated as subjects for a specified clinical trial. A healthcare provider conducting a clinical trial may recruit eligible subjects by calling for expressions of interest published in a press release and on its website. The published call for recruitment shall refer to the existence of official authorization for the clinical trial. The recruitment call shall not be for advertising purposes. The mention in the recruitment advertisement of the manufacturer of the IMP and, in the case of an IMP with a marketing authorization, the marketing authorization holder shall not constitute advertising. The sponsor and professional and patient organizations may publish the recruitment advertisement's contact details on the healthcare provider conducting the clinical trial's website, social networking, or other websites, indicating the subject of the recruitment.
Principal Investigator	Person responsible for the conduct of the trial at the trial site. If the trial is conducted by a team of several persons at the site, the Principal Investigator is the responsible leader of the team. The Principal Investigator is responsible for setting up and securing a trial-specific team. The Principal Investigator may be a specialist physician with a legal relationship to Semmelweis University and a qualification as defined by law, and, in the case of studies not directly involving human subjects, a researcher.
Investigator:	Responsible for the conduct of the relevant part of the trial and related tasks at the trial site, as required by the legislation, the GCP, the protocol, the Principal Investigator's instructions, and these rules, under the supervision of the Principal Investigator.
Trial pharmacist:	A mandatory member of the investigator team for drug clinic studies, responsible for maintaining the records of incoming drugs and ensuring that the quality requirements for drug storage are met.
Block coordinator:	A staff member assigned to the clinical block to assist in the clinical trials of the departments, who is a member of the bureau staff.
Study coordinator:	A member of the clinical trial team who coordinates the trial at the trial site in collaboration with the Principal Investigator and under

	the supervision of the Principal Investigator. Their primary responsibility is coordinating the trial site's logistical, administrative and organizational tasks.
Study nurse:	Performs nursing duties, observation of subjects, biological sampling and handling and transfer of specimens, performing tests and interventions not requiring medical training, document management (keeping recruitment diary, administration of patient visitor records, keeping a patient diary, keeping the daily temperature of refrigerator assigned for storage of study preparations, monitoring the classification of the equipment used during the study, keeping the relevant part of the service record in a separate document, reporting the need for Service to the trial site administrator in good time), issuing, returning and checking the test products.

2. CLINICAL TRIALS

2.1. General Provisions - Rules for the primary conduct of clinical trials at the University

2.1.1. Technical-scientific, legal and economic preparation of the clinical trial

(1) The initiator of the trial (Sponsor) shall, based on the subject of the trial, first seek
   a) the academic staff member to be appointed as the Principal Investigator and/or
   b) the Head of the department that is to be chosen for trial site and/or
   c) a member of the bureau's staff.
   The initiator shall also send its request for the conduct of a clinical trial in the electronic form to klinikaikutatas@semmelweis.hu.

(2) Where access to the data available at this stage requires the Principal Investigator to sign a confidentiality statement, they shall, before accepting and signing it, forward its contents to the Director of Legal Management of Clinical Research Legal Affairs of the Directorate-General for Legal Affairs and Administration (hereinafter referred to as "Legal Manager") at kkszerzodesek@semmelweis.hu to conduct a legal compliance check.

(3) In the event of contact with the bureau, including a joint request from the bureau with the Principal Investigator, the legal compliance review of the confidentiality statement shall be carried out by the Legal Manager.

(4) The Legal Manager shall be responsible for examining the legal adequacy of the declaration of confidentiality and for handling the Chancellery's authorization procedure for any derogation from the Hungarian jurisdiction clause. The Legal Manager shall be responsible for the verification of the declaration of confidentiality within three working days of receipt of the declaration of confidentiality:
   a) authorizes the acceptance of the confidentiality waiver submitted by the Sponsor or initiate its amendment; or
   b) initiates the conclusion of a university-wide confidentiality agreement between the investigator, the sponsor representing the university and the Sponsor.

(5) It is not necessary to enter into a confidentiality agreement if the party initiating the clinical trial already has an existing institutional or framework agreement for confidentiality.

(6) The Principal Investigator shall respond to a written request for a clinical trial from the Sponsor within 5 working days of receipt of the feasibility questionnaire sent by the Sponsor.

(7) If the test site and/or the Principal Investigator does not wish to participate in the conduct of the study and is permitted under the feasibility questionnaire or the existing confidentiality agreement, the Principal Investigator shall refer the Sponsor to the Bureau after prior consultation with the Sponsor.

(8) The Bureau may, at the Sponsor's request, within 5 working days of the Principal Investigator's refusal, propose the involvement of another Principal Investigator or another trial site in the same study.

(9) If the Principal Investigator accepts to conduct a clinical trial and the trial site has been selected by the Sponsor, the Principal Investigator shall inform the Bureau within 5 working days by sending the Declaration of Acceptance following Annex 1/A.

(10) The Declaration of Acceptance is also required if the clinical trial is conducted at an external trial site and is only linked to a University health service provider unit by a service contract. In this case, the Declaration of Acceptance following Annex 1/B shall cover the inclusion of the Service related to the clinical trial.

(11) The Bureau assigns a unique identifier (SE number) to the study and informs all the departments involved within five working days of receipt of the admission form. The unique identifier will be used to identify the trial and must be indicated on all documents generated, in addition to the protocol number.

(12) Following or simultaneously with the Declaration of Inclusion, the investigator shall propose the participants in the trial, the departments to be involved and shall also send the Office a declaration on the subject-matter of the trial (Annex 2).

(13) The staff member of the Bureau assigned to the clinical trial shall keep the documents generated in an organized manner, separated by clinical trial, until the trial is closed.

(14) The Chief Pharmacist, after informing the Bureau, sends the clinical trial notification form (Annex 3) to the Principal Investigator, who completes it and returns it electronically to the Bureau and the Chief Pharmacist within 5 working days.

(15) Within 5 working days, the Chief Pharmacist will arrange for the registration and, if necessary, consult with the Principal Investigator to appoint a Quality Assurance Officer (Annex 4). The pharmacy registration fee must be financed by the trial site from the clinical part of the trial fee. In a clinical trial, the countervalue of the trial medicinal product(s) must not be charged to the budgeted drug budget of the clinic. The institutional agreement shall specify the method and conditions for the provision of all trial drugs. The Principal Investigator and the head of the trial department shall be responsible for ensuring compliance.

(16) The further procedures for clinical trials related to the University Pharmacy Pharmaceutical Organization Institute (hereinafter: EGYGYSZI) shall be regulated by the EGYGYSZI in its rules of procedure.

(17) The regulatory and ethical approval of the clinical trial shall be carried out by the Sponsor under the ICH-GCP principles, the Hungarian legislation in force, and the Helsinki Declaration on Ethical Principles in Medical Research, for which the Principal Investigator

and the Bureau shall provide the necessary support. At the same time, the Sponsor shall notify the Principal Investigator and the Bureau of the issuance of the study authorization.

(18) If the Principal Investigator declares on the declaration of acceptance that

a) if the study includes diagnostic or therapeutic procedures involving high costs, the study director, in collaboration with the head of the economic office of the study site or the competent clinical block director, must prepare a cost estimate per patient (Annex 5/a) based on the study protocol before the conclusion of the institutional agreement, which must be sent to the Bureau. The cost price calculation must include the pharmaceutical registration fee, the fixed amount of which is set out in Annex 3 to the Regulations. If the Principal Investigator also states in their declaration that they do not incur any staff-related expenses from the institutional revenue, the revenue accruing to the investigator will be equal to the calculated cost price. If the Principal Investigator also intends to cover personnel-related expenses from institutional revenue, the amount and extent of these expenses must also be included in the calculation of the cost price (Annex 5/b), and in this case, the cover for these expenses is also part of the clinical revenue.

b) the direct costs incurred by the investigator in connection with the trial, calculated per patient enrolled, do not exceed 12 % of the total per-patient trial fee income planned in the institutional agreement for the clinical trial, and that no personnel-related expenses are incurred from the institutional income, the income accruing to the investigator is equal to 12 % of the per-patient trial fee. The direct cost of the testing site includes a mandatory pharmaceutical registration fee. If the investigator also intends to incur personnel expenses from the institutional revenue, the trial must be treated as a large self-cost, and the amount and rate of the personnel expenses must be included in the self-costing template (Annex 5/b). In this case, this coverage is part of the clinical income.

c) If the study is carried out under a single-contract or hybrid model, a declaration of the purpose of the revenue collected is also required to assess the recoverability of VAT.

(19) If the investigator also involves other health care services (laboratory, imaging, pharmacy, pathology) not specifically named in the protocol and the contract, for which the collaborating unit is entitled to income, the University will, without a separate declaration by the collaborating unit, treat the income according to the settlement scheme in the investigator's declaration. If the entity involved wishes to apply different rules, it must declare this to the Bureau and the Bureau's economic unit before the conclusion of the contract.

(20) The Bureau and its economic department shall provide professional guidance and support in the performance of financial and budgetary tasks. It shall support and monitor the calculation of the per-patient cost of standard operating procedures based on actual costs, the negotiation of prices based on the actual cost, the determination of the examination fee and the fees for services related to the clinical examination, and the inclusion of additional costs in the contract price.

(21) The price negotiation shall determine the following:

a) The per-patient study fee revenue for the study.

b) The unit price of the procedures conditionally incurred during the study.

c) The quantity and value of services required.

d) How to ensure and preserve the contract's stability of value.
e) The contracting fees (Annex 6) and other costs can be billed individually, independent of the study fee. The testing laboratory may not collect individual fees from principals for the titles specified in this Policy.

(22) 20% of the total examination fee revenue is paid to the University's central budget.
(23) The maximum rate of the investigator's remuneration is 25% of 68% of the total study fee for a low-cost study in a multi-contract model and 25% of the central part (20%) plus the amount after deduction of the cost price for a high-cost study in a single-contract or hybrid model. For collaborating doctors, the minimum remuneration is at least 5% of the central deductible, and the examination fee is less the out-of-pocket costs.
(24) Provision should be made for the remuneration of additional investigators in proportion to their participation in the trial.
(25) The Legal Manager shall make recommendations on draft contracts' economic and legal content to ensure that the contract evaluation process is as efficient and rapid as possible. The current version of the recommendations is published on the Bureau's website.
(26) The Bureau shall be assisted in its decision-making by the Committee for the Evaluation of External Research Projects, which shall give its opinion on the rules of procedure and the Bureau's annual accounts. It may assist in developing standard operating procedures describing clinical trials by providing authoritative samples and giving its opinion on the standard operating procedures developed.

2.1.2. Conclusion of contract

(1) The Sponsor shall send the draft institutional and/or Service contract to the following e-mail address: klinikaikutatas@semmelweis.hu.
(2) The Bureau assigns a file number to the draft contract(s) received and, after pre-screening, forwards it to the legal body for its opinion. The departments (legal, economic, medical, and service) comment on the contract on a common platform.
(3) The 4K Bureau carries out the following checks as part of the pre-screening process:
a) fees, based on the budget,
b) allocation of the inspection fee, based on the content of the declaration of acceptance,
c) self-costing data, if relevant,
d) in the case of service fees, their inclusion in the institutional contract or a separate contract, based on the contents of the hosting declaration,
e) the terms of payment (settlement periods and payment deadlines), the method of value retention
f) identification details of the University or trial site.
(4) No contract review process may be initiated before the draft contract is fully prepared (including, in the case of a clinical trial, the availability of an approved trial budget and, in the case of a service contract, the availability of a quotation accepted by the Sponsor). Regardless of the contract with the healthcare entity providing the services, the Institutional and related Service Contracts shall be reviewed and signed in a single procedure.
(5) The Bureau's designated staff member for review will send the draft Institutional and/or Service Contract(s) to kkszerzodesek@semmelweis.hu for legal review.

2.1.2.1. Contract review phase

(1) Mandatory documents to be sent for contract review:
   a) Declaration of Acceptance,
   b) an accepted study budget or a quotation accepted by the contracting authority in the case of a service contract,
   c) deviations from the 20% University contribution and/or the contracting fee may be made on a case-by-case basis, with justification, taking into account the long-term objectives of the University, with the prior approval of the Chancellor, which must be attached to the draft contract,
   d) Draft institutional and/or Service contracts,

(2) Mandatory specific elements of the final draft institutional contract prepared for signature:
   a) the provision that the contract shall enter into force only after all permissions of the competent authorities have been obtained,
   b) the provisions concerning the study plan,
   c) provisions concerning the inclusion of subjects in the study,
   d) provisions concerning trial medicinal products,
   e) the requirements for the Client's provision of equipment for the study: 1) the type and cost value of the equipment, 2) the University's obligation to register the equipment as third-party property due to the extension of insurance, 3) the obligation of the Client to carry out repair and maintenance 4) the University's liability in the event of intentional or negligent conduct,
   f) the number of planned patient enrolments,
   g) planned date of trial completion,
   h) data protection requirements, including
      ha) the data management status of the University,
      hb) data management of the study subjects,
      hc) data management of the Principal Investigator,
      hd) data management of the investigating staff
      he) the conditions for the processing of data for sponsor monitoring,
   i) monitoring, audit and inspection provisions,
   j) ownership of trial results, intellectual property rights,
      Hungarian law grants property and personal rights in respect of intellectual works. Property rights are transferable, but personal rights are not. It is necessary to stipulate that if any results are obtained during the course of the trial, the Sponsor is the beneficial owner of the results. Whether or not the "result" is protected by copyright or industrial property rights, the Institution/researcher/author must transfer the property rights resulting from the protection to the client. If the transfer of the property right is excluded by law (see copyright works), the Institution/researcher/author is obliged to grant the broadest possible right of use,
   k) Hungarian law shall prevail: in the event of conflicting interpretations of bilingual contracts, the Hungarian version shall be taken into account with regard to the provisions of Section 17 (3) of Act CXCVI of 2011 on National Property. The jurisdiction, competence, and jurisdiction of the Hungarian court shall be the jurisdiction of the Hungarian court and arbitration proceedings are prohibited. Only the Chancellor may authorise the application of foreign law or jurisdiction.

l) the contract shall contain a clause stating that the Sponsor shall be obliged to submit to the Bureau all contracts and amendments relating to the study in question to establish the contracting parties' rights and obligations.

la) or in a sealed envelope, indicating their name and the assignment's identification data must be submitted to the Bureau by the Sponsor in order for the rights and obligations of the contracting parties to be established during the ex-post control at the University. The sealed part of the envelope shall bear the signature of the **Principal's** authorized representative in such a way as to provide credible proof of the sealed envelope, subject to verification, if possible, in the presence of the Sponsor. The sealed envelope submitted in this way will be registered by a designated office staff member at the time of receipt and kept in a lockable cupboard without opening. The envelope may only be opened if there is a reason to do so, after prior notification to the **Principal** and, if possible, in the presence of the **Principal.**

lb) or the Sponsor sends the contracts related to the clinical trial in a compressed and encrypted document format to the email address. The password will remain in the Sponsor's possession as long as it is not necessary to consult the related contracts. In this case, the Sponsor will send the password for unlocking the account at the **Principal's** request.

m) the contract must include a transparency declaration pursuant to Article 3 (1) point (1) of Act CXCVI on National Property.

(3) The contract must stipulate that the University will charge a fee for the conclusion of the contract and other services to cover the administrative, legal, and insurance costs incurred. The University becomes entitled to invoice the contracting fee on the day the contract is signed. In the event of the cancellation of the conclusion of the contract, if the legal and economic opinion on the draft contract sent by the Client has been given, the University shall be entitled to invoice the Client sending the draft contract for the costs incurred under the heading of other service/other administrative charges on the day of the notification of withdrawal or cancellation. In this case, the fee for other services is the same as the contracting fee.

(4) The legal manager is responsible for initiating and coordinating the contract review.

(5) The legal manager shall ensure that the departments involved in the review can submit their comments in one procedure on a common platform.

(6) The departments and persons participating in the opinion procedure:

a) JIF for formal, legal, intellectual property, and data protection compliance,

b) Principal Investigator/Service/4K unit representative for professional compliance.

c) the economic organization of the 4K Bureau in terms of economic and financial adequacy.

(7) The time limit for commenting on the contract shall be 5 working days.

(8) The Legal Manager will send the Sponsor a summary of the opinion on the contract and any proposed amendments. In the absence of an amendment proposal, he shall notify the Sponsor or the University Service Provider of the adequacy of the contract(s) and its (their) suitability for signature.

2.1.2.2. Contract signature phasis

(1) The Contract signing is subject to the Sponsor's submission to the Bureau of the documents set out in Annex 8 to these Policy.
(2) Contracts shall be drawn up in the electronic form in one copy or triplicate in the case of a paper contract. If the Principal Investigator possesses an electronic signature, the contract will be in electronic form only. The order of signatures in the case of an institutional contract for a clinical trial:
   a) on the side of the party initiating the trial the contracting party,
   b) legal signature,
   c) financial countersignatory,
   d) Principal Investigator (head of a department in the case of a service contract),
   e) the signature of the head of the Bureau,
   f) financial responsible's signatory.
(3) In the case of electronic signatures, the order of the signatures set out in paragraph 3 may be derogated from on a case-by-case basis at the discretion of the Legal Manager.
(4) The time limit for the complete signature of contracts shall be 10 working days.
(5) The Bureau shall ensure that the signed contracts are forwarded to the Business Office, the Legal Manager, the Principal Investigator/Service Unit Manager, the Finance Directorate, and the Sponsor.
(6) The legal manager shall ensure the forwarding of signed contracts to the Contract Registry.

2.1.3. Conduct of trials

2.1.3.1. Tasks prior to the opening of a trial site

(1) Before opening the trial site, the Principal Investigator checks the following:
   a) existing conditions support the study protocol and the chosen method of data collection at the study site following regulatory and ethical approvals,
   b) anonymity and data protection legislation, as provided for in the permits and study contracts, can be ensured;
   c) the administrative requirements of the study (e-CRF, monitoring) are met.
(2) The Principal Investigator shall be responsible for sending the documentation required for the opinion of the Ethics Committee to the Sponsor.
(3) If the Sponsor wishes to allow patient recruitment within the limits of the legal requirements, the official authorization must also cover this. The official authorization specifies the methods of publication of the call for applications—in the printed press or on the University's website—and the text of the call for applications, which may not be deviated from.
(4) The Principal Investigator shall ensure that the participants in the study have the necessary knowledge for the study.
(5) Prior to the start of the clinical trial, the Principal Investigator shall issue a patient card to the subject for the purpose of the subject's keeping it with them and, if the subject requires emergency care during the trial, to present the information on the patient card to facilitate emergency care or otherwise make it available for the duration of care. The minimum

mandatory content of the patient card is set out in Decree 35/2005 (VIII.26.) of the Ministry of Health. The rules on medical records apply to the management of the medical card.

(6) If the trial requires international registration, the sponsor shall ensure this is done.

(7) A trial medicinal product intended for a clinical trial may only be used after registration with the CRO (Annex 9)

(8) The pharmacist responsible for quality assurance shall declare the storage conditions of the trial site. (Annex 10)

(9) Trial medicinal products intended for and registered for clinical trials and other medicinal products, preparations, and devices used in the trial shall be stored separately, as specified in the notification form.

(10) The opening of a trial site shall be subject to the possession and availability of the appropriate authorizations and signed contracts.

2.1.3.2. Tasks following the opening of a trial site

(1) The trial site must inform the Institutional Ethics Committee and the Bureau of the clinical trial opening by sending the documents per the IKEB's procedures.

(2) The Principal Investigator shall provide the bureau with a scheduled progress report as part of the data reporting for the trial:

a) real-time data on patient selection data (filtered, selected, visits) is provided through the Medsol IT system,

b) the completion of the selection and admission of patients,

c) after completion of the study: the total number of patients to be split into the following categories: filtered, selected, dropped out,

d) The progress of an trial in the following order: official control, audit, and decision to close an trial immediately after receipt of the decision.

(3) The Contractor shall issue a certificate of completion per the timetable in the contract. The Principal Investigator verifies the certificate of completion and, if accepted, sends it to the economic operator responsible for issuing the invoice at kkgazdasagi@semmelweis.hu.

(4) An exception to the centralized economic and financial provision of services is laboratory services, where the Sponsor sends the performance confirmation directly to the contact person of the service provider's department specified in the contract, who arranges for the invoice to be issued and sent to the Sponsor.

2.1.3.3. Tasks immediately before and after the closure of the clinical trial

(1) Within 5 working days of the Sponsor's notification to this effect, the trial site shall notify the bureau of the planned closure of the trial and the planned date of the final visit by sending Annex 11.

(2) The Bureau shall inform all the departments involved in the inspection within 5 working days of becoming aware of the planned closure of the inspection.

(3) After the completion of the trial, the Principal Investigator shall send a summary report on the closure of the trial to the Institutional Ethics Committee.

(4) Based on the study closure report, the study documentation shall be archived by the trial site per the File Management and Electronic Administration Regulations or, if the contract provides for a more extended retention period, under the latter, and then disposed of by a

disposal procedure per the File Management and Electronic Administration Regulations, unless otherwise provided for in the contract. The Principal Investigator shall represent the University at the external audit following the completion of the trial, in which the Bureau may assist.

2.2. Special provisions for specific clinical trials

2.2.1. Rules for non-interventional studies

(1) The procedural rules in section 2.1 shall apply with the exceptions in this section.

(2) Drug trials are authorized by the body specified in the legislation in force, the National Centre for Public Health and Pharmacology (hereinafter: NNGYK), after obtaining the authority statement of the competent Health Sciences Council Clinical Pharmacology Ethics Committee (hereinafter: ETT KFEB). In the case of studies submitted by the Sponsor for authorization under the new procedure according to Regulation No 536/2014/EU of the EUROPEAN PARLIAMENT AND THE COUNCIL, the Hungarian Ethics Committee, which is the competent national authority, shall act as the reviewer.

(3) Non-invasive testing of embryos, gametes, and stem cells is carried out by the Scientific Committee on Human Reproduction of the Health Council (hereinafter referred to as the Committee on Human Reproduction): ETT HRB), subject to the authorization of the National Chief Medical Officer,

(4) In all other cases, it may be carried out with the professional ethics approval of the Scientific and Research Ethics Committee of the Scientific Council for Health (hereinafter: ETT TUKEB).

(5) The Sponsor shall be responsible for sending the documentation required for the licenses to the licensing authority. The Principal Investigator will send a copy of the received authorizations or send them electronically to the Bureau (klinikaikutatas@semmelweis.hu) without delay after receipt.

2.2.2. Investigator Initiated Trial (IIT)

(1) The procedural rules set out in point 2.1 shall apply with the derogations provided for in this paragraph:

a) The investigator shall prepare the protocol.

b) The investigator shall carry out the licensing tasks, including the officially required control and monitoring of the trial.

c) The investigator shall bear the responsibility and costs.

d) Unless otherwise specified in the contract, any patents shall be held by the University/investigator and not by the sponsor.

e) All study costs shall be covered by the University or by an external grant; subject to the approval of the bureau's economic department during the cost calculation, the grant amount may be paid to the initiator of the study.

f) In the conduct of the studies carried out, account shall be taken of the fact that some of the studies are not of the financial interest and that their main benefit is of a scientific nature for the University and the investigator.

2.2.3. Rules relating to clinical trials of medical devices

(1) The procedural rules in section 2.1 shall apply with the exceptions in this section.
(2) REGULATION No 745/2017/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on clinical trials of medicinal products for human use entered into force on 26 May 2022; the Hungarian implementation of which is regulated on the Clinical Trial of Medical Devices by the modified Decree No. 33/2009 of the Ministry for Health (as of 20 October). This Regulation applies to clinical trials of medical devices intended for clinical trial in human subjects conducted in Hungary. Clinical trial of a medical device means the conduct of clinical trials of medical devices intended for clinical trial for human use carried out in Hungary, the scope of which does not extend to trials of IVD devices under the separate legislation on in vitro diagnostic medical devices.
(3) The NNGYK authorizes the study with the assistance of the ETT TUKEB. The Sponsor shall first submit the trial dossier to the ETT TUKEB for its opinion. Once approved, the contract can be concluded, and the official authorization from the NNGYK can be applied for by submitting the signed inspection contract together with the ethical opinion.

3. TASKS OF THE INSTITUTIONAL SCIENTIFIC AND RESEARCH ETHICS COMMITTEE OF THE SEMMELWEIS UNIVERSITY

(1) The Institutional Scientific and Research Ethics Committee of Semmelweis University shall perform the functions of the Institutional Research Ethics Committee (hereinafter: IKEB) concerning medical research and clinical trials at the University and its institutions.
(2) The tasks of the IKEB regarding research falling within the scope of Decree 35/2005 (VIII. 26.) of the Ministry of Health on the clinical trial of trial medicinal products for human use and the application of good clinical practice are the following:
   a) to control and monitor whether the personnel and material conditions are ensured during the conduct of the authorized and ethically approved research and whether the provisions and ethical requirements of the research design are observed, with particular regard to the protection of the research subjects;
   b) the interests of the research participants in the institution are safeguarded by an independent non-participating medical doctor appointed by the Chair of the IKEB from among the members of the IKEB. The designated doctor shall continuously monitor the progress of the research and shall maintain regular contact with the persons involved in the study, providing them with information and professional assistance;
   c) may lodge a complaint with the NNGYK if they consider that the clinical trial is being conducted in a manner not following the terms of the authorization or protocol; they may also communicate their observations to the Principal Investigator and the head of the service provider and send their observations to the ETT KFEB, which will, where justified, initiate an inspection by the NNGYK;

(3) Simultaneously with the report sent to the sponsor according to Article 41 of Regulation No. 536/2014/EU of the European Parliament and the Council; the investigator is to immediately notify the IKEB of any serious adverse event and send a detailed report to the IKEB; except for those not considered as immediately reportable according to the protocol or the brochure for investigators monitored by the IKEB. In the notification and the report, the subject is identified by its unique code only.

4. EMPOWERING PROVISION

The Senate authorizes the Rector, the Chancellor, and the President of the Clinical Centre to provide for the internal distribution of the University budget for the revenue from clinical research studies by employing a Rector-Chancellor-Clinical Centre Presidential Instruction.

5. ANNEXES

Annexes are available from the repository (except Annexes 6 and 12)

Annex 1/A Application for pre-admission (registration) to conduct a clinical trial - available from the repository
Annex 1/B: Request for pre-admission (registration) to conduct part of a clinical trial at an external site - available from the repository
Annex 2 Principal investigator's declaration on the staffing and facilities of the trial - available from the repository
Annex 3 Notification of the start of a clinical trial of a medicinal product to the Chief University Pharmacist - available from the Pharmacopoeia
Annex 4: Designation of pharmacist responsible for quality assurance and pharmacist roles - available from the form repository
Annex 5a: Excluded expenses declaration - available from the repository
Annex 5b: Excluded expenses costing - available from the repository
Annex 6: Clinical trial contracting and service fees
Annex 7: Principal investigator's declaration of fees for clinical trials and reporting obligations in MedSol - available from the repository
Annex 8: Semmelweis University checklist for clinical trials - available from the repository
Annex 9: Handover report for the delivery of clinical trial products - available from the repository
Annex 10: Pharmacist's declaration of responsibility for quality assurance - available from the repository
Annex 11 : Notification of the end of the clinical trial - available from the repository
Annex 12: Audit trail

Annex 6 - Contract fees

Title	**Amount of contracting fee**
Phase I, II, and III trial (without framework contract)	1100 Euro + VAT
Phase IV trial, non-interventional inspection	500 Euro + VAT
examination with medical devices	1100 Euro + VAT
investigator-initiated trial	without fee
service contracts (laboratory, pathology)	800 Euro + VAT
externally commissioned study - on request by industry, foundation, company	500 Euro + VAT
framework contract (3 years)	4000 Euro + VAT
individual contracts for new framework contract per study (valid on payment of new framework contract fee)	550 Euro + VAT
existing individual contracts under a framework contract not covered by the above fee of	800 Euro + VAT
cooperation contract	without fee
contract amendment*	25% of the original contract fee

Name of service	**Service fee**
study closure fee + archiving fee	500 Euro + VAT
emergency fee	100% surcharge (25 days)
IKEB fee	250 Euro + VAT

* for modification of study plan requiring official authorization/budget modification

Annex 12 Audit trails - Clinical research study

Process steps	**Preparation steps**	**Responsibility levels**					**Document resulting from the process**
		Responsible party	**Verification**	**Mode of verification**	**Approval**	**Mode of approval**	
Preparation of the research or study	preliminary verbal agreement between the initiator of the trial and the trial site on the content, details, content, and form of the contract, including the signatories of the contract according to the terms of engagement	head of the unit, Principal Investigator, economics head of unit, Bureau	Bureau economic unit of the Bureau legal manager	consultation	Head of the department, Principal Investigator	Electronic feedback	Contract of non-disclosure Declaration of acceptance Kick-off meeting Annexes to the Clinical Research and Trial Policy (See Annex 8.)
Preparation of the contracting documentation	draft and its preparation	initiator of the test	legal manager	consultation	legal manager	electronic feedback	electronic copy of the draft contract
Registration of contract	use of registration system	legal manager	n/a	n/a	n/a	n/a	registered contract
Filing	use of document management system	participating departments	n/a	n/a	n/a	n/a	filed documents
Pre-signature check	checking the completeness of the contract and its annexes	Bureau	member of staff responsible for checks	reconciliation based on the four eyes principle	n/a	n/a	
Signing of the contract	in the order laid down in the rules	legal manager	signatory	consultation	signatory	signature	signed contract
Execution of contract	n/a	Principal Investigator	initiator of the trial, external auditor	reconciliation	by contract	by contract	document closing the trial
Settlement	by contract	Bureau economic department	head of economic department	reconciliation, approval	Director of finance	signature of the Director of finance	invoice to be paid
Filing, archiving	Per the file management regulations and the contract	pharmaceutical examinations officer Principal Investigator	Head of Bureau	reconciliation, approval	Principal Investigator	File management according to the regulations	filed/archived copy

Process steps	Preparation steps	Responsibility levels					Document resulting from the process
		Responsible party	Verification	Mode of verification	Approval	Mode of approval	
Registration and storage of related contracts		Bureau	Head of Bureau	reconciliation	n/a	under these Policy	filed documents