AZIENDA OSPEDALIERA UNIVERSITARIA MEYER IRCCS

Determina del Dirigente n. 423 del 06-11-2024

Proposta n. 1158 del 2024

Oggetto: STUDIO NON-PROFIT DENOMINATO “STUDIO OSSERVAZIONALE RETROSPETTIVO E PROSPETTICO SULLE UVEITI CRONICHE NON INFETTIVE IN ETÀ PEDIATRICA”, CODICE PROT. RCHILDUV - APPROVAZIONE SCHEMA ACCORDO CON LA KOCAELI UNIVERSITY

Dirigente: FERRIGNO MARIANGELA

Struttura Dirigente: CONVENZIONI E AFFARI GENERALI

AZIENDA OSPEDALIERA UNIVERSITARIA MEYER I.R.C.C.S.
Istituto di Ricovero e Cura a Carattere Scientifico
Viale Pieraccini, 24 - 50139 FIRENZE
C.F. P.Iva 02175680483

DISPOSIZIONE DIRIGENZIALE

Oggetto	Studio osservazionale
Contenuto	STUDIO NON-PROFIT DENOMINATO "STUDIO OSSERVAZIONALE RETROSPETTIVO E PROSPETTICO SULLE UVEITI CRONICHE NON INFETTIVE IN ETÀ PEDIATRICA", CODICE PROT. RCHILDUV - APPROVAZIONE SCHEMA ACCORDO CON LA KOCAELI UNIVERSITY

Struttura	CONVENZIONI E AFFARI GENERALI
Dirigente Proponente	MARIANGELA FERRIGNO
Responsabile del procedimento	ALESSIO FABBIANO
Immediatamente Esecutiva	SI

Conti Economici			
Spesa prevista	**Conto Economico**	**Codice Conto**	**Anno Bilancio**

Estremi relativi ai principali documenti contenuti nel fascicolo		
Allegato	**N° di pag.**	**Oggetto**
1	8	Schema accordo

"documento firmato digitalmente"

IL RESPONSABILE S.O.S.D. CONVENZIONI E AFFARI GENERALI
(Dr.ssa Mariangela Ferrigno)

Richiamati:

- il Decreto Legislativo n. 502 del 30.12.1992 e successive modifiche ed integrazioni, recante "*Riordino della disciplina in materia sanitaria, a norma dell'art.1 della legge 23 ottobre 1992, n. 421*";
- il Decreto Legge n. 75 del 22 .06.2023, così come modificato dalla Legge n. 112 del 10.08.2023, recante "*Disposizioni urgenti in materia di organizzazione delle pubbliche amministrazioni, di agricoltura, di sport, di lavoro e per l'organizzazione del Giubileo della Chiesa cattolica per l'anno 2025"* ed in particolare l'art. 8-bis, contenente "*Disposizioni in materia di dirigenza sanitaria, amministrativa, professionale e tecnica del Servizio sanitario nazionale*";
- la Legge Regionale Toscana n. 40 del 24.02.2005 e successive modifiche ed integrazioni, di "*Disciplina del Servizio Sanitario Regionale*";
- la Legge Regionale Toscana n. 12 del 16.03.2023 e successive modifiche ed integrazioni "*Disposizioni in materia di istituti di ricovero e cura a carattere scientifico pubblici. Modifiche alla l.r. 40/2005*" con la quale si è proceduto alla disciplina degli istituti di ricovero e cura a carattere scientifico di diritto pubblico ed in particolare l'art. 13 con il quale sono state dettate le "*Disposizioni transitorie per il passaggio da Azienda Ospedaliero Universitaria Meyer ad Azienda Ospedaliera Universitaria Meyer IRCCS…*";

Dato atto che**:**

- con deliberazione del Direttore Generale n. 443 del 23.09.2022 l'A.O.U. Meyer ha disposto la presa d'atto del Decreto del Ministero della Salute del 02.08.2022, pubblicato nella Gazzetta Ufficiale n. 200 del 27.08.2022, con cui l'Azienda Ospedaliero Universitaria Meyer è stata riconosciuta Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), per la disciplina di pediatria;
- con deliberazione del Direttore Generale n. 286 del 09.05.2024 è stato adottato ai sensi dell'art. 50 novies comma 3 della L.R.T. 40/2005 e s.m.i., a seguito dei pareri favorevoli della Giunta Regionale e del Ministero della Salute, il Regolamento di organizzazione e funzionamento dell'AOU Meyer IRCCS;
- con deliberazione del Direttore Generale n. 296 del 10.05.2024 è stato approvato il nuovo assetto organizzativo dell'AOU Meyer IRCCS il cui organigramma ha decorrenza dal 01.07.2024;

Richiamata la deliberazione del Direttore Generale n. 551 del 02.10.2024 con la quale si è provveduto, a seguito delle azioni di sistematizzazione dell'organizzazione aziendale, alla declaratoria delle funzioni attribuite e/o delegate dal Direttore Generale ai singoli Dirigenti Responsabili delle Strutture Aziendali, anche ai fini dell'individuazione delle competenze nell'adozione degli atti amministrativi;

Ricordato che con disposizione dirigenziale n. 63 del 16.02.2022 questa Azienda, previo parere favorevole del Comitato Etico Pediatrico della Regione Toscana in data 08.02.2022, ha autorizzato la conduzione dello studio osservazionale non-profit denominato "Studio osservazionale retrospettivo e prospettico sulle Uveiti Croniche non infettive in età pediatrica", codice prot. RChildUV, di cui è responsabile il Prof. Gabriele Simonini;

Atteso che lo studio si configura come multicentrico e internazionale e che l'AOU Meyer IRCCS, oltre a essere centro di reclutamento, è anche il promotore e che, pertanto, con i vari centri esteri e italiani che

aderiscono allo studio si rende necessario sottoscrivere uno schema di accordo per la conduzione dello studio medesimo;

Considerato che la Kocaeli University, una università pubblica con sede in Turchia, è tra i centri che aderiscono allo studio di cui trattasi;

Verificato che dal presente atto non derivano oneri economici a carico dell'AOU Meyer IRCCS;

Ritenuto, pertanto, di stipulare lo schema di accordo con la Kocaeli University per la disciplina delle condizioni normative ed operative dello studio in oggetto secondo lo schema che, allegato N. 1 al presente atto, ne forma parte integrante e sostanziale;

Considerato che il Responsabile del Procedimento, individuato ai sensi della Legge n. 241/1990 nella persona del Dr. Alessio Fabbiano sottoscrivendo l'atto attesta che lo stesso, a seguito dell'istruttoria effettuata, nella forma e nella sostanza è legittimo;

DISPONE

Per quanto esposto in narrativa che espressamente si richiama,

1. Di approvare lo schema di accordo per la conduzione dello studio in oggetto da stipulare con la Kocaeli University che, allegato N. 1 al presente provvedimento, ne forma parte integrante e sostanziale.

2. Di precisare che dal presente atto non derivano oneri economici a carico dell'AOU Meyer IRCCS.

3. Di trasmettere il presente atto al Collegio Sindacale ai sensi dell'art. 42, comma 2, della L.R.T. n. 40/2005 contemporaneamente all'inoltro all'albo di pubblicità degli atti di questa A.O.U. Meyer I.R.C.C.S.

IL RESPONSABILE S.O.S.D. CONVENZIONI E AFFARI GENERALI
(Dr.ssa Mariangela Ferrigno)

DATA TRANSFER AGREEMENT

by and between

Kocaeli University, whose registred office is located at Kocaeli University, Kabaoglu, Baki Komsuoglu Boulevard No: 515, Umuttepe, 41001 İzmit/Kocaeli Turkey, represented by Dr. Hafize Emine Sönmez, head of the Division of Pediatric Rheumatology

(hereinafter referred to as "**Kocaeli University**")

and

Meyer Children's Hospital IRCCS, whose registred office is located at Viale Gaetano Pieraccini 24, 50139 Firenze, Italy, tax code/VAT number 02175680483, represented by its Contracts and General Affairs Department Manager, delegated to sign the present deed by Managing Director with resolution n. 551 of 2 October 2024

(hereinafter referred to as **"AOU Meyer IRCCS"***)*

Kocaeli University and AOU Meyer IRCCS are hereinafter also referred to, individually, as the "**Party**" and, jointly, as the "**Parties**".

WHEREAS

A) AOU Meyer IRCCS is the sponsor of the not-for-profit, observational study entitled "*Studio osservazionale retrospettivo e prospettico sulle Uveiti Croniche non infettive in età pediatrica*" ("Observational study about non-infectious chronic childhood uveitis") (hereinafter referred to as "**Study**"), protocol code, RChildUV, an observational, retrospective, multicentre study whose Principal Investigator is Prof. Gabriele Simonini, head of the Rheumatology Unit at AOU Meyer IRCCS, aimed to evaluate (i) the response to treatment in patients with non-infectious uveitis who failed the treatment with Adalimumab, (ii) if there are differences between the change of class of drugs (from an anti-TNF to another biologici called SWAP) or change of drug in the same class of drugs (to change different anti-TNF called SWITCH).

B) The Study is an official project that is not funded by any organization. Among its objectives, the Study is designed to create a collaborative database/registry (the "**Database**") to: (i) analyse and assess the characteristics of non-infectious uveitis in children; (ii) identify the most efficacious treatment for these patients; (iii) allow analyses that lead to a better comprension of this disease and its treatment; and (iv) establish an international cooperation.

C) The Database is made up of a main dataset for analysis out of different datasets collected by several partners of the Study. The Database is hosted at AOU Meyer IRCCS and managed

through a costumized RedCap tool andvia a secure network with encrypted transfer protocols and access credentials are provided/administered/revoked and controlled by the data manager and/or the clinical study coordinator. In its role as administrator of the Database, AOU Meyer IRCCS ensures the security, integrity, and availability of services and data, in accordance with EU applicable law on data protection and management, including the General Data Protection Regulation (Regulation (EU) 2016/679 – "**GDPR**")

D) Kocaeli University, as a trial site ("**Study Site**") within the Study, is willing to provide, through its Investigator Sheila Angeles-Han (the "**Study Site Investigator**"), PI at the Rheumatology division at Kocaeli University, patient-related data ("**Data**") relevant for the above-mentioned Study objectives and in compliance with the study protocol (as described in Annex 2 hereto), subject to the terms and conditions of this Data Sharing Agreement (the "**Agreement**"). Specifically, data shared is specified in Annex 1 ("Data processing particulars") hereto.

E) Data will be sent from Kocaeli University to AOU Meyer IRCCS as pseudonymised (de-identified) data and the Study Site will be responsible for keeping each patient's code associated with Data entered into the Database.

F) Data will be stored in the Database for a period of 25 years.

Now therefore, on the basis of the foregoing, the Parties agree to the following terms and conditions:

1) Data of patients of Kocaeli University, provided to AOU Meyer IRCCS under the responsibility of the Principal Investigator, will be inserted into the Database. Data is governed by RedCap through its Principal Investigator, which, together with Dr Ilaria Maccora as Subinvestigator/Study coordinator, shall treat the Data confidentially and not distribute them to third parties, except that AOU Meyer IRCCS shall be allowed to transfer extracts of datasets to the partners contributing data within the Study and upon consent of the partner to which Data belongs.

2) Before collecting Data, Dr. Hafize Emine Sönmez from Kocaeli University shall obtain written informed consent from patients involved in the Study, in accordance with GDPR provisions and applicable local laws and regulations regulating the use and processing of personal data.

3) The Database and all Study documentation will be held for 10 years after completion of the Project in accordance with the Study protocol. In the event Dr. Hafize Emine Sönmez from Kocaeli University should decide to withdraw from the Study and withhold its consent to the use of Data, he shall have a right to terminate this Agreement, upon prior written notice to AOU Meyer IRCCS. AOU Meyer IRCCS will then return and not further use the Data belonging to Kocaeli University, being it understood that Kocaeli University's Data shall be cancelled from the Database and not used for further Study-related activities. Without

prejudice to the foregoing, the Parties agree that the previous or the ongoing use of Data at the time of said written notice shall not preclude the Study activities related to the previous or ongoing activities which include the use of Data referred to in the communication of termination. Data already used and processed in the framework of the Study before the communication of termination cannot be the subject of disputes by the Study Site.

4) Data provided by Dr. Hafize Emine Sönmez from Kocaeli University shall be inserted onto the Database as pseudonymised data and Dr. Hafize Emine Sönmez from Kocaeli University shall guarantee that Data is provided in compliance with applicable national/local data protection laws. It is understood that AOU Meyer IRCCS shall not have access to any identifiable information, which shall be kept safely and de-idetified by [Dr. Hafize Emine Sönmez from Kocaeli University, in compliance with national/local data protection laws. Dr. Hafize Emine Sönmez from Kocaeli University shall safely keep a list of the codes corresponding to each patient. This list is for Kocaeli University's own internal use and it shall never be sent to AOU Meyer IRCCS, the Principal Investigator or the Study partners.

5) Each Party is independent controller in processing Data, in accordance with Article 4, par. 7 of GDPR.

6) If AOU Meyer IRCCS discovers a breach of personal data involving the Database, Dr. Hafize Emine Sönmez from Kocaeli University shall be informed within 36 hours from the breach as duly verified.

7) Parties agree that intellectual property (IP) generated in the course of the Study activities and arising from Data provided by Dr. Hafize Emine Sönmez from Kocaeli University shall be identified and settled in specific IP agreements between the Parties and, as the case may be, other partners of the Study. In the event any IP arising from the Study being it solely the result of the Study work, then AOU Meyer IRCCS will be tasked with leading the IP diligence and protection process. This will involve, where necessary, interaction with other Study partners to ensure IP is appropriately protected and shared through specific IP agreements.

8) Parties agree that this Agreement will become valid upon the date it is signed by the last Party ("**Effective Date**"), and will remain in effect until the Study is closed at the Study Site.

9) Either Party may terminate the Agreement should the other Party fail to comply with one or more of the essential obligations defined in this Agreement and fails to remedy within 15 (fifteen) days from receiving notification of such violation by the other Party or to provide proof of the impediment resulting from a case of "force majeure". Notification shall be communicated by registered letter with acknowledgement of receipt or certified E-mail.

10) Each Party may rescind this Agreement at any time for justified reasons to be given by written notice by registered letter with acknowledgement of receipt or certified E-mail. Rescission will take place after 30 (thirty) days from formal notification. Nevertheless, the rescinding Party shall honour its commitments hereof until rescission is effective.

11) In the event of termination or rescission, AOU Meyer IRCCS shall not further use Data of Kocaeli University, being it understood that Data will be cancelled from the Database and not used any more for future activities related to the Study.

12) Without prejudice to the foregoing, the Parties agree that the previous or the ongoing use of Data at the time of written notice for termination or rescission shall not preclude the previous or ongoing Study activities which include the use of Data referred to in the communication of termination rescission. Data already used and processed in the framework of the Study before the communication of termination or rescission cannot be the subject of disputes by the Study Site.

13) Any dispute relating to, arising from or, in any event, connected to this Agreement, its construction, performance or termination shall be firstly settled amicably through negotiations; if no settlement is amicably reached, the Parties agree to the exclusive jurisdiction of the courts of the defendant party's country and this Agreement shall therefore be governed and construed in accordance with the laws of the defendant party's country.

[*Signature page follows*]

Read, signed and approved by the Parties.

Kocali University	**AOU Meyer IRCCS**
Kocaeli, Turkey Date: 06.11.2024	Florence, Date: _____
_____	_____
Dr. Hafize Emine Sönmez Head of the Division of Pediatric Rheumatology at Kocaeli University	Dr Mariangela Ferrigno Contracts and General Affairs Department Manager

ANNEX 1

DATA PROCESSING PARTICULARS

The subject matter of the processing	Childhood non-infectious uveitis. Observational study entitled "Studio osservazionale retrospettivo e prospettico sulle Uveiti Croniche non infettive in età pediatrica" (*Observational study about non-infectious chronic childhood uveitis*)
Duration of the processing	25 years
Method of processing	Pseudonymisation
Nature of data to be processed	Demographic, clinical and laboratory data
Purpose of the processing	To evaluate the response to treatment in patients with childhood non-infectious uveitis who failed Adalimumab
The type of Personal Data being processed	Demographic (Age, sex, ethnicity, race, familiarity, associated disease), clinical (subtype of disease, subtype of uveitis, signs and symptoms associated, complications, visual acuity), laboratory data (inflammatory index, autoantibody, HLA B27 and HLA B51), treatment performed, and response to treatment.
The categories of data subjects	Patients affected by non-infectious uveitis
Permitted Recipient	AOU Meyer IRCCS
Permitted Provider	Kocaeli University
Method of data storage and security measures	Numerical code. The data will be stored in a secure RedCap tool on secure servers.

Annex 2

Study Description

Summary

An aggressive and tailored treatment is crucial in childhood chronic non-infectious uveitis (cNIU) in order to prevent severe sight threatening complications. The use of Adalimumab (ADA), a humanized antibody against Tumor necrosis factors α (anti-TNFα), has dramatically changed the prognosis of these patients; however up to the 25-30% patients failed to achieve or maintain long-lasting remission. At the moment there is no agreement among experts about which should be the next step in patients who failed ADA (to switch to another anti-TNF or to swap to another class of biologics). Current evidence comes mainly from small cohort study. Thus, it is vital to implement the collaboration across European and North American centres in order to collect data about the current management of Adalimumab non-responders cNIU, in larger cohort that include different clinical practice. Thus, the purpose of this international multicentre study is to evaluate in a large cohort which is the best therapeutic approach (to switch or to swap) in Adalimumab non-responder children with chronic non-infectious uveitis. Additionally, we aim to highlight if there are any clinical predictors of response to each specific drug.

This would be a non-interventional, retrospective study involving children with a diagnosis of chronic non-infectious uveitis with an onset before 16 years of age and treated before 18 years old. Patients would be included if they have failed at least one anti-TNF mainly adalimumab.

Demographic, clinical, laboratory and ophthalmological data will be collected in a customized electronic database on RedCap. The main measures of outcomes considered will be the achievement of inactive disease on treatment according to the MWIGUC definition, the time to achieve disease remission on treatment, rate of flare on treatment and flare off treatment.

For each patient, the following information will be collected: demographic data (gender, ethnicity, age at onset of the disease, and age when the drugs on studies were started), patient medical history (personal and familial history), characteristics of the disease (type of disease: idiopathic, JIA-associated uveitis,Behçet; laterality and anatomical site of uveitis), laboratory data at onset and at the moment of drug initiation (positivity for ANA, ANCA, HLA B27, HLA B51, erythro-sedimentation rate (ESR) expressed in mm/h, C-reactive protein (CRP) expressed in mg/dl), previous systemic treatment performed. We will collect information about the dose of the drug in study, the route of administration, the frequency and concomitant treatment (topical corticosteroid drops, administration of systemic corticosteroids, and concomitant DMARDs).

To evaluate the efficacy of treatment performed, the medical records of patients with CCU will be retrieved to collect, at the time of the drugs starting and then every 3 ± 1 months, the following data: anterior chamber cells and flare grading according to SUN, bio score, the presence of active retinal vasculitis, visual acuity reported in logMAR, and when this scale will not be available the appropriate conversion will be performed according to Schulze-Bonsel et al., the presence and number of complications, type of complications as cataract, increased

intraocular pressure (>21 mmHg), ocular hypotony (<5 mmHg), optic disc swelling, macular edema or thickness (defined as increased thickness in the macula on OCT scan), posterior synechiae, epiretinal membrane, band keratopathy, retinal vasculitis, multifocal choroiditis, choroidal neovascular membrane, and surgical treatment. We will collect also safety data in terms of number of adverse events (AEs) and any severe AEs with their description. A serious AE will be defined as an event secondary to a drug exposition that leads to death, life-threatening events, events conducive to prolonging hospitalization, enduring or significant disability/ incapacity, or medical events needing medical or surgical intervention to prevent a serious outcome or congenital anomaly/birth defects.

Main Outcomes Measures

The main outcome was the achievement of ocular remission on treatment defined as the inactive disease for ≥6 consecutive months, receiving systemic therapy.

The inactive disease was defined as less than or equal to 0.5+ anterior chamber cells, less than or equal to 0.5+BIO score/National Eye Institute (NEI), vitreous haze scale, no active retinal or choroidal lesions, after discontinued any steroid treatment, including topical treatment, and no declaration of treatment failure due to intolerability or safety concerns.

Treatment failure was defined as failure to reduce eye drops to 2 drops/day by or at the 12-week visit, the development of new complications, or intolerance/nonadherence treatment

To compare their potential long-lasting effect on maintaining remission, primary outcomes once the remission on medication was achieved were as follows: (a) the rate of patients who relapse after disease remission and (b) the time to the first relapse on treatment.

Additional secondary outcomes, once the drug in the study was started were as follows: (a) time to achieve remission, (b) the rate of relapse when the drug is discontinued, and (c) the time to the first relapse after the drug in the study was discontinued and (d) the visual acuity stratified as normal if LogMAR was <0.3, impaired if 0.4–1, and blindness if >1.

Statistical analyses will be performed with SPSS for Windows. Continuous variables will be reported as median and range, while categorical variables as frequencies and percentages. Mann– Whitney U-test, Wilcoxon's signed rank test for paired samples, chi-square tests, and Fisher's exact test, when appropriate, will be used to compare data. The following data, entered into a customized uveitis database, will be considered as covariates for the survival curves, age at diagnosis/age at the initiation of therapies in studies, gender, associated autoimmune disease, disease duration, uveitis duration, the interval between the uveitis onset and the initiation of the drug in the study, concomitant medications, previous corticosteroid use, previous disease modifying anti-rheumatic drug treatment duration. To identify the predictors of outcome, Kaplan–Meier curves will be constructed, each one at the mean of the covariates reported above. Cox regression and multivariate analyses will be additionally performed. A $p < 0.05$ was considered significative