Research Plan

DO MEASUREMENTS OF SERUM FERRITIN AND TSAT AS PERFORMED IN CLINICAL PRACTICE ACCURATELY GUIDE IV IRON THERAPY WITH FERRUM CARBOXYMALTOSE IN HEMODIALYSIS-PATIENTS?

Single center observational study

Short title: Iron status evaluation in hemodialysis patients on maintenance ferrum carboxymaltose dosing.

Type of Research Project:	Research project in which biological material is sampled from humans and/or health-related personal data is collected
Risk Categorisation:	Category A
Project Identifier:	N/A
Project Leader:	PD Dr. med. Andreas Kistler Klinik für Innere Medizin, Abteilung Nephrologie Kantonsspital Frauenfeld Spital Thurgau AG
Health condition / problem	Anemia in dialysis patients
Project Duration	18 months
Project Plan Version and Date:	Version 1.0; 24.02.2017

SIGNATURE PAGE

Project number	N/A
Project Title	Do measurements of serum ferritin and TSAT as performed in clinical practice accurately guide iv-iron therapy with FCM in HD-Patients?

The project leader PD Dr. med. Andreas Kistler has approved the research plan version 1.0 (24.02.2017), and confirms hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, the Principles of Good Clinical Practice (GCP) and the local legally applicable requirements.

Project Leader:

PD Dr. med. Andreas D. Kistler

Frankfurt, 27.2.17 _____

Place/Date Signature

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SYNOPSIS (SUMMARY)

Projektleiter	PD. Dr. med. A. Kistler
Projekttitel	Wird die intravenöse Eisentherapie mit Ferrumcarboxymaltose bei Hämodialyse-Patienten durch die Bestimmung von Serumferritin und Transferrinsättigung im Rahmen der klinischen Routine korrekt gesteuert?
Kurztitel	Evaluation des Eisenstatus bei Hämodialysepatienten unter Erhaltungstherapie mit intravenösem Eisen
Projektversion und Datum	V1.0; 24.02.2017
Risikogruppe:	Kategorie A
Art der Forschung:	Forschungsprojekt mit Sammlung und Auswertung von biologischem Material. Die Blutentnahmen werden nicht anonymisiert und im Rahmen der klinischen Routine stattfinden. Die Daten für die Auswertung werden anschliessend anonymisiert.
Design der Studie	Beobachtungsstudie an einem klinischen Institut.
Hintergrund	Die meisten Patienten mit dialysepflichtiger Niereninsuffizienz leiden an einer renalen Anämie. Zu deren entstehen trägt oft nebst anderen Ursachen ein Eisenmangel bei. Die Gabe hoher Dosen rekombinanten Erythropoietins (rhEPO) wurde mit unerwünschten Wirkungen in Zusammenhang gebracht. Daher werden heute in der Behandlung der renalen Anämie primär hohe Eisenspeicher angestrebt. Eisen wird bei Hämodialyse (HD)-Patienten in der Regel intravenös in regelmässigen Abständen verabreicht und die Dosierung anhand laborchemischer Parameter (Ferritin und Transferrinsättigung) angepasst. Die Bestimmung dieser Parameter erfolgt meist nicht koordiniert mit dem Zeitpunkt der letzten Eisengabe. In einer kleinen Studie konnte bei nicht dialysepflichtigen Patienten gezeigt werden, dass höhere Dosen von intravenös verabreichtem Eisen zu einem transienten Anstieg von Ferritin, totalem Serumeisen und Transferrinsättigung führen, welche jedoch nicht den aktuellen Eisenspeicher reflektieren. Ob es bei Dialysepatienten nach Verabreichung üblicher Eisendosen auch zu einem transienten Anstieg dieser Parameter kommt und entsprechend ein Mindestabstand zwischen der letzten Eisengabe und der Bestimmung dieser Parameter eingehalten werden sollte, wurde bisher nicht untersucht.
Zielsetzung:	Evaluation einer möglichen signifikanten transienten Änderungen der laboranalytischen Eisenparameter Ferritin und Transferrinsättigung nach niedrig dosierter i.v.-Eisgengabe bei HD-Patienten.
Endpunkte:	Primärer Endpunkt: Anstieg von Serumferritin und Transferrinsättigung 2 Tage nach einer i.v.-Gabe von 100mg bzw. 200mg Eisen gegenüber unmittelbar vor deren Gabe. Sekundäre Endpunkte: Verlauf von Ferritin und Transferrinsättigung über 4 Wochen nach einer Eisengabe; Verlauf von Hämoglobin über diese Zeit; Anstieg der Konzentration des löslichen Transferrinrezeptors.

Einschluss/Ausschlusskriterien:	Einschlusskriterien: a) >18 Jahre und gegebene Handlungsfähigkeit zur Einwilligung in die Studie b) Dialysepflichtige Niereninsuffizienz mit Hämodialyse bzw. Hämodiafiltration seit mindestens drei Monaten. c) Dreimal wöchentliche Hämodialysebehandlungen d) Stabiles Dosierungsschema der Ferinject-Injektionen seit mindestens zwei Monaten in einer Dosis von 100mg oder 200mg alle 4 Wochen. e) Stabile rhEPO-Dosierungen (=Dosierunganpassung von ≤25%) in den letzten drei Monaten f) Stabiles Hämoglobin in den letzten drei Monaten, definiert wie folgt: <125gl/l und >95g/l; Differenz von <15g/l zwischen dem höchsten und tiefsten prädialytisch gemessenen Wert. Ausschlusskriterien: a) Diagnostizierter oder vermuteter signifikanter Blutverlust in den letzten drei Monaten b) Signifikant erhöhte Entzündungsparametern (CRP >20mg/l) c) Hospitalisierung im letzten Monat d) Nachweis einer bakteriellen Infektion in den letzten zwei Monaten.
Untersuchungen und Interventionen	Im Rahmen der routinemässigen 4-wöchentlichen FCM-Injektionen werden unmittelbar vor einer Injektion 2, 4, 7, 14, 21 und 28 Tage nach einer Injektion die folgenden Parameter bestimmt: Ferritin, Transferrinsättigung, Hämatogramm und CRP. Zusätzlich erfolgt vor FCM-Gabe sowie 2 und 28 Tage danach eine Bestimmung der Retikulozytenzahl und des löslichen Transferrinrezeptors. Alle Blutprodukte werden sofort analysiert. Restliches Probenmaterial wird bei –80° bis 2 Jahre nach Abschluss der Studie asserviert.
Anzahl Patienten:	Eingeschlossen werden 30-40 Patienten.
Zeitplan:	Patienteneinschluss und Durchführung der Messungen: • 1. Juni 2017 bis 31. Dezember 2017 (je nach Rekrutierung ggf. Ausdehnung der Rekrutierungsperiode auf bis zu 18 Monate) Auswertung der Daten: • 6-12 Monate Schreiben des Manuskripts, Revisionen und ggf. Nachmessungen in gefrorenen Proben: • 6-12 Monate
Klinische Zentren	Single center Studie der Spital Thurgau AG, Nephrologie / Dialysestation mit den Standorten Frauenfeld und Münsterlingen.
Statistik:	Unterschiede zwischen den gemessen Werte von Ferritin und Transferrinsättigung vor bzw. 2 Tage nach FCM-Gabe werden mit einem Zweistichproben-t-test verglichen; Patienten, welche 100 bzw. 200mg FCM erhalten, werden gesondert analysiert. Werte, welche nicht einer Normalverteilung entsprechen, werden logarithmisch transformiert.
Andere methodologische Aspekte:	N/A
Risikoevaluation:	Da es sich um eine Beobachtungsstudie handelt, besteht nur ein minimales Risiko, namentlich die Entnahme kleiner zusätzlicher Mengen an Blut. Da die Blutentnahmen im Rahmen der routinemässigen Dialysebehandlungen erfolgen, ist keine zusätzliche Punktion notwendig. Es werden insgesamt ca. 60ml Blut entnommen.

ABBREVIATIONS

DoH	Declaration of Helsinki
EC	Ethics Committee
EGEP	Essentials of Good Epidemiological Practice
FOPH	Federal Office for Public Health
HRA	Federal Act on Research involving Human Beings (Human Research Act, HRA)
HRO	Ordinance on Human Research with the Exception of Clinical Trials (Human Research Ordinance, HRO)
ID	Identification
IIT	Investigator-initiated Trial
SE	Serious event
STROBE	Strengthening the reporting of observational studies in epidemiology
ESA	Erythropoiesis stimulating agents
TSAT	Transferrin saturation
FCM	Ferric carboxymaltose

SCHEDULE OF ASSESSMENTS (FLOW OF RESEARCH PROJECT)

Project Periods	Visits								
Dialysis	x	x	x	x	x	x	x	x	x
Time	within 2 months before baseline visit	-1 week	baseline (Monday or Tuesday)	+2 days	+4 days	+7 days	+14 days	+21 days	+28 days
Participant Information and Informed Consent	x								
Demographics	x								
Medical History	x								
In- /Exclusion Criteria	x	x							
FCM Injection (100mg/200mg)			x						x
Blood sampling:			x	x	x	x	x	x	x
Serumferritin			x	x	x	x	x	x	x
TSAT			x	x	x	x	x	x	x
Hematogram			x	x	x	x	x	x	x
CRP			x	x	x	x	x	x	x
Soluble transferrin receptor			x	x					x
Reticulocyte count			x	x					x
Assessment of Adverse Events			x	x	x	x	x	x	x

1. ADMINISTRATIVE STRUCTURE

Sponsor, Project Leader and Coordinating researcher	Name: PD Dr. med. A. Kistler Address: Kantonsspital Frauenfeld Pfaffenholzstrasse 4, Postfach 8501 Frauenfeld Email: andreas.kistler@stgag.ch Phone: 052 723 76 43 Fax: 052 723 75 90
Project site(s) and responsible researcher:	Institution: Spital Thurgau AG (STGAG), Kantonsspital Frauenfeld, Klinik für Innere Medizin, Abteilung Nephrologie. The project will be conducted at the two dialysis units in Frauenfeld and Münsterlingen. Responsible researchers see below.
Key Persons involved in research project:	Name: PD Dr. med. A. Kistler Address: Kantonsspital Frauenfeld Pfaffenholzstrasse 4, Postfach 8501 Frauenfeld Name: Matthias Diebold Address: Kantonsspital Frauenfeld Pfaffenholzstrasse 4, Postfach 8501 Frauenfeld
Other personnel	
Study nurse:	Name: Daniela Schmocker Address: Kantonsspital Frauenfeld Pfaffenholzstrasse 4, Postfach 8501 Frauenfeld Email: daniela.schmocker@stgag.ch Phone: 052 723 76 95 Fax: 052 723 75 90
Subinvestigators:	All physicians of the nephrology unit may be involved as subinvestigators and will be named on a delegation log.

2. ETHICAL AND REGULATORY ASPECTS

2.1 Ethical Conduct of Study

The research project will be carried out in accordance to the research plan and with principles enunciated in the current version of the Declaration of Helsinki (DoH), the Essentials of Good Clinical Practice, the Swiss Law and Swiss regulatory authority's requirements as applicable. The EC will be informed about project start and termination.

2.2 Risk categorisation

Risk categorisation Category A

2.3 Ethics Committee (EC) and Competent Authorities (CA), FOPH

The Principal Investigator will await approval from the Ethic committee before accepting any participants into the study. The study will be conducted in accordance with principles enunciated in the current Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH and the Swiss regulatory authority's requirements. The regular end, premature end or interruption of the research project will be reported to the EC within 90 days upon completion of the project.

2.4 Participant Information and Informed Consent

To enter the study, participants must be given a full explanation, an information leaflet and time for consideration by a member of the study team. Signed participants consent is obtained. Any participant has the right to refuse to participate. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

2.5 Participant privacy and safety

The Project Leader affirms and upholds the principle of the participants' right to dignity, privacy and health and that the project team shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
Individual participant medical information obtained as a result of this research project is considered confidential and disclosure to third parties is prohibited. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to medical information in the computer files.
For data verification purposes, authorised representatives of the Sponsor, a competent authority (e.g. FOPH), or an ethics committee may require direct access to parts of the medical records relevant to the project, including participants' medical history.

2.6 Early termination of project

If any health-related issue should appear the project will be stopped prematurely.

2.7 Amendments, Changes

Any significant changes to the project plan will be submitted to the EC and approval will be awaited before the changes will be put in place. The Project Leader will submit all documents, which are affected by the change. Furthermore, he will provide information on the reasons for the change.

3. INTRODUCTION

3.1 Background

Most chronic hemodialysis patients are in negative iron balance due to reduced dietary intake, impaired absorption from the gut and increased iron losses during dialysis. In addition, they suffer from functional iron deficiency due to chronic inflammation. These factors contribute to and aggravate renal anemia. Since potential adverse effects of high doses of erythropoiesis stimulating agents (ESA) have been recognized (7-9), use of i.v. iron has increased in dialysis patients, in order to ensure sufficient iron stores. In most European dialysis units, maintenance i.v. iron dosing is preferred over bolus dosing, with usual doses of 100 – 200 mg iron given every 2-4 weeks. While no laboratory parameters have been shown to reliably reflect total body iron stores, serum ferritin and transferrin saturation (TSAT) are generally used to assess the iron status of dialysis patients and to adjust maintenance iron dosing. International guidelines recommend adjusting iron supplementation to these laboratory parameters and to some extent provide target values (10,11). In our daily practice, we evaluate hemoglobin levels at least monthly and iron status based on the parameters ferritin and TSAT every three months in stable patients.

3.2 Rationale for the research project

It has been shown in non-dialysis patients that after a single infusion of ferric carboxymaltose (FCM), there occurs a transient, dose-dependent rise in serum ferritin, total serum iron and TSAT, which will then drop to the new baseline values within a few days (12,13). This transient raise is dose-dependent. During this transient rise, these parameters do not reflect total body iron stores. In hemodialysis patients, only a single study published 20 years ago has assessed short-term changes of serum ferritin and TSAT after relatively low doses of i.v. ferric gluconate (14), which is no longer in use in Switzerland. Iron parameters are usually assessed together with other anemia parameters on a regular basis in hemodialysis patients, and maintenance iron dosing is adjusted to these parameters. The timing of iron status evaluation (often occurring every three months), however, is not usually coordinated with iron dosing. Thus, short term variations of serum ferritin and TSAT might inadequately prompt adjustments of maintenance iron dosing.

The rationale of this study is to evaluate whether variations in the timing of blood sampling to evaluate the iron status in hemodialysis patients relative to the iron dosing schedule influence the parameters values to a relevant degree and whether, thus, a certain amount of time should elapse between the last maintenance FCM dose and evaluation of iron status.

3.3 Risk-Benefit Assessment

The risk for project participants will be very low in this non-interventional observational study. No additional punctures will be needed, since all laboratory assessments take place during routine hemodialysis treatments. Over the entire study duration of 4 weeks, a total of considerably less than 100 ml blood will be sampled. The result of this study will help to better guide the assessment of laboratory parameters for maintaining adequate iron stores with FCM in patients on chronic HD.

4. OBJECTIVES, ENPOINTS/OUTCOMES AND OTHER STUDY VARIABLES

4.1 Objectives

The objective of the study is to assess transient changes of laboratory parameters of iron metabolism / stores after a maintenance dose of 100 or 200mg FCM.

4.2 Primary and secondary endpoint/outcome(s)

Primary Endpoint:

Change in serum ferritin and TSAT values from baseline (before an FCM injection) to the next dialysis session after the FCM injection (2 days later).

Secondary Endpoints:

- Change in serum ferritin and TSAT values from baseline (before an FCM injection) to all other time points assessed until the next FCM injection and kinetic of these changes over time, including time required for serum ferritin and TSAT to return to baseline values.
- Change in soluble transferrin receptor levels after an FCM injection
- Change in all other parameters assessed after an FCM injection (hemoglobin, CRP)

4.3 Other study variables

In addition to the above mentioned laboratory parameters, a few additional routine laboratory parameters (e.g. Potassium, Phosphate) will be assessed.

5. PROJECT DESIGN

5.1 Type of research and general project design

Single center observational study.

5.2 Procedures

The study will include serial blood samplings over a period of 4 weeks.

The following laboratory parameters will be assessed at the beginning of the dialysis session during which the patients receive their FCM dose as well as at the beginning of the dialysis sessions at days 2, 4, 7, 14, 21 and 28 after FCM administration: serum ferritin, TSAT, hematogram, CRP. In addition, the following laboratory parameters will be assessed at baseline (i.e. at the beginning of the dialysis session during which the patients receive their FCM dose) as well as at the beginning of the next dialysis session and at the end of the study: soluble transferrin receptor and reticulocyte count.

Blood samples will be taken during regular hemodialysis sessions and will not require an additional venipuncture.

All blood samples will be processed and analysed immediately. The residual blood plasma not used in the mentioned analyses will be stored at -80°C for future use for ancillary analyses up until 2 years after the end of the study.

5.3 Recruitment and Screening

Patients will be recruited from the outpatient hemodialysis population treated at the STGAG in the dialysis units in Frauenfeld and Münsterlingen. Patient screening will be based on available results of routine laboratory testing and patient history, hence, no project-specific procedures will take prior to obtaining written informed consent. Patients will be asked for participation by their treating nephrologists who will be subinvestigators of the study.

5.4 Methods of minimising bias

This study will assess temporal changes of laboratory parameters over a defined period of time. Hence, each patient will serve as his / her own control. To minimize bias through the influence of other factors that might cause temporary changes in the parameters assessed, patients with fluctuations in these laboratory values in the previous 12 weeks or with health conditions that might cause fluctuations of these values independent from the index FCM-administration will be excluded (see inclusion and exclusion criteria).

6. PROJECT POPULATION

A total of 30-40 patients to be enrolled, each a minimum of 15 receiving 100mg and 15 receiving 200mg FCM on a regular basis.

6.1 Inclusion criteria

- Age > 18 years
- Able to provide written informed consent
- Chronic hemodialysis (>3 months since initiation of dialysis)
- Thrice weekly dialysis schedule
- Stable dose and dosing schedule of FCM for the last 12 weeks
- FCM dosing according to one of the two following schedules:
    - 100mg every 4 weeks (or every month)
    - 200mg every 4 weeks (or every month)
- Stable dose of erythropoiesis stimulating agent (defined by dose adjustments of <25% within the last 2 months)
- Stable haemoglobin values as defined by values <125g/l and >95g/l within the last 12 weeks with a difference between the lowest and the highest value of <15g/l

6.2 Exclusion criteria

- Evidence of significant blood loss within the last 12 weeks (e.g. gastrointestinal bleeding)
- Significant inflammation (CRP >15mg/l)
- Hospital admission within the last month
- Significant bacterial infection (e.g. pneumonia) within the last 12 weeks

6.3 Criteria for withdrawal / discontinuation of participants

- Withdrawal of informed consent
- Hospital admission during the study schedule
- Clinically relevant infection or significant blood loss during the study schedule
- Need for adjustment of the FCM-dosing schedule or erythropoiesis stimulating agent dosing during the study
- Non-compliance in dialysis schedule

7. PROJECT ASSESSMENTS

7.1 Project flow chart(s) / table of procedures and assessments

A detailed assessment schedule is shown at the section SCHEDULE OF ASSESSMENTS

7.2 Assessments of primary endpoint/outcome

The primary end points represent laboratory parameters and will be assessed by blood sampling.

7.3 Assessment of secondary endpoint/outcome(s)

The secondary end points represent laboratory parameters and will be assessed by blood sampling.

7.4 Assessment of other study variables

Baseline laboratory parameters and patient history will taken from the patient charts (no additional clinical assessment or history taking for the study will be performed).

7.5 Assessment of safety and reporting

Serious adverse drug reactions to FCM will be reported to Vifor Pharma Switzerland within one business day and to Swissmedic Pharmacovigilance.
All serious events will be reported to the local authorities (EC).

7.5.1 Definition of Serious Events (SEs)

A serious event is any unfavourable event for which a causal relationship to sampling of biological material or the collection of health related personal data cannot be ruled out, and which:

- requires hospitalisation or prolongation of an inpatients' hospitalisation,
- results in persistent or significant disability or incapacity, or
- is life-threatening or results in death,

In this study, SEs are extremely unlikely (no venipuncture necessary for blood sampling; no other study procedures). However, if a serious event occurs, the research project will be set on hold.

7.5.2 Assessment and Documentation of SEs

The assessment by the project leader with regard to the project-specific measure relation is done according to the following definitions:

Unrelated: The occurrence of the event has no temporal relationship to the project-specific measures applied and can be explained by the underlying disease or other factors.

Related: There is a plausible temporal relationship between the occurrence of the event and the project-specific, applied measures and cannot be explained by the underlying disease or other factors.

All SEs will be documented in the participants´ file.

7.5.3 Reporting of SEs, Safety and Protective Measures

The project leader shall report any occurring SE to the responsible EC within 7 days. He shall also submit a report which evaluates the relationship between the event reported and the methods of collecting health related personal data or sampling of biological material within that project, furthermore proposals how to proceed with the project.
The project leader shall notify the EC within 7 days of any immediate other safety and protective measures, which have to be taken during the conduct of the research project. In addition, the project leader shall explain the circumstances, which necessitated the safety and protective measures.

8. STATISTICAL METHODOLOGY

8.1 Determination of Sample Size

To detect an 80 ng/ml change in serum ferritin or a change in TSAT of 0.08 that would be clinically relevant, a sample size of 15 would be required, assuming a standard deviation of 100 ng/ml for the change in serum ferritin and of 0.1 for the change in TSAT, respectively, and using a paired two sample T-test (see below). Since we will separately analyze the patient group receiving 100mg FCM and 200mgFCM, respectively, we plan to enroll a minimum of 15 patients each. However, since no study has previously assessed this question, the estimate of the standard deviation is not based on clinical data or a pilot study. Hence, depending on the true standard deviations in our study, a larger sample might be required to exclude clinically relevant fluctuations in serum ferritin and TSAT after an FCM injection. Thus, in the case of a negative result (no effect of FCM on short-term fluctuations of laboratory parameters), our results will serve to decide whether a larger study might be required to exclude such effects and for an estimate of the required sample size.

8.2 Data processing

Values that do not show a normal distribution will be transformed (e.g. by log-transformattion) or non-parametric tests will be used.

8.3 Planned analysis

For both primary outcome measures, serum ferritin and TSAT will be compared between baseline and day 2 using a two-sided paired t-test.
For the secondary analyses, all other outcomes and timepoints will be compared to the basline values, also using a two-sided paired t-test. In addition, all laboratory values will be plotted against time in a descriptive way.

8.3.1 Datasets to be analysed

As described above, the analysis will be performed separately in patients receiving 100 mg or 200 mg of FCM, respectively. Given the small study size, we will not perform any subgroup analyses.

8.3.2 Handling of missing data

Patients with missing values for serum ferritin and TSAT at baseline or day 2 (i.e. the laboratory parameters used for the primary analysis) will be excluded from the analysis. However, we will take all possible measures to assure complete sampling. Since patients will be screened for participation also based on the planned availability for the required laboratory analyses and since follow up time is short, we expect a minimal drop out.

8.3.3 Ancillary analysis

The standard deviation of the change in serum ferritin and the TSAT will be calculated und compared to the assumption used for the sample size calculation (see above). No other ancillary analyses are planned.

8.3.4 Deviations from the original statistical plan

Depending on the results of the ancillary analysis described above, an increase of the sample size might be considered. In this case, an amendment would be submitted to the EC. Any deviations from the original statistical plan will be described and justified in the final report.

9. DATA AND QUALITY MANAGEMENT

9.1 Data handling and record keeping / archiving

Source data are stored in the electronic health records of the hospital, including a fully electronic reporting of laboratory data.
Outcome parameters and baseline parameters used for analysis will then be entered anonymized into an Excel file by a member of the study team (Matthias Dieblod). The Excel data file will be stored on the server of the nephrology department. For every relevant change of the file, a new version will be saved. In addition, all changes to the document can be tracked via regular backups of the server. Correct data entry will be verified by review of all entered data by a second member of the study team (Daniela Schmocker). Upon complete review, data will be locked on the Excel file. Data will then be imported directly from the Excel file into SPSS for statistical analysis.

9.2 Confidentiality, Data Protection

Data generation, transmission, storage and analysis of health related personal data and the storage of biological samples within this project will follow strictly the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5. Specifically, all data used for analysis will be stored anonymized. The file containing these data will be stored on the server of the nephrology unit and only be accessible to study personnel. Direct access to source documents will be permitted for purposes of monitoring, audits or inspections if required.

9.3 Coding

Patients will be coded by a three digit code. The key will be stored in a password-protected file on a separate location from the dataset. Only the principal investigator PD Dr. Andreas Kistler, the subinvestigator Matthias Diebold and the study coordinator Daniela Schmocker will have access to the key.

9.4 Archiving and Destruction

The dataset as well as all other study related materials (informed consent forms, study protocol) will be stored for at least 10 years after the termination of the study.
Biological samples will be destroyed 2 years after termination of the study. The destruction of the samples will be documented in the investigator file.

10. PUBLICATION AND DISSEMINATION POLICY

10.1 Publication of results

The results of the study will be submitted for presentation at the annual meeting of the Swiss Society of Nephrology (SSN), the American Society of Nephrology (ASN) and the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA). The study will be submitted for publication in a peer reviewed journal.

10.2 Data sharing

After completion of the study and publication of results, data will be shared in fully anonymized form with interested researchers on request.

11. FUNDING AND SUPPORT

The study will be funded by an unrestricted research grant provided by Vifor SA Switzerland.

12. INSURANCE

No insurance is needed.

13. REFERENCES

1. Declaration of Helsinki, Version October 2013, (http://www.wma.net/en/30publications/10policies/b3/index.html)
2. Essentials of Good Epidemiological Practice (EGEP; http://www.public-health.ch/logicio/client/publichealth/file/EGEP_en.pdf)
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14. APPENDICES

Informed consent form