Structured Evaluation of adRENal tumors Discovered Incidentally - Prospectively Investigating the Testing Yield.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials GCP Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**Serious Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Standard diagnostic work-up for adrenal incidentalomas (AI) consists of periodical biochemical analysis and CT-scanning in case the initial work-up does not demonstrate the presence of hormonal hypersecretion or adrenocortical carcinoma (ACC), respectively. With respect to the diagnosis of ACC, the health benefits of this strategy are controversial for the following reasons: a. critical appraisal of literature has revealed a much lower ACC frequency of 1.9% than previously presumed; b. CT sensitivity and specificity are suboptimal; c. risk of unnecessary adrenalectomies; d. exposure to ionising radiation; e. risk of CT contrast reactions (nephropathy, allergic reaction); f. health care related and economical costs. The hypothesis to be tested is that incorporation of a single baseline urinary steroid profiling (USP) into the management algorithm of AI is more cost-effective than a strategy solely based on repeat CT-scanning.

Objective: SERENDIPITY represents the largest prospective study on AI management thus far and aims to improve the cost-effectiveness of the diagnostic strategy by the application of a single baseline USP. In addition, we aim to examine the psychological impact for patients with AI being currently subjected to repeated laboratory tests and CT-scanning during several years.

Study design: This is a prospective observational multicenter study.

Study population: Patients are eligible if they meet the following inclusion criteria: adrenal mass > 1 cm in diameter incidentally discovered during CT or MRI-scanning, performed for reasons other than an evaluation for adrenal disease and age 18 years or older. The exclusion criteria are: extra-adrenal malignancy (i.e. active or past medical history of malignancy, except for basal cell carcinoma), radiologic diagnosis of simple cyst or bilateral adrenal masses, allergy to radiocontrast, renal insufficiency (i.e. eGFR < 30 ml/min/1.73m2), pregnancy or inability to understand written Dutch.

Intervention (if applicable): not applicable

Main study parameters/endpoints: The primary outcome parameter is the difference in cost-effectiveness of the current management strategy based on repeat CT-scanning to detect ACC among patients with an AI compared with a strategy using a single baseline USP.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participation is associated with a minimal burden for the study subjects, as they will be examined according to standard patient care. Patients will not be exposed to extra site visits or additional blood sampling. In addition to the standard patient care, study subjects will be asked to fill out QoL questionnaires (baseline and after 12 and 24 months). Furthermore, a urinary sample (10 mL) from the routinely collected 24h urine is stored for

USP and a blood sample (50 μL) from leftover material collected during the routinely performed 1 mg dexamethasone suppression test is stored for verification of cortisol measurements by LC-MS/MS. Thus, study subjects are not exposed to any additional health-related risks.

1. INTRODUCTION AND RATIONALE

Adrenal incidentalomas (AI) are clinically inapparent adrenal masses discovered serendipitously during radiologic imaging for other clinical conditions that are not related to suspicion of adrenal disease[1, 2]. The prevalence of AI ranges from 0.2% to 7% and increases with age[3, 4]. In 2012, 1.3 million CT scans were performed in the Netherlands, 55% of which included visualization of the adrenal glands (i.e. CT scans of chest and/or abdomen)[5]. Evaluation of AI is aimed to determine a) whether the AI is hormonally active b) whether the AI is malignant or benign[6, 7]. The majority of AI are benign, non-hyperfunctioning adrenal adenomas. Reported frequencies of adrenocortical carcinoma (ACC) among patients with AI varies from 1.2 – 12%[4]. Five-year survival rate of ACC is limited at 16-47%[8].

The standard care for patients with an AI is described in several guidelines[1, 4, 9, 10]. In September 2013, we conducted a survey among all members of the Dutch Society of Endocrinology (NVE) in order to examine the current clinical practice with respect to the management of AI. The response rate was 52%. It was shown that the recommendations issued by these guidelines were followed by a large majority of the respondents. A minority of the internist-endocrinologists ordered even more repeat CT-sans than advised by the guidelines. In short, standard care encompasses that the patient is being evaluated both for the presence of hypersecretion and/or malignancy of the adrenal gland. Adrenal function is assessed both clinically and biochemically, whereas the presence of adrenal malignancy is predominantly judged on CT-characteristics (phenotype) of the AI (in particular size and radiodensity). In case of clinically apparent hormonal hypersecretion and/or a malignant CT-phenotype, adrenalectomy is the treatment of choice. In case of normal adrenal function and a non-malignant CT-phenotype, follow-up is instituted with repeat CT-scans at various intervals during 1-2 years and annual hormonal testing during 3-4 years. If clinically apparent hormonal hypersecretion and/or a malignant CT-phenotype (including significant growth) develops during follow-up, then adrenalectomy is indicated. Follow-up is usually terminated after 3-4 years, if repeat testing has been uneventful.

The cost- effectiveness of the current diagnostic approach in a patient with AI has not been established prospectively. Based on retrospective data it has been suggested that the current approach is probably not cost-effective[11]. Guidelines for AI management recommend repeat CT-scanning to demonstrate growth of the AI as a sign suspicious for the presence of ACC[1, 4, 9, 10]. The health benefits of this strategy are controversial for the following reasons: a. critical appraisal of literature revealed a much lower ACC frequency of 1.9%[12]; b. CT sensitivity and specificity are suboptimal[13]; c. risk of unnecessary adrenalectomies[14]; d. exposure to ionising radiation[12]; e. risk of CT contrast reactions (nephropathy, allergic reaction); f. health care related and economical costs.

Urinary steroid profiling (USP) by gas chromatography/mass spectrometry (GC/MS) is a powerful diagnostic tool for defining steroid disorder metabolomes[15, 16]. Patients with ACC demonstrate several abnormalities in their USP[17-21]. Recently, USP was performed in patients with either adrenocortical adenoma (n= 102) or ACC (n=45)[22]. A sensitivity and specificity of both 90% was found. We studied the value of USP in patients with either a benign adrenal tumor (n=126) or ACC (n=18) and found a sensitivity and a specificity of 100% and 99%, respectively [Kerkhofs et al., submitted]. Until now, the diagnostic value of USP has not been tested prospectively in patients with AI. Obviously, USP is much more patient friendly than repeat CT-scanning with its associated extra hospital visits, waiting and procedure time and administration of intravenous contrast. In addition, the patient would no longer be exposed to the potential health risks of CT-scanning (i.e. ionising radiation, contrast nephropathy, contrast allergy). Also, the costs of USP are much lower than of CT-scanning. The cost difference between CT (€ 200) and urinary steroid profiling (€ 69.71) is substantial. Moreover, an estimated 7% of patients (i.e. 5% with an eGFR < 45 ml/min/1.73m2 and ~2% with an eGFR between 45-60 ml/ min/1.73m2 in combination with diabetes or multiple cardiovascular risk factors) are expected to require additional measures to allow safe administration of CT contrast (intravenous saline in day care facility, €250)[23, 24].

2. OBJECTIVES

Primary Objective: to improve the cost-effectiveness of the diagnostic strategy for AI.

Secondary Objective(s):

- to determine the prevalence of clinically relevant adrenal disorders (i.e. ACC, hormonal hypersecretion) among patients with AI.
- to determine the quality of life (QoL) in patients in whom an AI has been discovered.

3. STUDY DESIGN

Prospective observational cohort study.

4. STUDY POPULATION

4.1 Population

The research population consists of adult patients with a recently discovered adrenal incidentaloma who meet the selection criteria of SERENDIPITY. A total number of 1000 patients will be included. These subjects will be recruited from the group of patients in whom CT/MRI-scanning has been performed with visualization of the adrenal glands (i.e. CT/MRI scans of abdomen and/or chest, as the latter often include imaging of the upper abdominal region). We have estimated the number of eligible study subjects based on the following parameters: number of CT-scans performed during 1 year in each participating centre (numbers extracted from the radiology database of each centre), an AI frequency of 2%, an attrition rate of 65%[14],and an inclusion period of 18 months. Based on 22 participating centres, the number of eligible study subjects would thus be 1142. This is likely to be a conservative estimation for the following reasons: *a*. only CT-scans were taken into account, not MRI-scans *b*. AI frequency is likely to be higher than 2% *c*. currently, the number of participating centres is 27 instead of 22. .
Study subjects should be at least 18 years of age, but otherwise there are no restrictions with respect to age, gender or ethnic background.

4.2 Inclusion criteria

- discrete adrenal mass > 1 cm in diameter incidentally discovered during CT/MRI-scanning, performed for reasons other than an evaluation for adrenal disease
- age 18 years or older.

4.3 Exclusion criteria

- extra-adrenal malignancy (i.e. active or past medical history of malignancy, except for basal cell carcinoma)
- radiologic diagnosis of simple cyst or bilateral adrenal masses
- allergy to radiocontrast
- renal insufficiency (i.e. eGFR < 30 ml/min/1.73m^2)
- pregnancy
- inability to understand written Dutch.

Notes:

- extra–adrenal malignancy is an exclusion criterion because of the high pretest risk of adrenal metastasis and the fact that CT/MRI-scanning in these patients is

often performed for malignancy staging purposes. Patients with a basal cell carcinoma are not excluded, as this relatively frequent occurring malignancy is not known to metastasize to the adrenal glands.

- a simple adrenal cyst is not associated with hormonal hyperfunction or malignancy and does not require any further investigations[1].
- the differential diagnosis in case of bilateral adrenal masses is different from the aetiology underlying unilateral AI[7, 25]. Bilateral adrenal masses may result from disorders such as primary adrenal lymphoma, congenital adrenal hyperplasia, amyloidosis, infiltrative or granulomatous diseases. In addition, several of the disorders accompanied by bilateral adrenal masses are often associated with other symptoms and signs of the underlying disease. In these instances, the finding of bilateral adrenal masses may not always be incidental.
- patients with chronic kidney disease stage IV (i.e. eGFR < 30 ml/min/1.73m^2) are at increased risk for radiocontrast induced nephropathy.

4.4 Sample size calculation

As the prevalence of ACC among patients with AI is low, the general Poisson formula can be applied to describe the probability that a patient is diagnosed with ACC. If we assume the ACC prevalence to be 2.0%[12] it can thus be calculated that n=970 patients with an AI need to be included in order to achieve this ACC frequency of 2% with a 95% confidence interval between 1.36 – 3.0 %.

5. TREATMENT OF SUBJECTS

Not applicable.

6. INVESTIGATIONAL MEDICINAL PRODUCT

Not applicable.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The main study parameter is the difference in cost-effectiveness of the current management strategy based on repeat CT-scanning to detect ACC among patients with an AI compared with a strategy using a single baseline USP.

7.1.2 Secondary study parameters/endpoints (if applicable)

- frequency of ACC among patients with AI at baseline or during follow-up
- determination of the percentage of AI that meets the criteria of a malignant CT- phenotype at baseline or during follow-up
- distribution of pathologic diagnosis in surgically removed adrenal glands
- QoL in patients with an AI at baseline and during follow-up
- frequency distribution between hormonal hypersecreting and non-functional AI
- conversion rate from non-functioning AI towards a hypersecreting AI during follow-up
- costs of diagnostic procedures and surgical interventions

7.1.3 Other study parameters (if applicable)

- blood pressure
- body weight
- length
- medication (antihypertensives, statins, hypoglycaemic drugs including insulin)
- cardiovascular complications
- smoking
- routine laboratory measurements (haemoglobin, creatinine, sodium, potassium, glucose, lipid profile)

7.2 Randomisation, blinding and treatment allocation

Not applicable.

7.3 Study procedures

Study subjects are evaluated according to a standard care pathway which is based on available management guidelines and in agreement with the current practice in the Netherlands as reflected by the outcome of a nationwide survey among internist-endocrinologists (see also Introduction). This encompasses baseline hormonal workup, which is repeated annually for 4 years as long as hormonal hypersecretion

has not occurred. Hormonal evaluation comprises assessment of the plasma (nor)metanephrine (after 30 minutes of horizontal rest) and/or urinary fractionated metanephrines (Note: choice between metanephrines measurement in either plasma or urine depending on the local test protocol) and of the aldosterone-to-renin ratio (only in hypertensive subjects). A 24h urine sample is used for USP. In addition, in each patient a 1 mg dexamethasone overnight suppression test (1mg DST) is performed. Moreover, adrenal androgens in serum (i.e. DHEAS, androstenedione, 17-hydroxyprogesterone, testosterone; in addition, 17β- estradiol in men and postmenopausal women) are determined when a patient meets the criteria for an adrenalectomy. The risk of ACC is judged by the radiological characteristics of the AI on CT, i.e. the CT-phenotype. The CT-phenotype is either benign, malignant or indeterminate. Characteristics of a benign CT-phenotype are: unenhanced radiographic density of $\leq$ 10 Hounsfield Units (HU) AND largest diameter < 4 cm. Characteristics of a malignant CT-phenotype are: largest diameter $\geq$ 4 cm OR largest diameter between 1 - 4 cm AND relative percentage wash-out (RPW) of radiocontrast < 40% and absolute percentage wash-out (APW) < 60%. Characteristics of an indeterminate CT-phenotype are: unenhanced radiographic density of > 10 HU AND largest diameter between 1 to 4 cm AND RPW > 40% and APW > 60%. Adrenalectomy is indicated in case of hormonal hyperfunction (i.e. Cushing's syndrome, primary aldosteronism or pheochromocytoma), a malignant CT-phenotype or relevant growth of the AI as demonstrated on repeat CT-scanning. Relevant growth is defined as an increase in diameter of > 1 cm per year in an AI with a diameter > 3 cm on the last CT-scan. Repeat CT-scans are performed at predefined regular intervals. It should be noted, that administration of radiocontrast is routine practice in about 95% of all CT-scans of the thorax and/or abdomen. Thus, assessment of the unenhanced HU density is often not possible on the first CT-scan demonstrating the presence of an AI. Consequently, if the first CT-scan reveals an AI with a diameter < 4 cm, a dedicated CT-scan of the adrenal glands (i.e. imaging before and after radiocontrast administration) is performed after 4 months. Based on this repeat CT-scan, the initial CT-phenotype can be determined for an AI with a diameter < 4 cm. In case of a benign CT-phenotype, a repeat CT-scan without contrast is performed 12 months after the first CT-scan. In case of indeterminate CT-phenotype, a repeat CT-scan without contrast is performed 12 and 24 months after the first CT-scan. All these investigations (including periodic hormone testing and repeat CT-scanning) as well as the management decisions are part of the standard patient care pathway to which patients with an AI are normally subjected.

In addition to this standard care pathway, a single baseline sample from a 24h urine collection will be stored at -20^{0}C until further assay with USP. Notably, USP is performed at the end of the study at the Special Chemistry Laboratory of the University Medical Centre Groningen. Thus, the diagnostic value of USP will be determined post hoc and clinical management of the study subjects will not be influenced by the results of USP. The quality of life (QoL) will be examined in all study subjects through questionnaires at baseline and after 12 and 24 months. The following questionnaires will be used : Short Form 36 (SF-36), Hospital Anxiety and Depression Scale (HADS) and the Multidimensional Fatigue Inventory (MFI). Finally, participating centres are also requested to store from each patient a single serum or plasma sample of 50 μL derived from the blood volume collected during the 1 mg dexamethasone overnight suppression test at baseline. This offers the opportunity to validate serum/plasma cortisol measurements with a reference laboratory test, i.e. liquid chromatography- tandem mass spectrometry (LC-MS/MS) at the department of Laboratory Medicine of the UMCG. Such a validation is important in view of the large variability between laboratories in the different cortisol assays being employed. This central reference test requires no additional blood volume from the patient, as it is performed in leftover sample material that would otherwise be destroyed.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

7.5 Replacement of individual subjects after withdrawal

Individual subjects who withdraw from the study will be replaced in order to achieve the required number of 1000 study subjects with a 2 year follow-up.

7.6 Follow-up of subjects withdrawn from treatment

Not applicable.

7.7 Premature termination of the study

Not applicable.

8. SAFETY REPORTING

The METC of the University Medical Center Groningen has judged that the WMO does not apply to this study, as *a.* participants are subjected to standard patient care *b*. the study design is observational (not interventional) *c*. the additional investigations (USP from a routinely collected 24 h urine, QoL questionnaires, cortisol assessment in leftover sample material at a central laboratory) poses no health hazard and represent a minimal burden to the participants. Safety reporting, therefore, is not applicable.

8.1 Section 10 WMO event

Not applicable.

8.2 Adverse and serious adverse events

Not applicable.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Not applicable.

8.2.2 Annual safety report

Not applicable.

8.3 Follow-up of adverse events

Not applicable.

8.4 Data Safety Monitoring Board (DSMB)

Not applicable.

9. STATISTICAL ANALYSIS

9.1 Descriptive statistics

Continuous data are presented as mean ± SD or as median with interquartile ranges where appropriate. Categorical variables are presented as percentages in a frequency distribution. A two-sided $P < 0.05$ is considered to be significant. Calculations are performed using IBM-SPSS Statistics.

9.2 Univariate analysis

Sensitivity and specificity of USP are calculated and receiver operating characteristics (ROC) curve analysis will be performed by plotting sensitivity and 1-specificity for different cut-off values of the USP. Significant differences in steroid metabolite excretion between patients with and without ACC will be analyzed by ROC curve analysis for every individual metabolite.

9.3 Multivariate analysis

Multivariate regression analysis will be applied to establish which determinants are associated with a diagnosis of ACC. In case more sophisticated methods than ROC curve analysis are needed, partial least square discriminant analysis (PLS-DA) will be implemented. This type of methods is particular suitable to classify ACC and non-ACC patients on the basis of continuous measurements from complex analytical methods.

9.4 Interim analysis

Not applicable.

9.5 Cost effectiveness analysis (CEA)

The economic evaluation will be conducted alongside the clinical study to assess the cost-effectiveness of using USP as the first diagnostic step as compared to usual care using CT. The primary outcome measure of the cost-effectiveness analysis is the number of carcinomas detected. The result of the analysis will be an incremental cost-effectiveness ratio (ICER), expressing the additional costs (or savings) that are associated with detecting one additional carcinoma. In a secondary analysis, cost per QALY will be calculated The healthcare perspective will be adopted, since the observational design does not allow for the disentanglement of care as usual versus USP-strategy costs outside the healthcare sector. Costs within the health care sector will be attributed to the strategy in which they would occur in practice. For instance, the costs

of USP will always be attributed only to the USP strategy. The costs of CT will always be attributed to the CT-strategy, but in some cases may also be relevant to the USP-strategy. With the collection of data, explicit attention will be paid to indicating whether or not diagnostics, procedures, outpatient visits etcetera are exclusively CT-strategy or would also have taken place in the USP-strategy. The time horizon will be equivalent to the full follow-up of the clinical study, i.e.2 years. According to pharmacoeconomic guidelines[26], discounting will be applied for costs (4%) and effects (1.5%) in the second year. A number of sensitivity analyses will be performed to identify the impact of relevant variables such as unit costs, and the negative predictive value of USP, on cost-effectiveness. A cost-effectiveness acceptability curve will be constructed, based on bootstrap simulations, showing the probability of the USP-strategy being cost-effective at varying levels of the willingness to pay for detecting one extra carcinoma. Included costs will be those of diagnostic procedures, outpatient visits, hospital and day-care admissions and adrenalectomy. Data are collected in an electronic CRF. Unit prices will be determined according to Dutch guidelines[27] and according to the type of hospital (general or university). Measurements for the economic evaluation will be performed at baseline, and after 1 and 2 years

Number of ACC detected is used as a primary outcome measure in the cost-effectiveness analysis. Although Health Related Quality of Life (HRQoL) as derived from the SF-36 via SF-6D[28] is an outcome measure in the clinical study, it is not possible to calculate a cost per QALY ICER, because of the observational design. The HRQoL for the care as usual can be observed, whereas for the USP strategy, HRQoL is unknown. However, in a secondary analysis, QALYs for the USP strategy will be estimated hypothetically as follows: - For patients with ACC: average SF-36 utility score as observed (since the ACC will dominate the HRQoL in these patients). For patients without ACC, but still needing CT (because of uncertainty in USP): SF-36 utility score as observed.- For patients without ACC, no further screening needed: SF-36 utility score of a general population, comparable in age. Since these cost per QALY calculations will be based on group averages, it is not possible to perform bootstrap simulations or construct cost-effectiveness acceptability curves. This secondary analysis will only generate a point estimate for incremental cost or savings per QALY.

9.6 Budget impact analysis (BIA)

Based on the results of the clinical study and the cost-effectiveness analysis, a budget impact analysis will be performed to inform decision makers on the financial consequences of implementing USP as the first diagnostic step in AI in the Dutch

healthcare system. The BIA will be performed from both the perspective of the government (societal and BKZ – budgettair kader zorg) as well as a third party payer/healthcare insurers perspective. The trial results will be extrapolated, by means of a simple model, from a time horizon of 2 years to 5 years, and for the entire Dutch population concerned. The extrapolation will assume a constant incidence of both AI and ACC. Also, we expect that the detection rate as found in the trial will be stable over time. Therefore the extrapolation will be linear. A factor that is expected to change with time after the trial is the uptake of USP as a clinical standard. This factors will be used for scenario analysis in the BIA. Sensitivity analyses will be performed on relevant parameters such as the substitution rate of USP for CT, the uptake of USP, and unit costs.

The source of the unit prices will vary with the perspective, as described by the ZonMw guidance on BIA. Also according to this guidance, future costs will be indexed, but not discounted. The precision of costs will be in accordance with the described perspectives.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the Declaration of Helsinki (7th revision, October 2013) and the Wet op de Geneeskundige Behandelingsovereenkomst. (WGBO).

10.2 Recruitment and consent

Eligible subjects will be informed both orally and in written form by the local principal investigator (PI) involved in SERENDIPITY or their own doctor (who might be the same person as the local PI). Potential study subjects are given 2 weeks to consider their decision. See also the patient information letter and informed consent, both enclosed as a separate document.

10.3 Objection by minors or incapacitated subjects

Not applicable.

10.4 Benefits and risks assessment, group relatedness

The study is free of any health hazard for the participating subjects. Except for the questionnaires, the single baseline USP (sample from a routinely collected 24h urine) and the single cortisol measurement in a central reference laboratory (from left over sample material), all examinations performed are part of the routine clinical practice as described in the standard care pathway. The potential value of SERENDIPITY is that it will provide detailed information on the cost-effectiveness of the current management of AI. In addition, the study will offer reliable data needed to improve the risk assessment for the presence of malignancy in a person in whom an AI has been discovered. Moreover, it is expected that introduction of USP into the AI management algorithm will obviate the need for repeat CT-scanning in many subjects. In contrast to repeat CT-scanning, USP is not associated with any health risks and relatively inexpensive. Furthermore, USP is a much more patient friendly procedure than CT-scanning.

In order to achieve the study objectives, it is evident that SERENDIPITY requires the participation of patients with a recently discovered AI. This study, therefore, can be deemed to be group-related.

10.5 Compensation for injury

Both the sponsor and the investigator have a medical liability insurance. As participants are not exposed to any additional health risks other than those associated with standard patient care, an insurance for the study subjects is not provided.

10.6 Incentives (if applicable)

Not applicable.

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

All study data are handled confidentially. Data are extracted from the electronic patient record by the research physician. The handling of personal data is fully compliant with the Dutch Personal data Protection Act (in Dutch: de Wet Bescherming Persoonsgegevens, Wbp). Each study subject is appointed a study code consisting of 5 digits: the first two digits represent the participating centre and the last three digits represent the study subject in order of inclusion at that particular centre. The study data are only stored using this study code. Thus, all data handling (including storage, analysis and reporting) is based on coded data. The key to the code is safeguarded by the local PI. The electronic case report form (eCRF) can only be accessed within the UMCG network. The database is constructed by the Trial Coordination Center (TCC) Groningen, an ISO 9001:2008 certified academic contract research organization. Data validation by the TCC will include a data management plan, programming of automatic data validation procedures into the eCRF, data checking (on completeness, consistency, plausibility and adherence to the protocol) and creating a database lock after completion of the study data. The database is safeguarded by a password and is only accessible to the research physician and the project leaders (M.N. Kerstens, P.H.L.T. Bisschop). Study data are kept for 15 years. In addition, samples of urine (10 ml) are stored for 15 years at the department of Laboratory Medicine of the UMCG and may be used for additional investigations related to the objectives of the present study.

11.2 Amendments

Not applicable.

11.3 Annual progress report

Not applicable.

11.4 End of study report

In case the study is ended prematurely, the investigator will notify ZonMw, including the reasons for the premature termination. Within 6 months after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to ZonMw.

11.5 Public disclosure and publication policy

The study has been registered in the Dutch Trial Registry (NTR 4799). The results of the present study will be published in international peer-reviewed journals and presented at medical conferences.

Disputes between participants on the interpretation of study results should not delay the publication of these results. In case of a continued disagreement, the discussion should be pursued by means of correspondence to the journal involved. None of the parties has a veto and all parties should solve problems in mutual consultation.

A research consortium will be formed consisting of all local principal investigators who have contributed to SERENDIPITY by including study subjects. In each journal publication, the names of these investigators are listed at the end of the paper. Consequently, these investigators are registered in biomedical libraries (e.g. MEDLINE). In order to qualify for full authorship (publication of the investigators' name on the first page of the paper), an investigator should have made a substantial contribution to the study and take public responsibility for the content. Authorship credit will be based on the following criteria, as recommended by The International Committee of Medical Journal Editors(25):

1) Substantial contributions to conception and design, or acquisition of data (5% or more), or analysis and interpretation of data;
2) drafting the article or revising it critically for important intellectual content; and
3) final approval of the version to be published.

Authors should meet conditions 1, 2, and 3.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content and should certify that he has reviewed the final version, believes it is valid work and that he approves of its publication. In this multi-center study the coordinating investigator has the direct responsibility for the manuscript. When submitting a group author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name.

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