More precise dosing of acenocoumarol in patients aged 80 and above, a pilot study

Protocol

Short title	Eighty and a half
ABR number	NL58727.042
EudraCT number	2016-003086-25
UMCG Research Register	2016 006 20
Nederlands Trial Register	NTR6093
Protocol version	1.1
Protocol date	10 March 2017
Coordinating investigators	M. Piersma-Wichers, MD Internist, medical director Certe Trombosedienst Tel.: 088-2371126 Email: m.piersma@certe.nl J.H.A. van Miert, MD Physician-researcher, UMCG Tel.: 050 361 2791 Email: j.h.a.van.miert@umcg.nl
Principal investigator	K. Meijer, MD PhD Haematologist, UMCG Tel.: 050 361 0225 Email: k.meijer@umcg.nl
Sponsor	University Medical Center Groningen Afdeling Hematologie Hanzeplein 1, 9713 GZ Groningen, NL
Subsidising party	Certe Trombosedienst Postbus 909, 9700 AX Groningen, NL Stichting ter Bevordering van Onderzoek/Onderwijs op het gebied van Hemostase, Trombose en Reologie HPC AA24, Hanzeplein 1, 9713 GZ Groningen
Independent expert	M. de Groot, MD PhD haematologist
Laboratory sites **Pharmacy**	Not applicable. J.M. Boonstra, MSc University Medical Center Groningen Pharmacy

Protocol signature sheet

Name	Signature	Date
Head of Department G. Huls, MD PhD head of Department of Haematology		
Principal Investigator K. Meijer, MD PhD		

Table of contents

List of abbreviations and relevant definitions

Abbreviation	Definition
ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AF	Atrial Fibrillation
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
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
INR	International Normalised Ratio
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
NOAC	Non-VKA (or Novel) Oral Anticoagulant
RCT	Randomised Controlled Trial
(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
TTR	Time with INR in therapeutic range
VKA	Vitamin K antagonists
VTE	Venous thrombo-embolism
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

Summary

Rationale

40% of patients using anticoagulants is eighty years or older. In this vulnerable age group there is a delicate balance between haemorrhages and thrombosis. Good quality of anticoagulation is of paramount importance, but this is less frequently achieved with higher age. Decreasing acenocoumarol dosage may cause a higher variability. We hypothesise that dosing using tablets of half a milligram acenocoumarol increases anticoagulation control.

Objective

The main objective is to collect data on effect size for, and determine the feasibility of, a full scale RCT to assess the effect of dosing per 0.5 mg acenocoumarol on quality of anticoagulation, treatment satisfaction, and medication errors.

Study design

Randomised controlled trial, with 2 treatment groups (see below) with 40 patients each.

Study population

Patients aged 80 and above, who have been managed by Certe Trombosedienst for over 9 months, and use a daily dose of acenocoumarol between 0.5 and 2.0 milligram for any indication.

Intervention

One group is dosed using tablets of 0.5 milligrams of acenocoumarol, while the other group uses the regular 1.0 milligram tablets. Both will be dose-adjusted to their previously determined INR target range.

Main study parameters/endpoints

The main study parameter is quality of anticoagulation (individual time in therapeutic range and INR variability).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Patients already use dose-adjusted acenocoumarol, so we do not expect an added risk caused by the drug. All patients will be visited and administered a short questionnaire twice for the study. The intervention group will on average have to take twice as many tablets of acenocoumarol as before. This research will yield data relevant for the participating patients and other, similar patients.

1. Introduction and rationale

40% of patients using anticoagulation (VKA) is eighty years or older. Their share will further increase because the population ages, and indications for anticoagulation are more often acknowledged. However, the elderly are a vulnerable group. The risks of both haemorrhages and thrombosis increase with age (70% increase of those aged 75 and older, compared with those under 75 [1]). The HARM investigation[2] showed VKA are one of the most dangerous medication groups for medication-related hospitalisation.

Good anticoagulation control optimises the benefits and minimises the risks. Parameters such as time spend in therapeutic range (iTTR) and variability are a strong intermediary for clinical outcomes [3,4]. Good quality of anticoagulation is therefore of paramount importance.

Unfortunately, our own research shows that quality of anticoagulation decreases with age[5]. This is also true amongst the elderly: patients aged 80 and above are worse controlled than those aged 70-79. A possible cause is the diminishing acenocoumarol dose required with higher age. In our study it declined from on average 2.3mg in patients aged 70-79, to 1.9mg for those aged 80-89, to 1.6mg for those aged 90 or older[5]. This has to do with nutritional state, body composition and comorbidity. Because acenocoumarol is only available in tablets of 1 milligram, it is harder to spread out low doses over the week evenly. The scheme 1-2-1-2 causes larger relative differences than 2-3-2-3. Indeed, in our data we saw a lower iTTR but above all a higher variability in patients using less than 2 milligrams of acenocoumarol per day, versus those with a higher dosage.

In other words, usual care for elderly does not achieve the same quality as for younger patients, despite higher commitment of the thrombosis service, more frequent INR controls and more home visits. These interventions cost money, and -more importantly- lower quality of anticoagulation causes more thrombotic complications and haemorrhages[3,4]. Patients in the lower quarter of anticoagulation control are three times as prone to thrombotic complications or haemorrhages as the other 75%[3].

We hypothesise that more precise dosing regulation using tablets of 0.5 milligrams of acenocoumarol will increase quality of anticoagulation. If smaller dosing units for acenocoumarol lead to better anticoagulation control, the available care for patients using acenocoumarol can be directed more appropriately: fewer interventions might be needed in the growing group of patients aged 80 and above.

2. Objectives

The **primary objective** is to collect data on effect size for, and determine the feasibility of, a full scale RCT with the aims:

1. To evaluate the effect of smaller dosing units on quality of anticoagulation;
2. To evaluate if this alters treatment satisfaction
3. To evaluate if this prevents or causes errors in medication intake.

3. Study design

We propose an open-label, prospective, randomised controlled trial.

Many patients visit, or are visited by, the Thrombosis Service regularly for INR measurements. A day later they will receive a new dosing calendar via regular mail, with an overview of the daily dosages in the period until the next INR measurement. Potentially eligible patients selected by the Thrombosis Service (based on age and acenocoumarol dose) will be handed out an information letter about our study and a response card during one of these regular visits. Patients who express their interest in participating in the study will be visited by research personnel to inform them about the study, answer all questions, and collect informed consent. After consent, the subject will be randomised into one of two groups:

- **Intervention group**: dosing using tablets of 0.5 mg acenocoumarol
- **Control group**: dosing using the regular tablets of 1.0 mg acenocoumarol

Allocated treatment will begin the same day, and will last until the end of study visit six months later. The system of “therapy control” with INR-based dosage adjustments will not differ from everyday care in both treatment groups, only the dosing steps might differ. Directly following randomisation, and during the end-of-study-visit, subjects will fill in the PACT-Q2 questionnaire[6], a questionnaire developed specifically to assess patients’ perception of anticoagulation treatment.

We opt for a RCT (instead of for instance a before and after comparison) to avoid the “Hawthorne effect” (the phenomenon that quality would improve simply because one participates in a study). Due to the nature of the medication and its monitoring, it would be very difficult to do this in a blinded fashion. Because we use an objective endpoint, we do not foresee bias there. For the subjective measurements of patient satisfaction, unblinded assessment is crucial as the larger number of tablets is inherent to the intervention.

4. Study population

4.1 Population (base)

Certe Trombosedienst is the largest thrombosis service in Groningen. it treats 8000 patients aged 80 or older, of whom 55% (4400 patients) uses less than 2 milligrams of acenocoumarol per day.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Using acenocoumarol for any indication, and being managed by Certe Trombosedienst
- 80 years of age or older at time of inclusion
- Using acenocoumarol with an average daily dose of less than 2 milligrams in the previous three months
- Subject provided informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Initiated therapy with acenocoumarol in the last nine months
- Expected termination of VKA within six months
- Dosing step lower than or equal to “step 7”, i.e. usage of less than 3.5 milligrams acenocoumarol per week. Patients who use such a low dose generally have an unfavourable prognosis.
- Patients who determine the acenocoumarol dose themselves

4.4 Sample size calculation

We performed a power analysis for a larger follow-up study, based on the following parameters:

Parameter	Value	Standard deviation
TTR control group	69 %	19
TTR intervention group	72.5%	17
Alpha (type I error rate)	5 %	
Failure rate	10 %	
Power (1 - type II error rate)	80 %	

The TTR values above are based on observational findings in our clinical practice. It should however be noted that the INR target ranges have been modified (c.q. narrowed) as per January 1st, 2016, and that we expect this will affect the TTR in both groups. This underlines the necessity of a pilot study.

This resulted in a needed sample size of 917 patients, which is much less than the 140 000 patients aged 80 and above managed by the Dutch Thrombosis Services.

For this pilot study we want to randomise 2 x 40 patients. This should give us an overview of the point estimates in the power analysis (which are currently based on observational data), and -more importantly- about the time investment needed to conduct a larger-scale study. Due to the inter-individual variation in response to VKA, we think a smaller sample could distort the view.

5. Treatment of subjects

5.1 Investigational product/treatment

Both treatment groups will be treated with acenocoumarol:

- the control group will be treated with regular, registered 1 mg tablets (Summary of the Product Characteristics).
- for the intervention group, tablets of 0.5 milligrams will be manufactured by the UMCG Pharmacy in accordance with ICH-GMP[7] and the regulations imposed by the WMO and the *Geneesmiddelenwet*.

5.2 Use of co-intervention

There are no co-interventions in this study.

6. Investigational product

6.1 Name and description of investigational product(s)

Acenocoumarol is a vitamin K antagonist (VKA). VKA have an anticoagulant effect by interfering with the cyclic interconversion of vitamin K, which leads to a vitamin K depletion which lowers the production of vitamin K-dependent proteins including coagulant factors II, VII, IX and X. This results in less formation of thrombin and fibrin. The half-life of acenocoumarol typically is 8 to 11 hours (Farmacotherapeutisch Kompas). The liver inactivates the active substances followed by renal and faecal excretion. VKA only interfere with the production of new coagulation factors, and have no influence on already circulating factors. Therefore, due to the relative long half-life of factor II, the antithrombotic effect needs at least five days to reach full potential. Interactions with VKA are not uncommon: co-medication and food may influence the absorption, effect and inactivation of VKA. To monitor therapy, the thrombosis services determine the so-called international normalised ratio (INR) and adjust the dosage accordingly.

6.2 Summary of findings from non-clinical studies

There is ample experience and clinical data on acenocoumarol, so we refer to the Summary of the Product Characteristics and the clinical studies below.

6.3 Summary of findings from clinical studies

Because the mechanism of action of all VKA is similar (only half-lives differ), warfarin studies are considered also applicable to acenocoumarol.

Acenocoumarol has been an established treatment or prophylaxis for multiple indications:

- Atrial fibrillation [8–10]
- Venous thrombo-embolism [10,11]
- Valvular heart disease [12]

INR target range may differ between and within the indications. Usually the INR target range for “venous indications” is 2.0–3.0, while that for “arterial indications” is 2.5–3.5 or even higher.

Alternatives for VKA have been registered in the last years (NOAC: e.g. rivaroxaban, apixaban, dabigatran). While new guidelines favour NOAC over VKA for AF[13] and VTE[14,15], active switching of patients without problems is not recommended. Decreased renal function is a contra-indication for use of a NOAC: these most fragile patients will use VKA.

6.4 Summary of known and potential risks and benefits

Benefits of anticoagulant treatment is a lower incidence of thrombosis, but this comes at the expense of (major) bleeds. It is known that the better the quality of anticoagulation, the lower the overall risk of adverse outcomes[3,4]. The risk of major bleeding with VKA varies between 1.40 and 3.40% per year[16], but this increases with lower iTTR and higher age.

Because the active substance is the same in both treatment groups (which is the same as the one used in clinical practice), we do not expect any alterations in the potential risks and benefits of the pharmacological compound per se. Our hypothesis, however, suggests a net benefit of the intervention.

6.5 Description and justification of route of administration and dosage

Dose-adjusted acenocoumarol once daily, titrated to the pre-specified INR target range, with oral tablets of either 0.5 milligrams of acenocoumarol (intervention group), or the regular 1.0 milligram tablets (control group).

6.6 Dosages, dosage modifications and method of administration

As mentioned before, the sensitivity for VKA can differ between patients and also over time within patients. Frequent INR-measurements are required to achieve an anticoagulant effect within the target range. The frequency of monitoring depends on the stability of INRs, but can also be intensified due to changes in health status such as the need for invasive procedures or changes in co-medication. In case of under- and over-anticoagulation the dosage can be adjusted; for extreme over-anticoagulation vitamin K suppletion can be used. The procedures for this are laid down in protocols by the Thrombosis Services, and will not differ from regular care.

6.7 Preparation and labelling of Investigational Medicinal Product

Participants in the control group will get their regular 1 mg tablets with regular labelling from their usual out-patient pharmacy.

Details on preparation and labelling for participants in the intervention group, i.e. about tablets with 0.5mg of acenocoumarol, will be attached.

6.8 Drug accountability

The University Medical Center Groningen pharmacy will manufacture and label tablets of acenocoumarol in 0.5 milligrams in accordance with the guidelines of ICH-GCP[17] and ICH-GMP[7]. The drug will be picked up at the pharmacy by study personnel, who will then distribute it to subjects. Unused drugs will be returned to the pharmacy.

We will not perform any drug accountability for subjects in the control group. The Thrombosis Service routinely collects patient-reported data on acenocoumarol compliance.

7. Non-investigational product

No non-investigational products will be used in this study.

8. Methods

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main study endpoint is **quality of anticoagulation**, assessed using the following parameters:

- Individual time in therapeutic range (iTTR) Calculated using the Rosendaal method[18]
- INR variability Calculated using the Variance Growth Rate[19] and the SDTinr[20]

8.1.2 Secondary study parameters/endpoints (if applicable)

The secondary study parameters are **treatment satisfaction**, **medication errors** and **number of INR measurements**.

Treatment satisfaction will be assessed using the PACT-Q2 questionnaire[6].

Medication errors are routinely collected by the Thrombosis Service. These will be analysed on number and category of error.

All dates of INR measurements are routinely collected by the Thrombosis Service, so we can easily calculate the number of INR measurements.

8.2 Randomisation, blinding and treatment allocation

The study personnel will perform randomisation on-the-spot. To avoid technical difficulties, we will perform randomisation using ordered envelopes. We will stratify by INR target range (2.0-3.0 versus 2.5-3.5) within pre-specified blocks. The University Medical Center Groningen Pharmacy will provide randomisation lists.

Patients and professionals at the thrombosis service will know to which treatment group the patient has been randomised.

8.3 Study procedures

Visit	Regular visit	Study visit	[...] †	6 months
Age and VKA dose	X			
Information letter	X			
Informed consent		X		
Check of participation criteria		X		
Randomisation		X		
PACT-Q2		X		X
Start allocated treatment		X		
Follow-up data * §			X	X
INR measurement *	X	X	X	X
Possible dose adjustment *	X	X	X	X

* All items marked are (also) performed for usual care. † Every regular INR measurement, based on the previous INR values and change in co-medication etc., based on the regular algorithm of the Thrombosis Service. § Follow-up data is the information that is routinely collected by the thrombosis service, e.g. change in co-medication, planned surgical procedures, bleeding complications and errors in medication intake.

8.4 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.

8.5 Replacement of individual subjects after withdrawal

We will not replace individual subjects.

8.6 Follow-up of subjects withdrawn from treatment

Patients who want to withdraw consent will be asked to attend an end-of-study visit. If they refuse, the study time of that specific patient will end retrospectively at the last attended study-visit.

Another situation that can lead to implicit withdrawal is loss to follow-up. In case of loss to follow-up, the general practitioner and/or referring physician will be contacted to find out whether the patient died, has moved or any other explanation. If the contact can be fully restored all study time is taken into account, otherwise the study time of that specific patient will end retrospectively at the last attended study-visit.

8.7 Premature termination of the study

There are no pre-specified criteria for premature termination of the study.

9. Safety reporting

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Because acenocoumarol is a registered medicine with which there is ample experience, we will not collect any non-serious adverse events.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator. An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
    a. Summary of Product Characteristics (SPC) for an authorised medicinal product;
    b. Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal ToetsingOnline to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.
- The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States. This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported until end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Because we consider this a negligible risk study, we will not form a Data Safety Monitoring Board.

10. Statistical analysis

The data will be analysed in accordance with a statistical analysis plan that will be made before database lock. Due to the nature of this study, no formal statistical testing will be performed.

We will describe the primary endpoint parameters (iTTR, variance growth rate, SDTinr) by treatment group. The secondary endpoint parameter treatment satisfaction will be calculated as the difference between the score at randomisation and that at the end of study visit. This difference will be described per treatment group. The parameter medication errors will be summarised per treatment group and error severity.

To determine the feasibility of a full-scale RCT, we will calculate the size of the required patient population, based on the following assumptions and parameters:

- Significance level 0.05
- Power 0.80
- Effect size equal to the one found in this trial
- Inclusion ratio equal to the one found in this trial (i.e. percentage of selected patients that enrols in the trials)

We will not perform interim analyses.

11. Ethical considerations

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki[21] and ICH-GCP[17], and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

The Thrombosis Service will select from its files those patients who, based on their age and acenocoumarol dose, would be candidates for the study. This information is already collected for the purpose of usual care. We will give patients a patient information letter at one of their regular visits to or by the thrombosis service. Patient can express their (dis)interest by returning the attached reply card. Those who do not return the card within reasonable time will be telephoned. For those interested, study personnel will schedule an information visit (preferably combining it with visits for usual care) and will then explain the aims, methods, and potential hazards of the study to the potential subjects. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of their disease. The potential subject can ask all questions to the study personnel; a study doctor will be available for telephonic consultation. The patients will have sufficient time to consider their decision: there will be at least one week between the written information letter and the appointment. During or after the screening visit, the patient can take as much time as she/he needs before signing informed consent.

11.3 Objection by minors or incapacitated subjects

We will include minors nor incapacitated subjects.

11.4 Benefits and risks assessment, group relatedness

For **usual care**, all participants are exposed to the benefits and risks of anticoagulation, because their treating physician considered the benefit (protection again thrombosis) to outweigh the risk (bleeding). The pharmacological compounds used in this study are registered for this indication. All participants need to have regular blood collections for regular care.

For **this study**, all patients will have two (extra) visits by research personnel where they will fill in a questionnaire. Patients in the *intervention group* have the disadvantage that they have to take more tablets, possibly at the advantage of a more stable dosing rhythm.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. This insurance provides cover for damage to research subjects through injury or death caused by the study.

- € 650 000,– (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
- € 5 000 000,– (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
- € 7 500 000,– (i.e. seven million and five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable.

12. Administrative aspects, monitoring and publication

12.1 Handling and storage of data and documents

We will handle the data confidentially and anonymously. We will use a subject identification code list to link the data to the subject, when appropriate. The code will not be based on the patient initials and birth-date. The key to the code will be safeguarded by the investigator. The handling of personal data complies with the Dutch Personal Data Protection Act. Only professionals from the thrombosis service will have access to the source data.

12.2 Monitoring and Quality Assurance

This pilot study will be monitored by the coordinating investigator and/or the project leaders who will visit study centres at least monthly, to discuss any issues and check on conduction of the study. Logical checks are incorporated in the study database CRF.

12.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient’s last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year 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 the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

The results of this study will be published in a peer-reviewed journal and presented at national and international meetings.

13. Structured risk analysis

13.1 Potential issues of concern

Because acenocoumarol is a registered pharmaceutical compound, we refer to the SmPC.

a) **Level of knowledge about mechanism of action** The mechanism of action has been discussed in chapter 6.1. In short, VKA counter the production of the coagulation factors II, VII, IX and X, which results in an anticoagulated state.
b) **Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism** Acenocoumarol and other VKA have been used for decades.
c) **Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?** Not applicable.
d) **Selectivity of the mechanism to target tissue in animals and/or human beings** Not applicable.
e) **Analysis of potential effect** The anticoagulatory effect can be measured using the INR, which will also be used for dose-adjustment.
f) **Pharmacokinetic considerations** Not applicable.
g) **Study population** The study population consists of elderly people who use a lower dose of acenocoumarol. With higher age, both bleeding and thrombosis risk increase, as does the prevalence of comorbidities and co-medication. This creates a fragile balance, which we cannot fine-tune with the currently available tablets of 1.0 milligram of acenocoumarol. This population might benefit from lower dosed tablets.
h) **Interaction with other products** Many medications interact with the resorption, effect, or pharmacodynamics of VKA, which makes precise dosing very important. Interactions of VKA are summarised by the Federation of Dutch Thrombosis Services[22].
i) **Predictability of effect** As mentioned before, there is a significant difference between patients, but also within patients, depending on age, co-morbidity, co-medication, body composition, etc. VKA-naive patients achieve a lower quality of anticoagulation and are more at risk for adverse outcomes than experienced ones[23]. In this trial, all patients have used acenocoumarol before, so we have an idea of the appropriate dose for the individual.
j) **Can effects be managed?** When a patients is over-anticoagulated, acenocoumarol dose can be lowered, skipped, or vitamin K can be administered to counter the effect of VKA and resume coagulation factor production. When active bleeding occurs, the non-produced coagulation factors can be replenished with commercially available factor concentrates (e.g. prothrombin complex concentrate (Cofact)).

13.2 Synthesis

We do not expect potential issues of concern as we will use registered medicinal compounds within the indication, and with the care routinely provided with these medications.

14. References

[1] Lip GYH, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and Major Bleeding Risk in Elderly Patients Aged >=75 Years With Atrial Fibrillation: The Loire Valley Atrial Fibrillation Project. Stroke 2015;46:143–50. doi:10.1161/STROKEAHA.114.007199.

[2] Bemt PM van den, Egberts TC. Hospital admissions related to medication: Een prospectief multicenter onderzoek naar geneesmiddel gerelateerde ziekenhuisopnames 2006:1–80.

[3] Veeger NJGM, Piersma-Wichers M, Tijssen JGP, Hillege HL, Van Der Meer J. Individual time within target range in patients treated with vitamin K antagonists: Main determinant of quality of anticoagulation and predictor of clinical outcome. A retrospective study of 2300 consecutive patients with venous thromboembolism. British Journal of Haematology 2005;128:513–9. doi:10.1111/j.1365-2141.2004.05348.x.

[4] Björck F, Renlund H, Lip GYH, Wester P, Svensson PJ, Själander A. Outcomes in a Warfarin-Treated Population With Atrial Fibrillation. JAMA Cardiology 2016;1:172. doi:10.1001/jamacardio.2016.0199.

[5] Kooistra HAM, Calf AH, Piersma-Wichers M, Kluin-Nelemans HC, Izaks GJ, Veeger NJGM, et al. Risk of Bleeding and Thrombosis in Patients 70 Years Or Older Using Vitamin K Antagonists. JAMA Internal Medicine 2016;146:CD001367. doi:10.1001/jamainternmed.2016.3057.

[6] Prins MH, Guillemin I, Gilet H, Gabriel S, Essers B, Raskob G, et al. Scoring and psychometric validation of the Perception of Anticoagulant Treatment Questionnaire (PACT-Q). Health and Quality of Life Outcomes 2009;7:30. doi:10.1186/1477-7525-7-30.

[7] ICH Expert Working Group. Good manufacturing practice guide for active pharmaceutical ingredients 2000:49.

[8] Mant J, Hobbs FR, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370:493–503. doi:10.1016/S0140-6736(07)61233-1.

[9] Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation. European Heart Journal 2010;31:2369–429. doi:10.1093/eurheartj/ehq278.

[10] Guyatt GH, Akl Ea, Crowther M, Gutterman DD, Schünemann HJ. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:7–47. doi:10.1378/chest.1412S3.

[11] Büller H, Crijns H, Huisman M, Kamphuisen P, Leebeek F, Levi M, et al. Diagnostiek, preventie en behandeling van

veneuze trombo-embolie en secundaire preventie van arteriële trombose. 2008.

[12] Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Bar??n-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012). European Heart Journal 2012;33:2451–96. doi:10.1093/eurheartj/ehs109.

[13] John Camm A, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. European Heart Journal 2012;33:2719–47. doi:10.1093/eurheartj/ehs253.

[14] Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315–52. doi:10.1016/j.chest.2015.11.026.

[15] Nederlandse Internisten Vereniging. Richtlijn Antitrombotisch beleid 2016.

[16] Agarwal S, Hachamovitch R, Menon V. Current Trial-Associated Outcomes With Warfarin in Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation: A Meta-analysis. Archives of Internal Medicine 2012;172:623–31. doi:10.1001/archinternmed.2012.121.

[17] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Guideline for good clinical practice 1996;1996:i–53. doi:10.1056/NEJMp1012246.

[18] Rosendaal FR, Cannegieter SC, Meer FJ van der, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thrombosis and Haemostasis 1993;69:236–9. doi:8470047.

[19] Leeuwen Y van, Rosendaal FR, Cannegieter SC. Prediction of hemorrhagic and thrombotic events in patients with mechanical heart valve prostheses treated with oral anticoagulants. Journal of Thrombosis and Haemostasis : JTH 2008;6:451–6. doi:10.1111/j.1538-7836.2007.02874.x.

[20] Lind M, Fahlén M, Kosiborod M, Eliasson B, Odén A. Variability of INR and its relationship with mortality, stroke, bleeding and hospitalisations in patients with atrial fibrillation. Thrombosis Research 2012;129:32–5. doi:10.1016/j.thromres.2011.07.004.

[21] World Medical Association. Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects 2013.

[22] Federatie van Nederlandse Trombosediensten. Coumarine-interacties 2016.

[23] Sørensen R, Gislason G, Torp-Pedersen C, Olesen JB, Fosbøl EL, Hvidtfeldt MW, et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. BMJ Open 2013;3:1–9. doi:10.1136/bmjopen-2013-002758.