Type-2 interventional research involving human beings

INR-CAP

Assessment of weekly monitoring strategy of capillary INR versus monthly monitoring strategy of venous INR in elderly patients in nursing home: Multicentre randomised cluster trial.

Version 2.0 of May, 22th 2023

Dr David COSTA

Table of Contents

List of tables

1 Administrative information

1.1 Title

Assessment of weekly monitoring strategy of capillary INR versus monthly monitoring strategy of venous INR in elderly patients in nursing home: Multicentre randomised cluster trial.

Title in English	Evaluation of a strategy of weekly monitoring of INR by capillary puncture (INRc) versus monthly monitoring by venous INR (INRv) in elderly patients in nursing homes: A multicenter randomized cluster trial.
Acronym	INR-Cap

1.2 Trial registration

Sponsor Number:	**RCB Identification:**
PHRC-N/2019/DC-01	2022-A00516-37

1.3 Main correspondents

SPONSOR:

Nîmes University Hospital (NUH Nîmes University Hospital), Research and Innovation Department, Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 04.66.68.42.36; Fax: 04.66.68.34.00; Email: drc@chu-nimes.fr

NAME AND POSITION OF THE PERSON AUTHORIZED TO SIGN THE PROTOCOL AND ANY MODIFICATIONS IN THE NAME OF THE SPONSOR:

Director of Research, Hospital-University and International Partnerships: Anissa Megzari
Nîmes University Hospital (NUH), Department of Research, University and International Hospital Partnerships, Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 04.66.68.42.36; Fax: 04.66.68.34.00; Email: drc@chu-nimes.fr

STUDY COORDINATOR:

Dr David COSTA (MD-PhD), Department of Biostatistics, Clinical Epidemiology, Public Health & Innovation in Methodology (BESPIM), Nîmes University Hospital (NUH), Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 06.61.43.39.30; Email: drcostadavid@gmail.com

METHODOLOGIST:

Dr Pascale FABBRO-PERAY (MD-PhD), BESPIM department, Nîmes University Hospital (NUH), Place du Professeur Debré, 30029 Nîmes Cedex 09: Tel: 04.66.68.34.46; Fax: 04.66.68.34.33; Email: pascale.FABBRO@chu-nimes.fr

HEALTH ECONOMIST:

Dr Sihame CHKAIR (PhD), BESPIM department, Nîmes University Hospital, Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 04.66.68.35.53; Fax: 04.66.68.34.33; Email: sihame.chkair@chu-nimes.fr

1.4 Protocol approval

Name, date and signature of the NUH research manager

Mrs. Anissa MEGZARI - 22 May 2023

Name, date and signature of the study coordinator

Dr David COSTA - 22 May 2023

1.5 Summary of key trial characteristics

Trial classification:

- According to regulatory authorities: Interventional research involving the human person (Category 2, Jardé Law)
- According to the methodologist: interventional, prospective, comparative, superiority, multicentric, randomised by cluster, in closed cohort
- According to Clinicaltrials.gov: Interventional.
- Technology Readiness level: 9A
- Level of proof: Level 1. Randomised controlled trial
- Phase or equivalent for medical devices: Phase IV

Study duration (months):

- Inclusion period: **12**
- Follow-up period: **6**
- Data-management period: **4**
- Stats and writing period: **2**
- Total: **24**

Recruitment:

- Number of patients: **128**
- Number of centres: **32**

1.6 Versioning

Current version Date: Version N°2.0; May, 22th 2023.

Table 1-1 Protocol versions, changes made and associated documents

Version	Date	Changes (initials)
0.0	July, 2nd 2018	Start of protocol writing (JP)
0.1	July, 18th 2018	Improvement of the project (CS, JP)
0.7	September, 4th 2018	Last reading corrections (CS, JP)
0.8	July, 24th 2019	Modifications of the protocol following the assessments received during the evaluation of the protocol for the PHRC-2018 campaign (JP,CS,PFP,SC)
0.9	September, 10th 2019	Last version (CS, JP, PFP) and reviewing by an English native speaker
0.10	February, 14th	Updates 2022 before submission at the "Comité de Protection des Personnes" (CPP) and ANSM information
1.0	March, 15th 2022	CPP first submission
1.1	May, 16th 2022	CPP response
2.0	May, 22th 2023	MS1

1.7 Funding

Financial support for this study has been provided by the PHRC-National 2019 grant.

1.8 Trial management and committees

An adjudication committee composed of a general practitioner, a haematologist or a cardiologist and a geriatrician will be established.

This adjudication committee will meet twice throughout the project: at the end of the follow-up of half of the included patients and at the end of the follow-up of the last included patient. It will only look at files that have had adverse events reported during the study.

1.9 Protocol contributors

David COSTA [NUH], Chloé SIKIRDJI [NUH], Pascale FABBRO-PERAY [NUH], Julie PISANO [NUH, medical writer].

DC & CS conceived of the study.

CS & PFP contributed to the scientific and methodological aspects.

PFP provided expertise in clinical trial design.

CS, PFP & JP were in charge of the protocol writing.

1.10 List of investigators & including centres

Surname, first name of study investigators		Address	E-mail	Phone Number	RPPS Number
Dr David COSTA	Principal investigator of the study	Nîmes University Hospital (NUH) Place du Pr. Debré 30029 NIMES Cedex9	drcostadavid@gmail.com	06.61.43.39.30	10004411400
Dr Chloé SIKIRDJI	Coordinating Investigator		chloesik@gmail.com	06.15.56.80.28	10100903862
Dr Mélanie BADIN	Co-investigator	68 rue du Charron 30310 VERGÈZE	melanie.badin@hotmail.fr		10100569093
Dr Murielle GLONDU-LASSIS	Co-investigator	SCM Médicale St Bauzille de Putois 1193 avenue du chemin neuf 34190 ST BAUZILLE DE PUTOIS	mglondulassis@hotmail.fr		10101505849
Dr. Hermine Saguy	Co-investigator	2 rue Ibn Sinaï Dit Avicenne 66330 Cabestany	rminesaguy@gmail.com	04.26.03.06.90	10101677762
Dr. Anne-Sophie Odoul	Co-investigator	392 Boulevard Pedro de Luna 34070 MONTPELLIER	as.odoul@gmail.com	06 21 80 15 99	10101767902
Last name First name of the investigator in each nursing home	**Investigator Center (EHPAD)**	**Address of the Investigator Center**	**E-mail**	**Phone Number**	**RPPS Number**
Dr David COSTA	EHPAD "My home"	156 Rue de Bouillargues 30000 NIMES	drcostadavid@gmail.com	0609881745	10004411400
Dr. Karen ZERBIB	EHPAD «Korian Mas de Lauze »	17 Chemin du puits de Louiset 30900 NIMES	karen.zerbib-popiolek@korian.fr	04 66 05 00 22 06 86 85 27 40	10100157840

Dr Patrick DUTILLEUL	EHPAD Residence "l'Accueil"	75 Rue Louis Aragon 30600 VAUVERT	dutilleul.p@wanadoo.fr	06 03 51 11 17	10003191631
Dr Alain BROUSSE	EHPAD "Les Jardins de l'Escalette"	1 Avenue Maréchal Foch 30700 UZES	a.brousse@chuzes.fr	04 66 63 72 57	10003189791
Dr Elodie MILLION	Malbosc nursing home	345 Avenue de Fez 34090 MONTPELLIER	elomega@free.fr	04 99 63 72 32	10004086665
Dr Philippe SERAYET	"Sophia la Capitelle" nursing home	57 Rue Henri Pitot 30840 MEYNES	philippe.serayet07@gmail.com	04 66 01 04 40	10002958931
Dr Thierry CORNILLE	"Doctor Henry Granet" nursing home	23 Chemin de la grave 30390 ARAMON	t.cornille@chuzes.fr	04 66 02 23 80	10003245767
	EHPAD "Les oliviers"	420 Chem. de Ceserac 30490 MONTFRIN			
Dr Gilles SEYLER	EHPAD Residence "les Caprésianes"	111 Rue Alphonse Daudet 30210 CABRIERES	g.seyler@chuzes.fr	04 66 37 53 00	10003193082
	"Villa Rediciano" nursing home	6 Rue du 19 Mars 1962 30129 REDESSAN			
Dr Gil MEYRAND	EHPAD "Les Jasses"	155 Rue des Clapas 30730 FONS	g.meyrand@chuzes.fr	04 66 74 66 70	10003198586
Dr Philippe VERNEDE	"Jacques Saurin" nursing home	Avenue des Loisirs 30190 MOUSSAC	p.vernede@chuzes.fr	04 66 20 82 75	10003198107
Dr Katia BRUNEL	"Jean Lasserre" nursing home	Chem. of the Camisards 30360 EUZET	k.brunel@chuzes.fr katia.brunel@wanadoo.fr	06 25 14 02 83	10003196945
Dr Georges ALVADO	EHPAD "Les Capitelles"	The Thebaid Impasse	medecin-bernis@lesopalines.fr	04 66 71 70 50	10002675998

		30620 BERNIS	ag8400@yahoo.fr		
Dr Christine DE TADDEO	EHPAD Serre-Cavalier – Site 1 EHPAD Serre-Cavalier – Site 2	Pitot Street Extended 30000 Nîmes	christine.DE.TADDEO@chu-nimes.fr	04 66 68 40 52	10003738787
Dr Marie-Hélène GRAS-JAEN	ORPEA "Château Notre Dame" nursing home	Pl. du Château 30730 PARIGNARGUES	m.jaen-gras@orpea.net	04 66 02 78 80 06 82 33 85 78	10003194742
Dr Marc BORGHERO	Samdo Rochebelle nursing home	17 Rue des Châtaigniers 30100 ALES	marc.borghero@samdo.fr	04 66 34 76 76 06 16 07 27 18	10003185864
Dr Anne-Laure VITEAU	EHPAD "Les Cinq sens Garons"	Carieire dis Amourous 30128 GARONS	emmasolene@hotmail.fr		10004044532
Dr. Abderrahmane ALOUI	Korian "Les Meunières" nursing home	Place Denfert Rochereau 34400 LUNEL	abderrahmane.aloui@korian.fr	04 67 83 27 80 07 60 40 86 39	10100581981
Dr. Pierre Merle	Nursing home of the Langogne Hospital Center	Clos de la Tuilerie 48300 LANGOGNE	dr.pierre.merle@orange.fr	04 66 69 78 00 06 80 42 88 99	10003230942
Dr Marc DUPUIS	Saint-Vincent de Paul nursing home	16 Rue de l'Égalité 30240 LE GRAU-DU-ROI	ehpad.stvincent@ville-legrauduroi.fr dupuis.30240@gmail.com		10002955226
Dr Julie LANO	EHPAD "Canal Side"	116 Rue Jacques Cœur 30220 AIGUES-MORTES	mco.cotecanal@mutuelle-mbv.fr	04 66 80 06 06 06 85 46 81 92	10100340248
Dr Florence CHAPOUTOT	EHPAD "La belle viste"	149 Rue du parc BP 2 34980 ST GELY DU FESC	florence.chapoutot@belleviste-stgely.fr	04 67 60 17 00	10003226973

Dr Nicole GARCIA	EHPAD "Les monts d'Aurelle"	Euromedicine Park 1632 St Priest Street 34097 MONTPELLIER CEDEX 5	n.garcia@orpea.net montsdaurelles@orpea.net	04 99 74 75 00	10003890521
Dr Robert LE STUM	Protestant Retirement Home	2252 Rte de Mende 34090 MONTPELLIER	x.guido@mrp34.org	04 67 63 64 30	10003221842
Dr Marie-Aude BONNEL	EHPAD "Les Dominiques"	2 Rue du Thirondel 34190 GANGES	dr.bonnel.marieaude@gmail.com	07 85 91 69 62	10100616332
Dr Adrien ROMARY	EHPAD "Résidence les Magnans"	85 Rue du Dix Neuf Mars 1962 30520 SAINT-MARTIN-DE-VALGALGUES		06 17 44 12 93	10100971067
Dr. Victor LIVIOT	Léon Bourgeois nursing home	1 Puig Tarrous Square 66740 VILLELONGUE DELS MONTS	v.liviot@adpep66.org	04.68.68.71.32	10001882835
Dr. Philippe Roure	La Pinède nursing home	110 chemin des Cades 30310 Vergèze	philippe.roure6@orange.fr	04 66 35 76 00	10003199089
Dr. Franck Raschilas	Bellevue-Montpellier University Hospital Center	1 Pl. Jean Baumel 34090 Montpellier		04 67 33 90 05	10001433969
Dr. Chloé Loeffler	La Murelle nursing home	Avenue de la Gare 34480 - LAURENS	loeffler.c@outlook.fr	04 67 90 69 94	10101227154

1.11 Abbreviations

ASH	American Society of Hematology
AF	Atrial Fibrillation
ANSM	National Agency for the Safety of Medicines and Health Products
CRA	Clinical Research Associate
BESPIM	Department of Biostatistics, Epidemiology, Public Health and Innovation in Methodology
CI	Confidence interval
CNIL	National Commission on Information Technology and Freedom
CPP	Independent French ethics committees
CRA	Clinical Research Assistant
CRF	Case Report Form
DOA	Direct oral anticoagulants
DVT	Deep Venous Thrombosis
eCRF	electronic Case Report Form
HAS	In english: "Haute Autorité de Santé"
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
INR	International Normalised Ratio
INRc	capillary INR
INRv	venous INR
NUH	Nîmes University Hospital
GOLD	Odds Ratio
OTT	Out of therapeutic target
PMSI	Programme for the medicalisation of information systems
TT	Therapeutic target
TTR	Time in Therapeutic Range
VKA	Vitamin-K Antagonists

1.12 Synopsis

1. RCB Number

2022-A00516-37

2. Full title of the research

Evaluation of a strategy of weekly monitoring of INR by capillary puncture (INRc) versus monthly monitoring by venous INR (INRv) in elderly patients in nursing homes: A multicenter randomized cluster trial.

3. Rationale and critical analysis of the relevance of the research

Eighteen percent of subjects over the age of 85 are treated with vitamin K antagonists (VKAs). VKAs are indicated for the prevention of stroke in patients with atrial fibrillation (AF), deep vein thrombosis (DVT) or heart valve carriers. VKAs have a narrow therapeutic range and require laboratory monitoring by the International Normalized Ratio (INR). The INR target is 2.5 (tolerance between 2 and 3) for AF and DVT. Venous INR (INRv) follow-ups occur monthly, except when the INRv is off-target, in which case monitoring is close.

"Time in the therapeutic interval (TTR)" refers to the time spent in the therapeutic target of the INR. It makes it possible to evaluate the benefit/risk ratio. In French nursing homes, the average TTR is 57.9%, compared to 70% recommended. Thus, these elderly patients would require better INR monitoring. However, venous access being very limited in elderly patients, it constitutes a major obstacle to the INRv in daily practice. The advantage of monitoring INR by capillary puncture (INRc) is that it can be performed more frequently (weekly monitoring), thus increasing the TTR through better control of VKAs.

The general objective of this study is therefore to compare the TTR between a weekly monitoring strategy by INRc and the usual monthly monitoring strategy by INRv in patients in nursing homes.

4. Hypothesis and objectives

Hypothesis: Following the results of our pilot study (manuscript accepted in *Internal Medicine Journal* in August 2019), we hypothesize that a weekly capillary INR monitoring strategy would increase the TTR of patients in nursing homes by 12% compared to the usual control by venous INR, leading to a decrease in thrombotic or hemorrhagic events.

Objective hand:

The main objective of this study is to compare the TTR between a weekly cRNI monitoring strategy and the usual monthly vRNI monitoring strategy in nursing home patients.

Secondary Objectives:

A. Objectives A:

A1. To compare the occurrence of venous thromboembolic events or bleeding events in each of these two monitoring strategies.

A2. To compare the occurrence of venous thromboembolic events in each of these two surveillance strategies.

A3. To compare the occurrence of bleeding events in each of these two surveillance strategies.

B. To compare the TTR between a weekly cRNI monitoring strategy and the usual monthly follow-up with rRNIs in two subgroups of patients: ≤ 90 and > 90.

C. Describe the monitoring conditions in each group.

D. To evaluate over a period of 6 months following inclusion, the economic repercussions in terms of the cost of hospitalization (for hemhemogic/ischemic/thromboembolic events) of patients in the two study groups and the cost of the device (equipment and consumables, from the point of view of the health insurance and the nursing time from the point of view of the health establishment).

E. Extrapolate to the national level the economic repercussions in terms of the cost of hospitalization (for hemhemorrhagic/ischemic/thromboembolic events) of the generalization of the experimental strategy, in a budget impact analysis, from the point of view of the Health Insurance and the health establishment (for the mobilization of staff).

F. Assess, over a 6-month observation period, the concordance between cNRI and vNRIs.

5. Benefits and risks

Benefits:

Thanks to the INRc, we will be able to better balance the anticoagulant treatment of patients in nursing homes. The INRc has the advantage of:

1. to be fast (i.e. result in 5 minutes).
2. be able to be performed more frequently than the rRNI (i.e. weekly and more if necessary).
3. to be easily used in case of emergency (e.g. in the afternoon / night / weekend, and/or in case of an intercurrent event).
4. to allow better control of the INR and the adjustment of the VKA dose.
5. to immediately adjust the dose of VKA by the nurse, thanks to a standardization of the protocol.

The benefits of better monitoring of VKAs include:

6. fewer DVT events, stroke and bleeding.
7. fewer emergencies among the elderly (reduction in visits to the emergency department).
8. improve the quality of life of elderly patients.

Risks:

The risks related specifically to INRc are: minimal test-related pain when taking a drop of blood from the finger (capillary puncture), and improper handling that may require a new capillary puncture. Since the correlation between rRN and cRN has already been demonstrated in our previous pilot study, the risk of error in VKA dose modification is extremely low.

6. Procedure implemented to inform and obtain the consent of patients or their legal representatives/relatives

Patient consent: When a patient meets the eligibility criteria, he or she will receive clear and understandable information adapted to his or her ability to understand the study (objectives, objectives, duration of the research, expected benefits/constraints/foreseeable risks, constraints related to the study, etc.) by an investigating medical oncologist (in accordance with Article L1122-1). He will give the information note and give the explanations to the patient, rectify errors of assessment, and take up the misunderstood data. When the investigator is satisfied that the patient understands the implications of participating in the study, the consent form will be given to the patient.

Consent of the legal representative/person of trust/guardian: When a patient meets the eligibility criteria, his or her legal representative/person of trust/guardian will receive clear and understandable information adapted to his or her ability to understand the study (objectives, objectives, duration of the research, expected benefits/constraints/foreseeable risks, constraints related to the study) by a medical oncologist (in accordance with Article L1122-1). He will give the information note and explanations to the legal representative/person of trust/guardian, rectify errors of assessment, and take up misunderstood data. When the investigator is satisfied that the legal representative/trusted person/guardian understands the implications of participating in the study, the consent form will be given to him/her.

7. Description of the population and eligibility criteria

This is an interventional, prospective, comparative, superiority, multicenter, cluster-randomized, closed-cohort study.

Population:

Our population corresponds to patients living in nursing homes who have been treated for more than six months by VKA. The two groups in the study are:

• Control group (n = 16 nursing homes, 64 patients): Patients will be managed according to the usual procedure by INRv. Practices will not be modified (*i.e.* prospective observation of actual practices).
• Intervention group (n = 16 nursing homes, 64 patients): Patients in the interventional group will be monitored by INRc every week, and more if the INR is not in the therapeutic target. [See protocol for more information]

Patient inclusion criteria:

• The patient is an adult and lives in a nursing home

• The patient has been treated with VKA for more than six months

• The patient has a target INR of 2.5 [2-3] or 3 [2.5-3.5].

• The patient or his/her trusted person/legal representative/guardian has signed the consent form

• The patient is enrolled in a health insurance program

Criteria for non-inclusion of patients:

• The patient participates in a type 1 interventional study (Jardé law).

• The patient is in an exclusion period determined by another study

• The patient is under judicial protection.

• It is not possible to give informed information to the patient (or to his or her trusted person/legal representative/guardian).

• The patient has a life expectancy of less than one month (< 1 month)

• The patient's Karnofky index is ≤ 20%

8. Investigation procedures carried out and differences from usual management

Patients will be recruited in nursing homes. For those who have agreed to participate in the study, the consent form will be given and signed and the patient will be included in the study. Randomization of the center will be performed after the inclusion of all patients in the center (Closed Cohort). Depending on the nursing home in which the patient is located, he or she will belong to the interventional group or the control group (cluster randomization).

Once included, patients will be followed for six months.

Interventional group:

An INRv and an INRc will be performed at the beginning of the study to verify the concordance between the two monitoring methods (before starting weekly monitoring by INRc). Then, the frequency of the cRNI will be once a week or even once every two weeks, except in the case of cRNI values outside the therapeutic target, in which case, the frequency of the cRNIs will be brought closer together [For more information, refer to the protocols].

During each measurement, the nurse will complete the VKA dose software. As for the pilot study, the software will indicate the day of the next puncture and the dose of VKA to be done, in accordance with the recommendations of the HAS. Whereas if the INR is > 4, an alert will tell the nurse that she will have to contact the doctor to find out what to do for the rest of the follow-up.

In addition, once a month, an INRv will be performed (the result of the INRv will be blinded to the investigators) for the sole purpose of calculating the TTR under the same conditions as in the control group. An adjudication committee will blind the files of patients who have had bleeding or thromboembolic events or serious events during the follow-up period. He will verify the accuracy of the events studied.

Control group:

For patients in the control group, the usual management will be respected (i.e. monthly monitoring by INRv):

• 1 INRv made each month.

• 1 additional INRv performed after 3 and 6 days in case of INR disorder.

9. Procedures and amount of compensation for persons participating in the research

Patients included in the study will not be compensated.

10. Reasons for setting up or not setting up an independent oversight committee

Not applicable because this study is placed in category 2 of the Jardé law.

11. Anticipated number of individuals to be included in the research

A total of 128 patients will be included in the study (64 in each group).

2 Introduction

2.1 Background and rationale

2.1.1 Background information/ Studies available/state of the art

2.1.1.1 Generalities about VKA

Eighteen percent of subjects over 85 are treated with vitamin-K antagonists (VKA) (1). For elderly patients with atrial fibrillation (AF) or deep venous thrombosis (DVT), stroke prophylaxis is a real clinical challenge (2). VKA treatments are indicated for the prevention of stroke in patients with AF, DVT or those who have received heart valve implants (3). VKA have a narrow therapeutic range: in case of under dosage, the embolic risk (AVC and DVT) is high, while in case of overdose, the risk of bleeding is raised. Given the severe haemorrhage annual incidence of 3-5%, their main side effect is the haemorrhagic risk (4). The incidence of intra-cerebral haemorrhage is 0.6 per 100 patient-years, that of gastrointestinal bleeding is 1.0 per 100 patient-years, and that of other serious bleeding is 1.4 per 100 patient-years (5). This bleeding risk is usually assessed using the HAS-BLED score (Table 2-1) (6). The risk of haemorrhage is 4.2% per year in patients over 75 versus 1.7% per year for those under 75 (7).

Table 2-1 HAS-BLED score (3).

Letter	Clinical sign	Number of allocated points
H	High blood pressure (SBP > 160 mmHg)	1
Has	Renal (Serum creatinine > 200 µmol/L) or hepatic (cirrhosis or bilirubinemia > 2N and transaminases > 3N) failure	1 or 2
S	History of stroke	1
B	Bleeding (history of bleeding or bleeding predisposition)	1
L	Unstable INR (< 60 % in the therapeutic target)	1
E	Age > 65 years old	1
D	Drugs (antiplatelet, nonsteroidal anti-inflammatory drugs) or alcohol 1 point per item	1 or 2

2.1.1.2 Benefit/risks ratio: The Time in Therapeutic Range parameter (TTR)

Biological monitoring is essential to avoid stroke, DVT, and haemorrhage. It generally consists of a venous sampling of the international normalised ratio (INR), for which the therapeutic target is 2.5 (tolerance range between 2 and 3) or 3 (tolerance range between 2,5 and 3,5) (3). When the target is 2,5: INR values lower than 2 indicate high risks of stroke or DVT, while those above 3 refer to high risks of haemorrhage.

When the target is 3 : INR values lower than 2,5 indicate high risks of stroke or DVT, while those above 3,5 refer to high risks of haemorrhage.

INR follow-ups must occur monthly, and even more frequently if the HAS BLED score is ≥ 3 (3).

A parameter used to evaluate the benefit/risk ratio is the "time in therapeutic range" (TTR), which refers to the time spent in the INR therapeutic target (i.e. INR between 2 and 3 for patients with AF/ DVT or between 2.5 and 3.5 for patient with a heart valve implant) (9). It is calculated using the Rosendaal method (8). According to the "European Society of Cardiology" (ESC) guidelines, the minimum threshold necessary for a good risk/benefit ratio is 70% (9). In other countries, it has been shown that the TTR is higher: 61% in Canada, 64.4% in Spain, 68.9% in

Italy and 76.2% in Sweden (9, 10). Moreover, the TTR determines the benefit/risk ratio of the treatment, which means that patients with a TTR < 60% had more than 2% absolute total mortality per patient-year compared to patients with TTR > 60% (11).

2.1.1.3 INR conditions of elderly patients

In French nursing homes, the mean TTR is 57.9% (12), yet these elderly patients require better INR monitoring. The poor venous access in elderly patients is a major obstacle to venous punctures in daily practice. In consequence, INRv are often reported or performed under poor conditions (e.g. several punctures needed, with a tourniquet or on winged needles). No study has focused on the quality of INRv samples in nursing home.

There are lots of good practices to follow for INRv punctures. It is recommended that the venipuncture should be performed straight, with a needle of 0.7 to 1mm diameter. The tourniquet should be left less than a minute. The venipuncture must be on a citrated tube, and on the second tube collected (13). The tube should contain one volume of sodium citrate for 9 volumes of blood. It must be rejected by the laboratory if it is not more than 80% full. During transport, it must be held vertically to avoid contact with the cap, and at room temperature. Moreover, the time between sampling and analysis must be less than 6 hours (14). In ambulatory care, 65% of INRv readings do not comply with these recommendations, leading to inaccurate results (15).

To avoid INRv monitoring, two options are possible: (I) the use of DOA, or (II) INR monitoring by capillary puncture (INRc). Since February 2018, VKA and DOA are both recommended as first-line treatment in case of embolic event prevention of patients with FA or DVT (24). Clinical studies of DOA are: RELY for dabigatran (16), ROCKET for Rivaroxaban (17), ARISTOTLE for apixaban (18). These non-inferiority studies (16-18) showed that DOA and VKA are comparable in terms of prevention of thromboembolic events, and that, in comparison with warfarin, DOA have a lower incidence of intracranial haemorrhages, but higher digestive haemorrhages, which has been demonstrated by real-life observational studies (19). The mortality related to digestive haemorrhages increases with age (20). Furthermore, when TTR is greater than 75%, no studies showed non-inferiority (21). The 2016 European guidelines recommend that VKA should be prescribed when the TTR is above 70% (9). To date, no interventional or superiority study of DOA has been specifically performed on this fragile population of elderly patients. The HAS recommendations of February 2018 specify that the prescription of a DOA or VKA should be studied on a case-by-case basis and should take into account age, renal function and weight (22). In nursing homes, the average age of VKA-treated patient is 87, with 75% displaying bad renal function (creatinine clearance ≤ 60mL / min) (12), and 15-38 % suffering from malnutrition (23). These factors limit the use of DOA in nursing homes. In case of INR target [2,5 – 3,5], most currently for heart valve implant, DOA are not indicated.

Second, INRc monitoring can be performed weekly or bi-weekly; it thus increases the TTR because of better VKA control. Indeed, in a meta-analysis including 3,049 patients, it has been demonstrated that INRc monitoring decreased thromboembolic events (OR: 0.45, 95% CI: 0.30-0.68), overall mortality (OR 0.61, 95% CI 0.38-0.98), and bleeding (OR: 0.65, 95% CI: 0.42-0.99) in the group of patients controlling their INR by capillary puncture (self-management) compared to a conventional control that used the INRv (24). In Scandinavian countries and the USA, patients treated with VKA are already performing INRc monitoring in self-management (10, 27). INRc is used by hospital departments, both when starting treatment and during emergency management of stroke (28, 29). A significant intraclass coefficient correlation between INRv and INRc has already been demonstrated (27). In France, INRc monitoring devices are marketed but have only been reimbursed since 2016 for patients who have received heart valve implants, and since 2012 for children (28). In 2008, the HAS ("*the French National Authority for Health*") estimated that the therapeutic education of the 1,100,000 VKA treated patients was a prerequisite for self-measurement and self-management of the INRc (29). It had not been able to provide therapeutic education for all patients on VKA, and, consequently, reimbursement was not accepted (29), except for patients who have received heart valve implants because they are less numerous and therapeutic education structures have been organized (28).

In nursing homes, care is delegated to caregivers. Therefore, patients are not affected by therapeutic education. To the best of our knowledge, there is currently no published data on the INRc monitoring for this elderly and fragile population in nursing homes. Only one short-term correlation study has been performed in elderly patients in a French geriatric hospital. It showed an "excellent" ICC (ICC = 0.97; p < 0.0001), which refers

to an excellent numerical correlation between INRc and INRv (30). Recently, in a 6 month short-term correlation pilot study performed in 2016 in a French nursing home (nursing home from the Pont Saint Esprit hospital) including 40 patients (over half of whom were older than 90), we demonstrated that the decisional concordance between INRv and INRc was good (K = 0.76; 95% CI = [0.72, 0.81], (p<0.0001)). Moreover, we observed a 78% TTR with the weekly INRc supervision strategy, which must now be confirmed in a randomised control trial. The results of this study will soon be published in a rank C journal (Internal Medicine Journal) (manuscript accepted in August 2019).

Advantages of INRc monitoring devices [CoaguChek INRange®] are that they are small (145x75x30 mm) and portable and provide INR value in a few minutes. This allows the establishment of standardised protocol for dose adjustment of VKA. This type of protocol is allowed by the article R.4311-7 of the French public health code. Article R. 4311-7 allows the nurse to administer medications in line with a written protocol, qualitative and quantitative, previously established, dated and signed by a doctor (31). The existence of a protocol has been shown to improve the initialisation duration of VKA treatment: the therapeutic equilibrium delay of 10.6 days (± 5.9 days) for patients whose prescribers had followed the protocol and 13.5 days (± 7.6 days) for patients whose prescribers had not followed this kind of protocol (32). The American Society of Hematology (ASH) recommends using validated decision support tools (paper nomograms or computerised dosing programs) for dose adjustment (33). HAS does not have a recommendation on how to adjust the anticoagulant dose, but only on whether or not to skip a dose and/or take vitamin K (see Table 2-2) (34). For dose adjustment, the ASH recommends adjusting the dose by 0 to 20% depending on the situation (see Table 2-3) (35).

Table 2-2 Management of VKA overdose according to HAS (34)

Measured INR	INR therapeutic target = 2.5 (2 ≤ INR ≤ 3)
INR < 4	- usual medication - No VKA
4 ≤ INR < 6	- Skip one treatment - No VKA
INR 6≤ < 10	- Stop treatment - 1 to 2 mg of oral VKA (grade A)
INR ≥ 10	- Stop treatment - 5 mg of oral VKA

Measured INR	INR therapeutic target = 3 (2.5 ≤ INR ≤ 3.5)
INR < 4	NC
4 ≤ INR < 6	- usual medication - No VKA
INR 6≤ < 10	- Skip one treatment - 1 to 2 mg of oral VKA with cardiologist advice
INR ≥ 10	- cardiologist advice or hospitalisation

Table 2-3 Management of VKA dose according to the ASH (35)

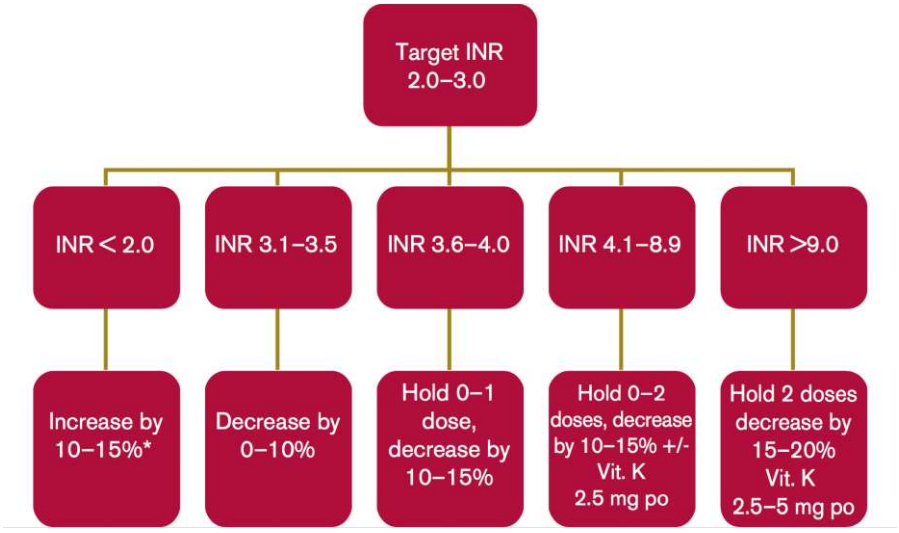

Table 2-4 Management of VKA dose according to the BC Guidelines (34)

INR	**Intervention –** Refer to Figure 1 for timing of next INR
< 1.5	Give one time top-up equal to 20% of weekly dose and increase weekly dose by 10 – 20%.
1.5 < INR < therapeutic range	No change in dose. If two consecutive INRs are low, increase weekly dose by 10 – 20%.
INR in therapeutic range	No change.
INR > therapeutic range but < 5.0	Lower weekly dose (10 – 20%) or consider omitting one single dose. Increase the frequency of INR monitoring and resume therapy at 10 – 20% lower weekly dose when INR therapeutic. Note: If the INR is only minimally elevated (0.1 – 0.4 above upper limit of the therapeutic range), dose reduction may not be necessary.[25]
INR 5.0 – 9.0*	Omit 1-2 doses then recheck INR. Increase the frequency of INR monitoring and resume therapy at 10 – 20% lower weekly dose when INR therapeutic. If the patient is at high risk of serious bleeding, consider administering vitamin K** 1 – 2 mg orally.
> 9.0 no bleeding	Discontinue warfarin temporarily, consider administering vitamin K 2 – 5 mg orally then recheck INR.*** Increase the frequency of INR monitoring and resume therapy at 20% lower weekly dose when INR therapeutic. Give additional vitamin K if INR is not substantially reduced by 24 hours.***

Abbreviation: INR = international normalized ratio.
Footnotes: * Bleeding risk increases exponentially from INR 5 to 9[26] and should be monitored closely. ** If vitamin K is not available in your local pharmacy, it can be obtained from your local emergency department. Avoid intramuscular injections of vitamin K to prevent local injection site bleeding which also reduces bioavailability. *** The effect of a single dose of vitamin K on the INR can be expected between 8-24 hours.

In nursing homes, INRc monitoring could be performed by nurses to decrease VKA-related iatrogenesis. According to a meta-analysis, the design of a study on INRc monitoring should use TTR as the primary outcome variable and event rates as a secondary outcome and base the sample size calculations upon a 5-10% absolute improvement in TTR (36). Increasing the TTR by 7% would reduce the risk of major haemorrhage by 1/100 patient-years, and by 12% the risk of thromboembolic by 1/100 patient-years (37).

The general aim of this study is thus to compare the TTR between a weekly monitoring strategy by INRc versus the usual monthly monitoring strategy by INRv in nursing home patients.

2.1.2 Originality and innovative aspects

Elderly patients in nursing homes receive polypharmacy treatments and are poly-pathological, increasing their iatrogenic risk. Indeed, they represent a population particularly sensitive to drug side effects because aging causes renal function decrease, hypoprotidemia, osteomuscular loss and adipose gain, which modify drugs pharmacokinetics.

When granting marketing authorization, safety evaluation of a new drug/medical device in elderly is usually limited to relatively small numbers (38). Interventional studies including elderly patients are thus rare. The numerous studies describing an increase in iatrogenesis in elderly patients clearly show the need to specifically test drugs, medical devices or therapeutic strategies in this fragile population.

No interventional study has focused on nursing home patients, yet 800,000 persons currently live in nursing homes in France and only 2.5% studies in elderly patients were carried out in nursing homes (37). Consequently, the Ministry of Health believes that we do not have sufficient data to promote optimal care for people living in nursing homes. So, the Ministry of Health emphasizes the need to develop studies in elderly patients from nursing homes and not only from University Hospitals: "It is important to value the studies, researches, actions that aim at improving the drug prescription in nursing home" (39).

DOA are increasingly used in place of AVK, while their superiority over VKA has not been studied. No interventional DOA studies have been conducted in the elderly, although they are more sensitive to iatrogenic events than younger people (22). Moreover, there is a misuse of DOA: in 29% of cases, the DOA are prescribed in a way that are not conform to their indication, against indication or dosage (22). Since June 2018, HAS have recommended AOD & AVK but the use of DOA in nursing home patients is limited by their age, nutritional status and renal function (22).

VKA should be privileged if their TTR is greater than 70% which is the objective of the INRc. The average TTRs of the VKA arms in the three major trials (RELY, ROCKET, ARISTOTLE) are all < 65% (16, 17, 18). In our pilot study, we showed an average TTR of 78%, which is very encouraging and must now be confirmed in a randomized control trial (Manuscript accepted in August 2019 in *Internal Medicine Journal*).

Finally, the cost of DOA is much greater than that of VKA. For example, taking into account the cost estimates for anticoagulant treatments of the 2013 ARS Bourgogne, they obtained for 32 residents treated a cost of 5,894.40€ per year, instead of 29,099.52€ annually under DOA . According to the European recommendations, there is no reason to replace a well-balanced VKA treatment (TTR > 70%) with a DOA (9). In total, 17% of nursing home residents are currently treated by VKA (40). The weekly surveillance strategy by INRc could reach this threshold of 70% of TTR and thus improve the safety of VKA, the organisation of care and the cost of treatment.

To date, no study has focused on a weekly monitoring strategy by INRc in elderly patients, except the short-term correlation study performed in a French geriatric hospital (30), and our pilot study (Manuscript accepted in August 2019 in *Internal Medicine Journal*) that confirmed (a) the concordance between INRv and INRc, and (b) the feasability of this kind of protocol in nursing homes. Indeed, in the pilot study, even if manipulation of the INRc devices required specific training for nurses and a short adaptation time, 67% of INR required a single blood capillary sample. Moreover, deviations from the protocol were rare: only 40/394 concomitant capillary and venous samples could not be taken the day as planned because of difficulties to practice INRv punctures during the week-end. During this study, we also showed that it is possible to implement a weekly INRc monitoring protocol with delegation of tasks to nurses.

If the project is selected, it will become the research priority of the Department of General Medicine of Montpellier University in order to insure its implementation. This department benefits from a network of 200 general practitioner masters internship and 450 interns per year. Moreover, our Group of territory Hospitals, the UMECO union (union of coordinating doctors of the Gard), and the National College of Teaching Generalists support this study.

So, this primary care study aims to compare the TTR of two INR monitoring strategies for 6 months in nursing homes. The population is composed of frail elderly patients for whom VKA treatments are frequent, and that are consequently more prone to embolic and hemorrhagic complications. As for the pilot study (Manuscript accepted in August 2019 in *Internal Medicine Journal*), we expect approximately half of the patients to be over 90. Patients will be recruited in nursing homes where monitoring is conducted by nurses and managers of the quality of care are responsible for verification of good clinical practice compliance. This limits the risk of non-compliance with INRv preanalytical conditions.

2.1.3 Expected patient or public health benefit

- **Patient benefits:**

Elderly patients treated with VKA need appropriate anticoagulation monitoring because their risk of haemorrhage is high and difficult to control. VKAs affect many elderly patients (18.5%). By monitoring their INR more precisely by INRc, we will be better able to balance their anticoagulant treatment. INRc monitoring is quick (i.e. result in 5 minutes) and more can be made more frequently (i.e. weekly (and more if necessary)) than INRv. INRc measurements will consequently increase TTR, and thus also reduce hemorrhagic and thromboembolic events. Our pilot study (Manuscript accepted in *Internal Medicine Journal*) showed that the TTR of patients over 90, for whom historical TTR was low and the VKA not stable, was higher when the INRc monitoring was used.

The use of INRc allows:

(1) Immediate dose adjustment by the nurse, thanks to protocol standardization. Usually, physicians visit nursing home patients only once a week. That organization implies that adaptations of VKA doses are not directly performed (because monitoring is often performed by nurses the following day, and samples have to be sent to medical laboratories which takes time to get results and adjust patients' VKA doses), and that errors frequently occur (especially when dose adjustments are carried out by phone). Our protocol for dose adjustment that has been modeled from means of capillary blood glucose (i) allows immediate dose adjustment, (ii) avoids adjustments by phone and (iii) allows to keep a computer trace thanks to delegations of task to nurses, thus securing the prescription and the administration of the dose.

(2) Emergency use (e.g. in the afternoon/night/week-end and/or in case of intercurrent event). Intercurrent events that require immediate control of the INR are haemorrage assessed by the BARC score (BARC score, see Appendix 9.4), and thromboembolic events (phlebitis, pulmonary embolism, stroke).

Intercurrent events that require INR control within 48-72h are:

- events with risk of bleeding: falls, confusion, fever, systolic blood pressure > 160mmHg, acute renal failure (9)
- change of a medication predisposing to bleeding: acetylsalicylic acid, antiplatelet or anti-inflammatory, NSAID, miconazole, paracetamol> 3g/day, St. John's wort, glucocorticoids, LMWH, selective serotonin reuptake inhibitors, antibiotics (cephalosporin, cyclin, fluoroquinolone) (41).
- Acute digestive disorder or diet occasionelly rich in vitamin K (41).

(3) A better respect of the control time when VKA dose has to be adjusted (i.e. INR control must be carried out 3 days after each dose change. Since the analysis laboratories are closed at the weekends, these controls are frequently postponed).

(4) a better balance of VKA (which limits iatrogenic events and hospitalisation episodes).

- **Public health benefits:**

The benefits of a better monitoring of VKA are:

- fewer DVT, stroke and haemorrhage events
- fewer emergencies in the elderly (reduction in emergency room visits)
- improvement of the quality of life of elderly patients.

A national cohort study of the budgetary impact of weekly INRc monitoring versus monthly INRv monitoring in the Netherlands showed that increasing weekly monitoring usage from the current 15.4% to 50% resulted in savings from €8 million in early years to €184 million after 5 years. In the Netherlands, there are 260,000 patients treated by VKA (42). A meta-analysis of 26 randomised controlled trials concludes that INRc self-monitoring is a safe and cost-effective option versus monitoring with INRv (43).

Thus, reducing the number of complication events and emergency visits or hospitalisation could have a positive budget impact for patients treated with VKA and for the Ministry of Health.

- **Risks:**

The risks related specifically to the use of INRc monitoring are: minimal pain related to the test by taking a drop of blood from a finger stick (capillary puncture), and a mishandling could require a new capillary puncture. Given that the correlation between INRv and INRc has already been demonstrated in our previous pilot study, the risk of error in the dose modification is extremely low.

As INRc monitoring will be performed more frequently than INRv (i.e. weekly instead of monthly), out-of-range results will be rarer. The risks associated with the common practice of venous punctures are more numerous: allergic contact dermatitis, pain, ecchymosis at the point of puncture, vasovagal syncope. Thus, as we will be monitoring VKA using the current recommendations, there will be no risk over usual surveillance for the control group.

However, we are not immune to risks directly related to VKA (e.g. haemorrhage, or their indication: stroke or DVT) but this is not directly related to this study objective.

2.1.4 Assumptions

Following results of our pilot study (Manuscript accepted in *Internal Medicine Journal*), we hypothesise that a weekly monitoring strategy of capillary INR should increase the TTR of nursing home patients by 12% compared to the usual monitoring by venous INR, resulting in a decrease of thrombotic or haemorrhagic events.

2.2 Objectives

The primary objective and the secondary objectives "A" and "B" pertain to the individual participant level.

The secondary objective "C" pertains to the cluster level.

2.2.1 Primary objective

Compare the TTR between a weekly monitoring strategy by INRc versus the usual monthly monitoring strategy by INRv in nursing home patients.

2.2.2 Secondary objectives

Has. Objectives A:

A1. Compare the occurrence of venous thromboembolic events or haemorrhagic events that occurred under each of these two monitoring strategies.

A2. Compare the occurrence of venous thromboembolic events that occurred under each of these two monitoring strategies.

A3. Compare the occurrence of haemorrhagic events that occurred under each of these two monitoring strategies.

B. Compare the TTR between a weekly monitoring strategy by INRc versus the usual monthly monitoring by INRv in two subgroups of patients: ≤90 and >90.

C. Describe monitoring conditions within each group

D. Compare the cost of both monitoring strategies in terms of hospitalisations (due to haemorrhagic, ischemic and thromboembolic events): the weekly INRc monitoring strategy vs the usual monthly monitoring strategy and the cost of the device (equipment and consumables) from the public health insurance's perspective and the nursing time from the point of view of the health care institution. This economic analysis will be interpreted in light of the clinical results obtained in a cost-consequences study at 6 months

E. Assess the budget impact analysis (BIA) in order to estimate the financial consequences in terms of hospitalisations (due to haemorrhagic, ischemic and thromboembolic events of adopting the new intervention in France, in this population from the public health insurance's perspective at 3 years (Budgetary sustainability evaluation).

F. Assess, over the 6-month observation period, the concordance between INRc and INRv.

2.3 Study design

This study is interventional, prospective, comparative, superiority, multicentric, randomised by cluster, in closed cohort.

It aims to compare the TTR of two INR monitoring strategies (INRc *versus* INRv) in 32 nursing homes for 6 months. Nursing homes represent the clusters. Nursing homes will be randomised after inclusion of patients (closed cohort) (Figure 1&1bis).

There will be two groups of nursing homes:

- **Control group (n = 16 nursing homes, 64 patients):** Patients will be monitored as usual using the INRv strategy (see 3.8.2 & Figure 1 & 1bis for more details). Practices will not be changed (i.e. prospective observation of real-life practices; according to recommendations, at least 1 INRv per month will usually be performed) and patients will not receive any supplementary intervention specific to the trial. A reminder of INR good practice will be provided to nurses and prescribers (Appendix 9.3).

- **<u>Intervention group (n = 16 nursing homes, 64 patients):</u>** Patients from the interventional group will be monitored using the INRc strategy every week, and more often if the INR is not in the therapeutic target (see 3.8.2 & Figure 1/1bis for more details). INRv punctures will also be performed as described for the control group in order to calculate TTR equivalently in both groups. Specific training in handling the device and the dose adjustment protocol will be provided to nurses and prescribers.

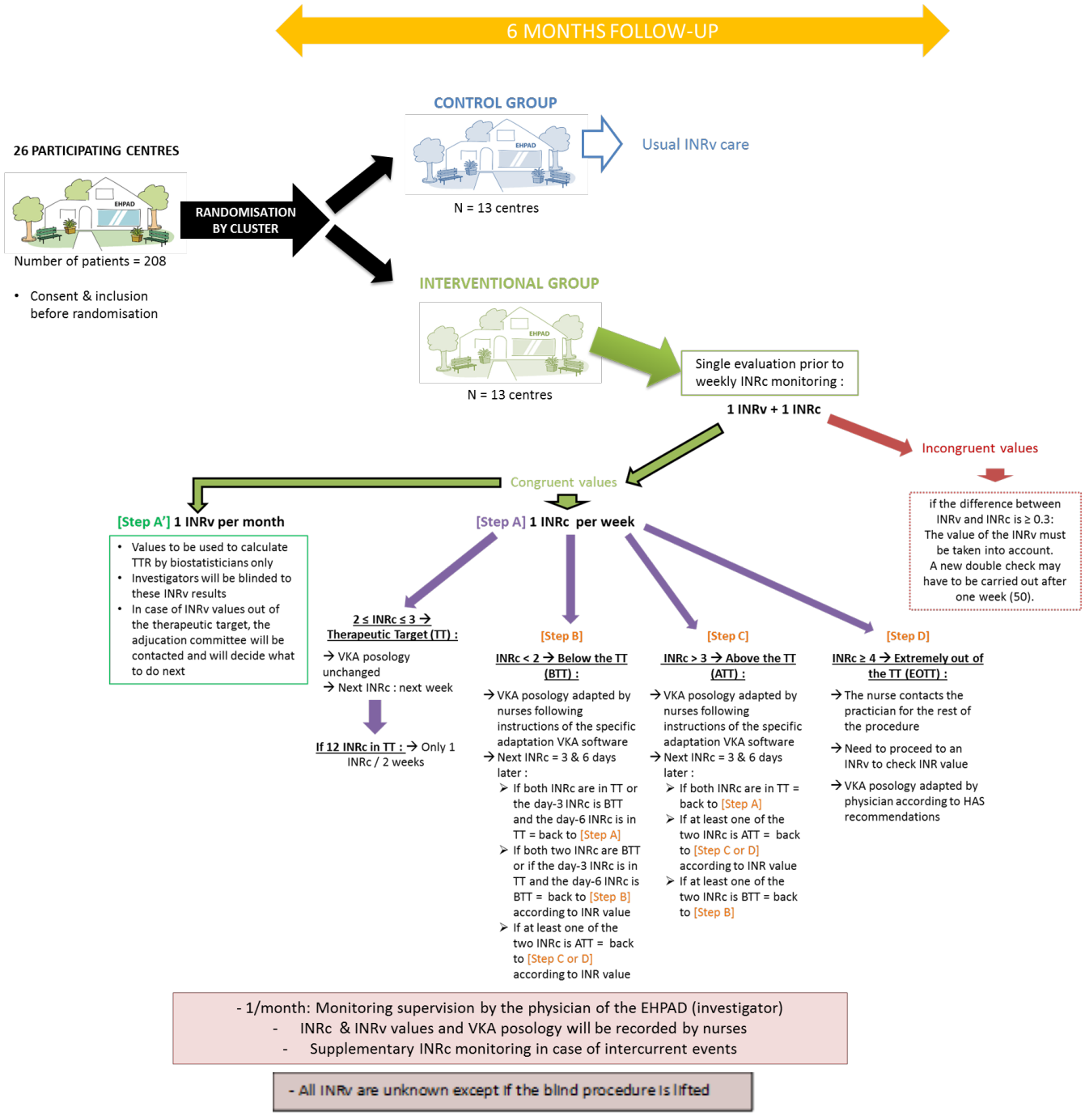

Figure 1 Diagram of the study – Target range [2-3].

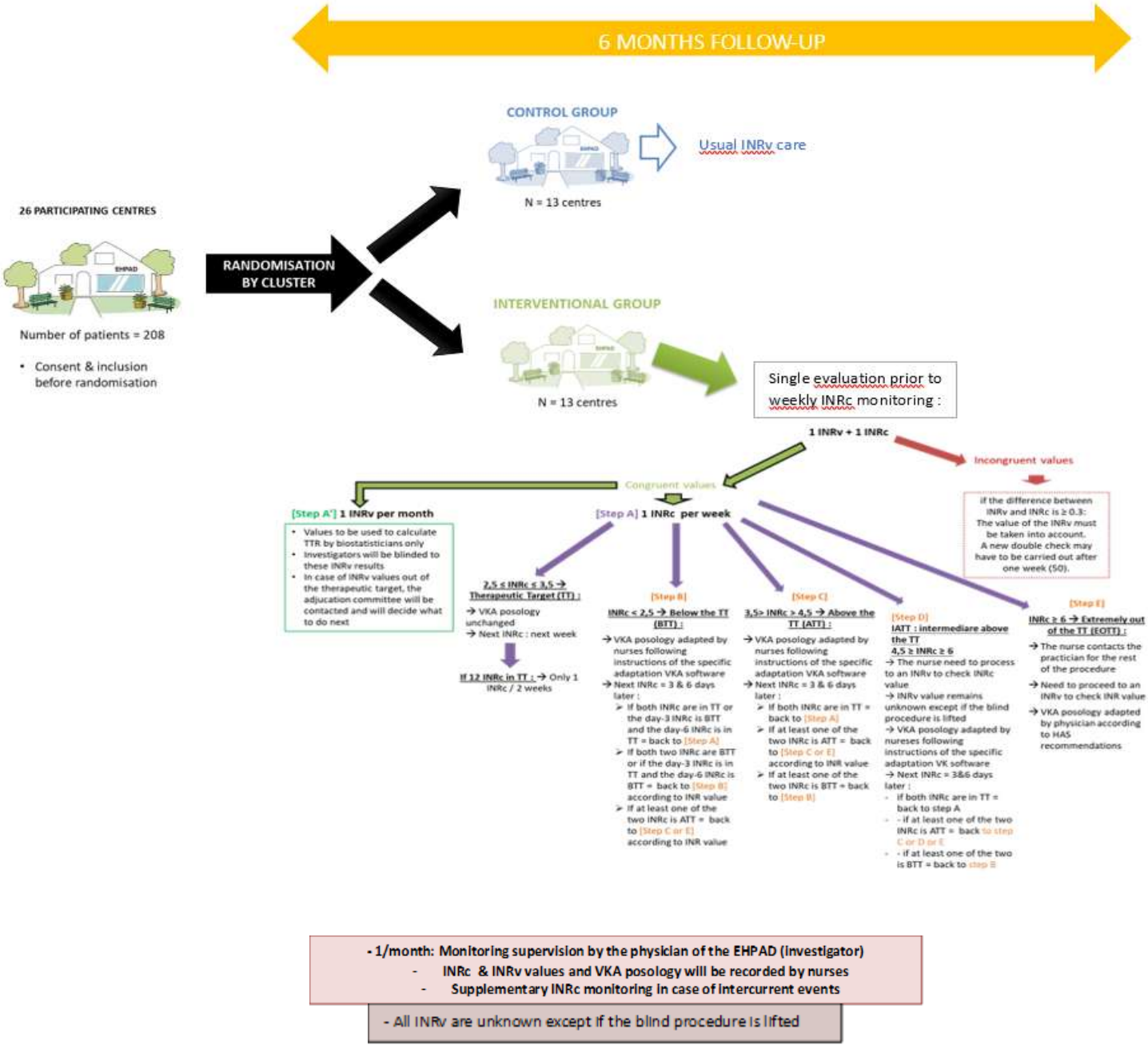

Figure 2 bis - Diagram of the study – Target Interval [2.5-3.5].

The cluster design meets our objectives as the evaluated intervention applies at the organisational level. It would be logistically challenging for a nursing team to switch between strategies using an individual randomisation. This design prevents risk of contamination between the two arms.

Patients will be recruited in nursing homes. According to the centre affiliation, either the usual monthly INRv monitoring (control group) or the experimental weekly INRc monitoring (interventional group) will be performed. The experimental weekly INRc monitoring is: one INRc per week and more when INRc are out of the therapeutic target (see Figure 1 & 1bis for more details). Monthly INRv (and more if out of target) will be performed in both groups in order to apply the same type of TTR measurement. But, in the experimental group, the investigator of the centre will be blinded to the INRv results performed during the [step A'] to avoid influencing patient care.

All eligible patients from a centre will be screened (closed cohort), informed (information letter), and recruited (consent) before centre randomisation in order to avoid bias. Centres will, *a posteriori*, be informed about their arm allocation.

To inform patients and his/her trusted person/tutor/legal representative about the study, one of the caregivers from the nursing home or the clinical study technician will call the trusted person/tutor/legal representative to fix an appointement at the nursing home. During the appointement, they will be informed by the investigator about the study. The investigator will answer their questions and give them the information note and the consent form (Appendix 9.1).

Patients and their trusted person/tutor/legal representative will have 48 hours to confirm the study participation. 48 hours after the information appointment, the caregiver or the clinical study technician will call the trusted person/tutor/legal representative to find out whether they accept to participate and if so, to organise signing of the consent form (Appendix 9.1).

Patients and their trusted person/tutor/legal representative will be informed that they will have the right to leave the study at any time without any consequence on their usual medical care.

All attending physicians will be informed by an information letter about the eventual inclusion of their patient in this study (Appendix 9.7).

Once included, patients will be followed-up for six months:

1. PATIENT FROM THE INTERVENTIONAL GROUP:

Before weekly INRc monitoring, one INRv and one INRc will be performed to check the congruence between monitoring methods (single evaluation). When INRv & INRc values are congruent, INRc will be performed: once every week (step A), reducing to every 2 weeks if 12 consecutive INRc are in the therapeutic target; after 3 and 6 days (step B+C); or in association with an INRv (step D) (see below and Figure 1 &1bis for more details).

For each measurement, the nurse will complete the VKA dose software (i.e. number of punctures, number of strips, current VKA type, current VKA dose, INRc value). As during the pilot study (Manuscript accepted in *Internal Medicine Journal* in August 2019), the software will indicate to the nurse the next puncture day and the VKA dose according to the HAS recommendations (Table 2-3) (35); and if the INR is > 4, an alert will signal that the nurse will have to contact the general practitioner to know how to proceed for the rest of the INR monitoring.

The INR procedure is (Figure 1&1bis):

At the beginning of the study, before weekly INRc monitoring, one INRc and one INRv will be performed (single evaluation):

- If INRv and INRc values are incongruent (*i.e.* the difference between INRv and INRc is ≥ 0.3): the value of the INRv must be taken into account. A verification (INRv + INRc) will have to be carried out one week later (50).
- If INRv and INRc values are congruent (*i.e.* the difference between INRv and INRc is < 0.3), the following steps will be followed:

  [Step A]

INRc monitoring will occur once a week. If 12 consecutive INRc are in the therapeutic target (TT) (*i.e.* 2 ≤ INR ≤ 3 or 2.5 ≤ INR ≤ 3.5), INRc will be performed once every 2 weeks (32).

[Step B] (for the case of 2 ≤ INR ≤ 3)

If INRc < 2 (*i.e.* value below the therapeutic target (BTT)):

- The VKA posology will be adapted by nurses using the specific adaptation VKA software.
- Next INRc will occur 3 & 6 days later :
  - If both INRc are in TT OR if the day-3 INRc is BTT and the day-6 INRc is in the TT: for the next INRc, the procedure will recommence at [Step A].
  - If both INRc are BTT OR if the day-3 INRc is in the TT and the day-6 INRc is BTT: for the next INRc, the procedure will recommence at [Step B].
  - If at least one of the two INRc > 3 (i.e. above the therapeutic target (ATT)): back to [Step C] or [Step D] according to the INR value.

[Step C] (for the case of 2 ≤ INR ≤ 3)

If the INRc is > 3 (i.e. value above the therapeutic target (ATT)):

- VKA posology will be adapted by nurses using the specific adaptation VKA software
- Next INRc will occur 3 & 6 days later:
  - If both INRc are in TT : next INRc = [Step A]
  - If at least one of the two INRc is BTT = back to [Step B]
  - If at least one of the two INRc is ATT = back to [Step C] or [Step D] according to INR value

[Step D] (for the case of 2 ≤ INR ≤ 3)

If the INRc ≥ 4 (i.e. extremely out of the TT):

- An INRv will be performed to check the INR value.
- VKA dosage will be adapted by a general practitioner according to HAS recommendations (see Table 2-2)

[Step B] (for the case of 2.5 ≤ INR ≤ 3.5)

INRc < 2.5 → Below the TT (BTT):

- The VKA posology will be adapted by nurses following instructions of the specific adaptation VKA software
- Next INRc will occur 3 & 6 days later :
  - If both INRc are in TT OR if the day-3 INRc is BTT and the day-6 INRc is in TT : for the next INRc, the procedure will recommence at [Step A]
  - If both two INRc are BTT OR if the day-3 INRc is in TT and the day-6 INRc is BTT : for the next INRc, the procedure will recommence at [Step B] according to INR value
  - If at least one of the two INRc is ATT = back to [Step C or E] according to INR value

[Step C] (for the case of 2.5 ≤ INR ≤ 3.5)

3.5> INRc> 4.5 (i.e. value above the therapeutic target (ATT)):

- VKA posology will be adapted by nurses following instructions of the specific adaptation VKA software
- Next INRc will occur 3 & 6 days later :
  - If both INRc are in TT = back to [Step A]
  - If at least one of the two INRc is ATT = back to [Step C or E] according to INR value
  - If at least one of the two INRc is BTT = back to **[Step B]**

[Step D] (for the case of 2.5 ≤ INR ≤ 3.5)

4.5 ≥ INRc ≥ 6 - IATT : intermediate above the TT

- The nurse need to process to an INRv to check INRc value
- INRv value remains unknown except if the blind procedure is lifted
- VKA dosage will be adapted by nurses following instructions of the specific adaptation VK software
- Next INRc = 3&6 days later :
  - if both INRc are in TT = back to step A
  - if at least one of the two INRc is ATT = back to step C or D or E
  - if at least one of the two is BTT = back to step B

[Step E] (for the case of 2.5 ≤ INR ≤ 3.5)

INRc ≥ 6 → Extremely out of the TT (EOTT) :

- The nurse contacts the practician for the rest of the procedure
- Need to proceed to an INRv to check INR value
- VKA dosage adapted by physician according to HAS recommendations

+ In case of intercurrent event (i.e. heamorrage type 1, falls, confusion, fever, blood pressure > 160mmHg, acute renal failure, acute digestive disorders, diet occasionally rich in vitamin K, change of a medication predisposing to bleeding; see 3.4 for the exhaustive concomitant medication list), the procedure will recommence at [step A] but with INRc monitored every 3 days for duration of the event.
+ In case of heamorrage type 2 or suspicion of phlebitis or pulmonary embolism: the nurse will perform an INRc and call the general practitioner, who will adapt the treatment according to the HAS recommendations (34)
+ In case of heamorrage type 3 or more, or suspicion of stroke or severe pulmonary embolism: it is an emergency situtation, the nurse must perform INRc and call the general practitioner, who adapts the treatment according to the HAS recommendations. Urgent hospitalisation must be considered (34).

If an ischemic or haemorrhagic stroke is suspected, a scan will be performed at the hospital to confirm diagnosis.

Once a month, the investigator of the nursing home will visit all patients to check intercurrent/adverse event and the concomitant medications (yes/no: Acetylsalicylic acid, antiplatelet or anti-inflammatory dose ++, Antiplatelet, Nonsteroidal anti-inflammatory drugs ++, Miconazole ++, Paracetamol, *Hypericum,* Glucocorticoids, Selective serotonin reuptake inhibitors, Antibiotics, cephalosporin, cyclin, fluoroquinolone).

[Step A']

Once a month, INRv will be performed, with investigator blinded to these INRv results to avoid influencing patient cares, to allow TTR calculated under the same conditions as the control group.

[For more information about the INRc device, see 3.3.1]

2. CONTROL GROUP:

Patients will receive usual medical care following the monthly INRv monitoring:

- One INRv will be performed every month.
- Supplementary INRv will also occur after 3 and 6 days in case of INR disorder as described below:
  - In case of intercurrent event (heamorrage type 1, thromboembolic events, falls, confusion, fever, blood pressure > 160mmHg, acute digestive disorders, diet occasionally rich in vitamin K, change of a medication predisposing to bleeding; see 3.4 for the exhaustive concomitant medication list).
  - In case of heamorrage type 2 or suspicion of phlebitis or pulmonary embolism.
  - In case of heamorrage type 3 or more, or suspicion of stroke or severe pulmonary embolism.

For each INRv, the nurse will proceed to usual venous puncture; prepare the tube to send to the biological laboratory and complete the "shuttle sheet" (Appendix 9.6). The tube will be transmitted to the laboratory as usual. Once at the laboratory, the biologist will proceed to INR analyses and will complete the relevant section of the "shuttle sheet" (Appendix 9.6). The biologist will have to send the results by mail in the provided stamped addressed envelope.

3 Methods: Participants, interventions, and outcomes

3.1 Study setting

This trial will take place in participating nursing homes located in France. 32 centres will participate (see 1.10 and Figure 2). Our Group of territory Hospitals, our University Department of general medicine "Montpellier-Nîmes", the UMECO group ("*Union des MEdecins COordinateurs du Gard*"), the National College of Teaching Generalists and the Regional College of Teaching Generalists support this study.

Figure 3 Maps of the South of France showing the distribution of the participating centres.

We have chosen the participating centres for the following reasons:

- Nursing homes from our territory hospital complex (in French: GHT for "*Groupement hospitalier du territoire*")
- Nursing homes where practicians from our University department of general medicine work.

This research protocol is created and supported by general practitioners and the main actors of primary care. Researches in primary care are a priority for the World Health Organisation (WHO) since 2008 (44). In France, the lack of a strong and long-standing committee of the primary care health system research is causing difficulties in structuring networks of investigators and databases (45). The development of primary care research is a public health issue. White *et al.* (44) showed that in a population of 1,000 adults followed for one month, 750 patients reported a problem health condition or a disease, 250 consulted a doctor, 9 were hospitalised, 5 were referred to another doctor and 1 hospitalised in a university center (46). The latest update of this work highlights that the

majority of the most common health problems are not seen in secondary or tertiary care. Good practice recommendations based on inpatient studies therefore cannot address primary care issues (47).

Concerning the two main investigators of this study:

- David Costa is a general practitioner, specialised in primary care. He had been university clinical leader, and he is now university lecturer at the department of general medicine of the University of Montpellier-Nîmes, thanks to his expertise in primary care. He has participated in several specific studies on primary care.
- Chloé Sikirdji is a university clinic leader at the University department of Montpellier-Nîmes. She wrote, directed and published (in September 2018) the pilot study on capillary INR in a nursing home. She received the scientific prize for the best poster for this study at the Congress of French General Medicine in April 2017. The manuscript of this study has now been accepted in August 2019 in the *Internal Medicine Journal* and will be published soon.

3.2 Eligibility criteria

3.2.1 Patients eligibility criteria

Our population corresponds to nursing homes patients treated with VKA for more than six months, because INRc cannot be used during the introduction of an anticoagulant treatment.

Patients and/or their trusted-person/legal representative/tutor will be informed and their consent will be collected (i.e. presentation of the information letter and the consent form) before cluster's randomisation.

Participant inclusion criteria:

- The patient or his/her trusted-person/legal representative/tutor signed the consent form
- The patient is an adult and lives in a nursing home
- The patient is treated with VKA for more than six months
- The patient's target INR range is 2.5 [2-3] or 3 [2.5-3.5]
- The patient is affiliated to a health insurance programme

Participant exclusion criteria:

- The patient is participating in a type-1 interventional study involving human beings (Jardé law).
- The patient is in an exclusion period determined by another study
- The patient is under safeguard of justice.
- It is not possible to give the patient (or his/her trusted-person/legal representative/tutor) informed information.
- The patient has a short life expectancy (< 1 month)
- The Karnofky index is ≤ 20%

3.2.2 Study centres and investigators eligibility criteria

Investigator/Evaluator inclusion criteria:

- The nursing home physician (the investigator) has accepted to participate in the study
- The local biologist of the nursing home agrees to participate

Investigator/Evaluator exclusion criteria:

None

Participating centre exclusion criteria

- The organisation of the nursing home does not respect good sampling practice of INRv (see Appendix 9.3).

3.3 Interventions

Nursing homes will be randomised (randomisation by cluster) in closed cohort (see Figure 1&1bis).

3.3.1 Experimental group: INRc

Patients from the interventional group will get the experimental weekly INRc monitoring strategy (weekly monitoring by INRc and adaptation of VKA doses according to the protocol and by delegation of tasks to the nurses).

Medical device presentation: INRc monitoring device [CoaguChek INRange®] will be used in this study. This medical device has already been used in several studies [*e.g.* 43]. It can be used in hospital beds.

Procedure: The nurse will wash the hands of the patient. She/he will insert the strip test into the device, massaging fingers and the hand to activate blood circulation, and perform a capillary puncture using the lancet. The drop of blood must be 8 µL. It must be deposited on the test strip less than 180 seconds after insertion of the strip in the device and within 15 seconds after the start of blood drop formation. The INR is displayed within one minute.

When the nurse has the result, he/she will complete the VKA dose software (i.e. number of puncture, number of strip, current VKA type, current VKA dose, INRc value). The software will give the next puncture day and the correct VKA dose. If the INR > 4, there will be an alert and the nurse will have to contact the general practitioner for the rest of the procedure.

Medical device description: INRc monitoring device [CoaguChek INRange®] is small (145x75x30 mm) and portable. It requires the use of a test strip. The strips are stored at room temperature.

Who: Nurses will be in charge of INRc monitoring. They will be taught by the coordinator of the study how to use the CoaguChek INRange®, to monitor results and to adjust VKA posology during a specific workshop before the study starts.

Where: Patients from nursing homes included in the experimental group will get the capillary monitoring strategy.

When: During the six-month follow-up.

Adaptation of VKA doses will be delegated to the nurses via the use of VKA adaptation software. The nurse will also collect the INRc & INRv values and VKA posology modifications. INRc monitoring will be performed weekly by nurses (see Figure 1 & 1bis and point 2.3 for more details about the INRc monitoring), excepted in case of INRc > 4 in which case the nurse will have to contact the general practitioner for the rest of the procedure.

3.3.2 Control group: INRv

Patients from a control nursing home (i.e. control group) will get the usual monthly INRv monitoring strategy (Appendix 9.3) and will not receive any supplementary intervention specific to the study. A shuttle-sheet for each study-specific sample will be completed by the nurses and by the laboratory biologist to collect preanalytical conditions and INR value (Appendix 9.6).

INRv samples will be analysed to estimate:

- Their value and frequency

- Their quality: According to the GEHT ("*Study Group on Thrombosis Haemostasis*"), INRv sampling must respect several conditions. These pre-analytical conditions will be studied using a checklist (Appendix 9.2).
- The venous access of each patient (number of samples for one analysis, postponed analysis, state of venous access according to the nurse).

3.3.3 Intervention modifications criteria

In case of withdrawal of consent by the participant, the data collection will be stopped but data collected will be kept for the statistical analyses.

3.3.4 Measures taken to homogenise interventions among participating centres

A meeting will be organised in each of the participating centres before starting the study. The modalities of intervention will be addressed. The Main Investigator and the Coordinator will also be available to answer any questions and problems during the proceedings of the protocol.

3.3.5 Monitoring adherence to interventions

For interventional nursing homes, INRc adherence will be checked by the nursing team.

3.3.6 Relevant concomitant care

All concomitant care is permitted. This is therefore no reason for non-inclusion or discontinuation of treatment.

3.4 Outcomes

Table 3-1 Outcomes and time frames associated with each relevant objective

Objective	Outcome	Measurement tool	Unit	Time point
Primary, B	The Time in Therapeutic Range (TTR), calculated according to Rosendaal's method	calculation from INRv measurements	% (individual data)	From D0 to M6, or from D0 until the occurrence a major thromboembolic or hemorrhagic event or death
A1	Composite censored outcome: occurrence and interval until the first thromboembolic event (phlebitis, pulmonary embolism, ischemic stroke, death of embolic origin) or haemorrhagic event (Bleeding according to the BARC classification; Appendix 9.4)	Electronic Patient File	Day	From D0 to M6
A2	The number of thromboembolic events (phlebitis, pulmonary embolism, ischemic stroke, death of embolic origin) per patient	Electronic Patient File	number	From D0 to M6
A3	The number of haemorrhagic events per patient (Bleeding according to the BARC classification; Appendix 9.4)	Electronic Patient File	number	From D0 to M6
F	The intraclass correlation coefficient (ICC)	Calculation from Simultaneous INRv and INRc	%	From D0 to M6, or from D0 until the occurrence a major

Objective	Outcome	Measurement tool	Unit	Time point
		Measurements		thromboembolic or hemorrhagic event or death
	C – Control group			
C1	Frequency of INRv	Electronic Patient File	number (6-24)	From D0 to M6
C2	Mean number of punctures needed per patient	Shuttle sheet (Appendix 9.6)	number (1-4)	From D0 to M6
C3	Sampling conditions for INRv (percent per patient)	Shuttle sheet (Appendix 9.6)	Yes/no	From D0 to M6
C4	Transport & treatment conditions for INRv (percent of good conditions per patient)	Shuttle sheet (Appendix 9.6)	Yes/no Yes/no	From D0 to M6

	C – Interventional group			
C5	Mean number of punctures needed per patient	Electronic Patient File	Number (1-4)	From D0 to M6
C6	Number of strips needed	Electronic Patient File	number (1-4)	From D0 to M6
D	The number of hospitalisations due to haemorrhagic, ischemic and thromboembolic events and material and consumables (for the weekly monitoring strategy by INRc) from the payer's perspective (public health insurance) and the nursing time from the point of view of the health care institution	Electronic Patient File	€, time (minutes)	M6
E	The financial consequences of adopting the new intervention (in terms of hospitalisations due to haemorrhagic, ischemic and thromboembolic events) by considering the short-term (3 years) of healthcare (payer's perspective) for all people affected by this intervention	Modeling	€, time (minutes)	M36

Clinical relevance of the primary outcome:

An important parameter for evaluating the benefit / risk ratio is the time spent in the target INR (i.e. the TTR, "Time in the Therapeutic Range"). The minimum threshold for a good risk benefit ratio would be 65% according to Rosendaal et al. (8), and 70% according to ESC guidelines (9).

According to Samsa & Matchar (35), the correlation between TTR and clinical events is strong, and the considerations to take into account for a study evaluating a device for monitoring the INR are as follows:

- has a control group whose INR equilibrium is representative of the average INR,
- includes different INR test frequencies,
- uses TTR augmentation as a primary goal and adverse events as secondary goals,
- bases its calculations on an increase of at least 5 to 10% of the TTR (35).

For other studies, 6.9% increase in TTR, a significant reduction in the risk of major haemorrhage (1/100 patient-years) and 11.9% increase in thrombotic risk (1/100 patient-years). (36). Patients with a TTR < 60% had more than 2% absolute mortality per patient-year compared to patients with TTR > 60% (11).

There are two reference methods for calculating the TTR: (1) The Rosendaal method (from the INR one-off measurements) which INR-specific person-time is calculated by incorporating the frequency of INR

measurements and their actual values, and assuming that changes between consecutive INR measurements are linear over time, and (2) a linear regression method (from the INR point measurements on the execution of a linear interpolation between two measurements deduced from the TTR.) These two methods are equivalent (8).
If a patient presented with a major thromboembolic or haemorrhagic event, requiring the temporary suspension of his treatment with VKA, the capillary INR surveillance strategy will be suspended on the date of the event and will not be prescribed again even in case of resolution of the event during the study period, but its data will be used in the analysis.
Monthly INRv and more if out of target will be performed in the experimental group in order to apply the same type of TTR measurement and to have the same frequency of measurement (monthly TTR in both groups).

Other variables necessary for the study:

- Age (years), Sex (m / f), height (cm) and weight (kg)
- Indication of the VKA (check one of the following):
  - Complete arrhythmia with AF
  - deep vein thrombosis
    - phlebitis
    - pulmonary embolism
- Type of VKA used
  - Warfarin (Coumadine)
  - Fluindione (Previscan)
  - Acenocoumarol (sintrom, minisintrom)
- concomitant medications (yes / no for each):
  - Acetylsalicylic acid, antiplatelet or anti-inflammatory dose ++
  - Antiplatelet
  - Nonsteroidal anti-inflammatory drugs ++
  - Miconazole ++
  - Paracetamol
  - *Hypericum*
  - Glucocorticoids
  - Selective serotonin reuptake inhibitors
  - Antibiotics
    - cephalosporin
    - cyclin
    - fluoroquinolone

• Medical history / comorbidities (yes / no for each):
  - heart failure
  - myocardial infarction
  - Percutaneous Coronary Intervention
  - bypass surgery of the coronary artery
  - stroke
  - Transient ischemic attack
  - Arterial claudication
  - surgery or percutaneous intervention on the abdominal aorta or vessels of the lower limbs
  - diabetes
  - chronic hypertension
  - chronic dialysis
  - kidney transplant
  - Chronic liver disease (*e.g.* cirrhosis)
  - haemorrhagic event (BARC classification (46; Appendix 9(4))
  - Anaemia Event
- renal function
  - last creatinemia

- liver function (last performed)
  - bilirubin
  - Aspartate transaminase
  - Alanine transaminase
- TTR during the last 6 months before inclusion
- Frequency of INR during the last 6 months (date)
- Karnofsky index

3.5 Justification of sample size

In the pilot study, we observed a TTR of 0.65 in the INRv arm and of 0.78 in the INRc arm, with a common standard deviation of 0.21. We penalised the baseline control value of the TTR and the expected difference between the groups because of the multicentric nature of the study, to get closer to real life. In addition, we considered an intracluster correlation coefficient of 0.05 due to the heterogeneity of venous INR surveillance practices between centers, and we took into account the variation in size of clusters (range 1 to 25) [49].

In this inequality cluster randomized trial comparing two TTR (continuous variables), a sample size of 16 nursing homes (clusters) with 4 residents per cluster on average in group 1, and a sample size of 16 clusters with 4 individuals per cluster on average, in group 2, **i.e a total of 128 individuals**, achieves 80,54% power to detect an inequality between two arms of 0,12, assuming that the standard deviation of subjects is 0,21, the intracluster correlation is 0,05, the coefficient of variation of cluster sizes is 0,67, and the test is based on a two-sided, two-sample t-test at the 5% level, with the degrees of freedom based on the number of clusters (n'Query, version 8.7.2.0).

3.6 Recruitment

Elderly patients that need VKA treatments (for more than 6 months) will be recruited in nursing homes where INR monitoring is conducted by nurses. We expect approximately half of the patients to be over 90. We specifically selected nursing homes where eligible patients are already referenced. These patients will screened (closed cohort), informed (information letter), and included (consent) before centre randomisation. Patients will not receive any compensation for their participation in this study, but patients from the interventional group will be compensated for their risk of haemorrhage by monitoring their INR more precisely by INRc and by finding a better balance for their coagulant treatment.

Here is the expected number of patients to be recruited in each centre:

Name	First name	City	Country	Expected recruitment/month	Total
LEROY	Philippe	Vialas	France	10	10
LEROY	Philippe	Genollhac	France	7	7
PUGIBET	Maryvonne	Roquemaures	France	9	9
GIORDANO	Jacques	Saint Hilary of Brethmas	France	9	9
BOUVOT	Jean-Bernard	The Roach Halls	France	12	12
BORGHERO	Mark	Alès	France	11	11
SERAYET	Phillipe	Meynes	France	9	9
MILLION	Julia	Montpellier	France	10	10
ANDRE	Susan	Alès	France	11	11
ANDRE	Susan	Saint-Martin de Valgagues	France	10	10
DUTILLEUL	Patrick	Vauvert	France	8	8
JULLIEN	Christelle	Saint Saturnin les Avignons	France	13	13
ROQUES	Jacques	Morière les Avignons	France	9	9
ROUSSY	Charles-Antoine	The Ponteils	France	5	5
SANJUAN	Philippe	Leucate	France	12	12
BUSH	Alain	Uzès	France	12	12
GRANIER	Pierre	Béziers	France	7	7
MEISSNER	Heather	Tuchan	France	5	5
FAYAD	Ghassan	Courthezon	France	5	5
CABANEL	Bernard	Agdes	France	6	6
DUVNJAK	Sandra	Nîmes	France	51 (across all sites)	51

ARENAS	Julia	Montredon les Corbières	France	7	7
COUE	Eric	Couiza	France	7	7
BUCA	Doïna	Perols	France	30 (across all sites)	30

3.7 Participant timeline

Table 3-2. Timetable of planned visits and associated procedures and examinations. D, day. M, Month. "Vinc" stands for the inclusion visit. "Vf" for follow-up visits.

		Vinc	Vf
	H-48	D0	D0-M6
*** Information and presentation**	✕		
*** Validation of eligibility criteria**	✕		
*** Signature of the informed consent form**		✕	
*** Collection of INR measurements**		✕	✕
*** Follow-up of associated costs**		✕	✕

* These elements are not part of routine patient care, and are specific to the study.

3.8 Patient pathways

3.8.1 Screening (H-48) & Inclusion (D0)

Patient will be recruited in nursing homes. According to the centre affiliation (randomisation per cluster), either the usual monthly INRv monitoring or the experimental weekly INRc monitoring will be performed.

To inform patients and his/her trusted person/tutor/legal representative about the study, one of the caregivers from the nursing home or the clinical study technician will call the trusted person/tutor/legal representative to fix an appointement at the nursing home. During the appointement (H-48), they will be informed by the investigator about the study. The investigator will answer their questions and give them the information note (Appendix 9.1).

Patients and their trusted person/tutor/legal representative will have 48 hours to confirm study participation:

- 48 hours after the information appointment, the caregiver or the clinical study technician will call the trusted person/tutor/legal representative to find out whether they accept to participate and if so, to fix an appointment to come and sign the consent form (Appendix 9.1).

Patients and their trusted person/tutor/legal representative will be informed that:

- they will have the right to leave the study at any time without any consequence on their usual medical care.

All attending physicians will be informed by an information letter about the possible inclusion of their patient in this study (Appendix 9.7).

Inclusion will occur at Day 0 (D0).

Variables to collect at D0:

- Age (years), Sex (m / f), height (cm) and weight (kg)
- Indication of the VKA (check one of the following):
  - Complete arrhythmia with AF

- deep vein thrombosis
  - phlebitis
  - pulmonary embolism
- Type of VKA used
  - Warfarin (Coumadine)
  - Fluindione (Previscan)
  - Acenocoumarol (sintrom, minisintrom)
- concomitant medications (yes / no for each):
  - Acetylsalicylic acid, antiplatelet or anti-inflammatory dose ++
  - Antiplatelet
  - Nonsteroidal anti-inflammatory drugs ++
  - Miconazole ++
  - Paracetamol
  - *Hypericum*
  - Glucocorticoids
  - Selective serotonin reuptake inhibitors
  - Antibiotics
    - cephalosporin
    - cyclin
    - fluoroquinolone

2. Oral Hypoglycemic Agents
3. Insulin
4. antihypertensive

• Medical history / comorbidities (yes / no for each):

- heart failure
- myocardial infarction
- Percutaneous Coronary Intervention
- bypass surgery of the coronary artery
- stroke
- Transient ischemic attack
- Arterial claudication
- surgery or percutaneous intervention on the abdominal aorta or vessels of the lower limbs
- chronic dialysis
- kidney transplant
- Chronic liver disease (*e.g.* cirrhosis)
- haemorrhagic event (BARC classification (46); Appendix 9.4)
- Anaemia Event

- renal function
  - last creatinemia
- liver function (last performed)
  - bilirubin
  - Aspartate transaminase
  - Alanine transaminase
- TTR during the last 6 months before inclusion
- Frequency of INR during the last 6 months (date)
- Karnofsky index

3.8.2 Six-month follow-up

Once included, patients will be followed-up during six months:

- Interventional group:

One INRv and one INRc will be performed to check the congruence between both monitoring approaches. Then, INRc will be performed once every week (step A, Figure 1 & 1bis), every 2 weeks (step A), after 3 and 6 days (step B), or in association with an INRv (step C). The nurse will complete the VKA dose software (i.e. number of punctures, number of strips, current VKA type, current VKA dose, INRc value). The software will give the next puncture day and the VKA dose. If the INR > 4, there will be an alert and the nurse will have to contact the general practitioner for the rest of the procedure. INRc monitoring is detailed in Figure 1 &1 bis and point 2.3.

The INRv will also be, blindly of investigators, performed in order to calculate TTR and to have the same frequency of measurement as the control group (monthly TTR in both groups and more if out of therapeutic target, see Figure 1 & 1 bis).

- Control group:

The nurse will perform usual venous puncture; prepare the tube to send to the biological laboratory and complete the "shuttle sheet" (Appendix 9.6). The tube will be transmitted to the laboratory as usual. Once at the laboratory, the biologist will perform the INR analyses and will complete the relevant section of the "shuttle sheet". The biologist will have to send the results by mail in the provided stamped addressed envelope.

During the six months of follow-up, these variables will be collected:

1. INR:
    - Date
    - value
2. haemorrhagic events according to BARC classification (Appendix 9.4), or thromboembolic events (i.e. phlebitis, pulmonary embolism, stroke)
    - for each event, these information will be collected:
        - Date
        - Type:
            - haemorrhagic events to BARC classification (0 to 5b)
            - Venous thromboembolic events:
                - phlebitis
                - pulmonary embolism
                - other + description
            - Arterial thromboembolic object:
                - Ischemic stroke
                - Cardiac stent thrombosis,
                - myocardial infarction
                - Acute ischemia of lowers limbs
                - other + description
3. Intercurrent event {i.e. falls, confusion, fever, blood pressure > 200 mmHg, acute renal failure, acute digestive disorders}, change of a medication predisposing to bleeding (Concomitant medications: antiplatelet Nonsteroidal anti-inflammatory drugs, Miconazole, Paracetamol, Glucocorticoids, Selective serotonin reuptake inhibitors, Antibiotics: cephalosporin, cyclin, fluoroquinolone)}
    - for each event

- Date
- Type

If an ischemic or haemorrhagic stroke is suspected, a scan will be performed at the hospital to confirm diagnosis.

The TTR score will be recalculated at month 6 using the latest biological values available in the Electronic Patient File.

The sheet for the end of the study participation will be completed for any patient who has completed the study. The usual follow-up will be done by the investigator, who will decide on the frequency of follow-up visits.

3.8.3 Provisions for patient transport

Unenforceable

3.8.4 Provision of patient calendars and communication with study staff

Unenforceable

3.9 Study Calendar

The maximum study duration (i.e. from inclusion to the final study visit) for a given patient is 6 months.

The anticipated study calendar plans 12 months of inclusion, 6 months of follow-up, 4 months of data management, and 2 months of statistical analysis and report writing.

Table 3.9 - Study milestones and anticipated calendar

Milestone	Date
Ethical and regulatory authorisations	March 2022
Beginning of the inclusion period	July 2022
End of the inclusion period	July 2023
End of the follow-up period	Jan. 2023
End of statistical analysis and report writing	July 2024

4 Methods: Assignment of interventions (for controlled trials)

4.1 Generation sequence allocation

All the patients in a same center will be in the same arm strategy. Study centres will be randomised to either study arm in a 1:1 ratio. Centre randomisation will be stratified on expected number of patients in centers (n ≤ 10 vs n > 10) and performed after the inclusion of the patients. Centres will *a posteriori* be informed about their arm.

The randomisation list is the responsibility of an independent methodologist at the BESPIM. A specifically designed SAS program (Cary, NC, USA) will be used to carry out randomisation.

4.2 Allocation concealment mechanism

A web application for patient inclusion will be created for the needs of the study. Following user login, patient identification (first letter of last name + first letter of first name + year of birth) and verification of eligibility criteria, the study arm will be indicated to the user. Patients from the same nursing home will be included in the same group. The use of a web application ensures a high degree of security.

Patient inclusions will be performed via an online software called "Inclusio" (inclusio.bespim.fr).

"Inclusio" is an inclusion-randomisation software designed for clinical research projects by the BESPIM. Using Inclusio, an online inclusion and randomization application will be created for the study and made available to all appropriate study staff. The program provides real-time inclusion alerts to study staff requesting such alerts. Follow-up and reporting tables are provided via the click of a button.

4.3 Implementation

The allocation sequence will be generated by an independent methodologist at the BESPIM (NUH). During the implementation visit in each recruiting centre, investigators will be informed about the procedure.

The study coordinator will enroll clusters in a same geographic area, according to inclusion criteria cluster and will collect investigators'consent.

The methodologist will provide to the coordinator the list of randomised clusters and their affiliated arm.

In the clusters, all the patients meeting inclusion criteria will be recruited during the inclusion period.

- The consent of patients (and/or their trusted-person/legal representative/tutor) will be collected before their inclusion in the study.

5 Methods: Blinding

5.1 Procedures

- Adjudication of the thrombotic and haemorrhagic events should be assessed by an adjudication committee composed of a general practitioner, a haematologist or a cardiologist and a geriatrician, without knowledge of the randomization group.

- Monthly INRv (and more if out of target) will be performed in the experimental group (see step A' in Figure 1&1bis) in order to apply the same type of TTR measurement but the investigator of the centre will be blinded to the INRv results to avoid influencing patient cares. The adjucation committee will be informed about INRv results out of the therapeutic target and in case of risks for the patient, the adjucation committee will decide what to do next.

5.2 Emergency unblinding

Unenforceable.

6 Methods: Data collection, management, and analysis

6.1 Data collection methods

6.1.1 Clinical observations

Clinical observations will be recorded in the case report form as the study progresses.

6.1.2 The questionnaires to be administered

Unenforceable

6.1.3 Laboratory tests

Results of the laboratory analyses will be recorded in the case report form as the study progresses.

6.1.4 Subject withdrawal

6.1.4.1 Reasons for withdrawal

The subject's participation in the study may be stopped if:

- The subject decides so (patient participation in the trial is discontinued if consent is withdrawn);
- The subject dies;

The reasons for withdrawal must be noticed in the end-of-study form.

6.1.5 Premature termination or suspension of study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the clinicaltrials.gov administrator and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.

6.1.6 Data entry

6.1.6.1 Data entry tools

Two data entry tools will be set-up for this study: (1) Inclusio platform and (2) the eCRF interfaced to it.

- The e-Santé team at the BESPIM will be in charge of setting up Inclusio for the needs of this study.
- An eCRF will be created for the needs of this study by the e-Santé team at the BESPIM. The eCRF will be web-based and made accessible to authorised study participants via a secure login procedure.

Careful attention will be given to the following when creating the eCRF:

- Restricting patient identification to anonymous codes so that it will be impossible to use the final study database to reverse-engineer back to the identity of a patient.

- Data interoperability: variable definitions will meet e-Santé team (BESPIM) requirements for interoperability.

6.1.6.2 General policy

Data will be collected for each patient on a standardised eCRF completed by the investigator or co-investigator. An eCRF will be required for each subject in the study; observational and medical monitoring for the study will be included in the source document.

All study data will be transcribed in the eCRF and/or stored on computer by investigators or their delegates.

6.1.6.3 Data entry

The data entry will be done by a designated person.

This data entry will be done on an e-CRF directly or from the paper version of the CRF.

Only those persons participating in the research project and identified will have access to the "RedCap" software allowing this input.

"RedCap" is software that generates electronic CRFs (e-CRF), electronically capture data, manage and return data. It also makes it possible to follow the progress of studies in terms of data entry and to manage them. It is extensible, modular open source software based on international standards.

"RedCap" allows:

• Data entry, validation and annotation by clinicians and research associates

• Data extraction, filtering and analysis by investigators

• Study management by study coordinators

• Monitoring, auditing, configuration and reporting by administrators

The entry into the e-CRF is controlled and formatted to prohibit the input of out-of-bounds or outliers. In case of modification of data entry, traceability and monitoring of activities is ensured. An electronic signature committing the responsibility of the investigator of each center will allow the validation of the visit and the e-CRF.

This software is hosted on a website at the NUH. Access to this application is secure and is done via the address https://oc.bespim.fr with an identifier and a password. The data collected through this software is the subject of daily backup on a secure network. The network is connected to the internet, the access is protected by a firewall.

The clinical data of the study will be stored on a specific directory of the server. Only the administrators of the network and the authorized persons of the clinical research unit of the medical information department can have access to this directory.

The extraction of the data for analysis will be carried out either by a person in charge of the BESPIM department of CHU of Nîmes or by the data manager who will have the rights in the application.

6.1.7 Health economic analysis

6.1.7.1 Objectives

The health economic objective consists in comparing the cost of hospitalisations due to haemorrhagic, ischemic and thromboembolic events at 6 months between a weekly monitoring strategy by INRc versus the usual monthly monitoring strategy by INRv and assessing the budgetary sustainability of experimental strategy for the French health care system. This economic analysis will be interpreted in light of the clinical results obtained in a cost-consequences study at 6 months

6.1.7.2 Modalities / Process

6.1.7.2.1 Cost consequences analysis

Type of study:

We propose a cost consequence analysis, one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost-benefit analysis or costeffectiveness analysis, it does not attempt to summarise outcomes in a single measure (such as the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.

Indeed, a cost consequence analysis is justified since no difference in life years at 6 month is expected. It is relevant to assess the medical event rate (clinical endpoint) and to compare the cost of the strategies evaluated.

Outlook:

The national health institute recommends adopting the community perspective which includes medical and non-medical costs reimbursed by health system, informal care and out of pocket. However, public health coverage is total for this population (100%) and the out of pocket expenses are very low and the informal care not mobilised. Therefore, we chose to consider the French public health insurance perspective. In addition, we also consider the point of view of health care institution by estimating the nursing time for the weekly monitoring strategy by INRc.

Time Frame:

The time frame of the study is defined from the day of inclusion for six months.

Endpoints:

The health economic endpoint is a presentation of costs and outcomes in discrete categories, without aggregation or weighting. Two components must be considered: cost and clinical incomes.

(I) Cost income:

The cost of hospitalisations due to haemorrhagic, ischemic and thromboembolic events will be estimated according to French health insurance.

Those data of hospitalisations will be collected from the medical file of the patients and reported in the eCRF. We will need the GHS (French DRG) in order to estimate the cost of each hospitalisation. Indeed, considering the objective of the study, the most important optimization in terms of the cost of the care pathway concerns the hospitalisations which are the most expensive.

The nursing time for the weekly monitoring strategy by INRc will be collecting and reported in the eCRF. The valuation of nurse time will be based on the average gross annual salary for each center.

(ii) Clinical components: the clinical endpoints A1, A2 and A3 of this study will be used in order to allow decision-makers to determine whether, overall, the treatment is worth carrying out. Those components are the composite censored outcome (occurrence and interval until the first thromboembolic event) or haemorrhagic event, the number of thromboembolic events (phlebitis, pulmonary embolism, ischemic stroke, death of embolic origin) per patient and the number of haemorrhagic events per patient.

6.1.7.2.2 Budget impact analysis (BIA)

All patients eligible in France for the new intervention will be considered; the number of eligible patients will be assessed with the national database (French DRG), the French national institute of demographic studies (INED) and the French national institute of statistic and economics studies (INSEE). The hospitalisation's cost of the two

groups will be compared. The time horizon is three years, in order the estimate the repercussions in terms of hospitalisations at medium term.

In order to demonstrate net hospitalisation costs to the overall health care system, the BIA, considering the French health insurance system, will incorporate costs relevant for the cost consequences analysis. These costs will be generalized in order to obtain data on the financial impact for the whole French population. The analysis will be based on the methodology described in the updated guidance of good practice by ISPOR TASK FORCE (2014) and the guidelines published by French National Authority for Health (2016).

6.2 Data management

Data management will be performed in line with ICH requirements. The related documents will be stored on the BESPIM server.

6.2.1 eCRF data

eCRF fields will be formatted so as to enforce homogenous value types and require confirmation, especially for out-of-expected-range values. All modifications should be fully traceable (who, when, why?) to allow a complete audit trail. An electronic signature by the investigator engages his/her responsibility.

6.2.2 eCRF data security

The software used to create eCRFs is hosted on a website within the NUH. Access to this software is secured via a password. The data collected through generated eCRFs are subject to daily backup on a secure network. The network is connected to the Internet; access is protected by a firewall.

Clinical study data will be stored in a specific directory on the server. Only network administrators and BESPIM authorized professionals have access to this directory.

The following measures are taken to implement confidentiality:

- The required information technology is located at the BESPIM; access is controlled and secured.
- Data are stored on a server hosted in a secure room at the NUH.

In case of hardware or software problem, a specific safety procedure will be implemented.

6.2.3 eCRF data export

The export of data for analysis will be conducted by a BESPIM authorized professional.

6.2.4 Regulatory Archiving

The closing of the trial, including the closure of the centres, will be conducted in accordance with Good Clinical Practices and ICH. Medical and administrative records and CRFs will be kept for the duration of the study in the service and then archived for a minimum of 30 years.

6.3 Statistical methods

The statistical analysis will be performed by the BESPIM Department at the Nîmes University Hospital Centre using SAS software (SAS Institute, Cary, NC, USA) version 9.4 (or higher) or the R statistics package version 3.5.1 (or higher).

6.3.1 Description of the sample and main parameters studied

Data analysis will describe the total sample and the groups (intervention and control), at cluster level and individual level. The normality of quantitative variable distributions will be assessed.

Statistical results will be presented in the form of mean and standard deviation for quantitative variables showing a normal distribution, and median and interquartile intervals for other variables. Numbers and associated percentages will be given for qualitative variables.

6.3.2 General principles of analysis

Multilevel modelling refers to a family of analytic techniques that are appropriate when data has a nested structure, such as when individuals are nested within groups (e.g., patients in EHPAD) and repeated measurements are nested within patients. So, all analyses will be performed on the individual level adjusted for clustering. Primary analyses will include intention-to-treat analysis. Patient data Cluster-adjusted regression models will be used for all kinds of outcomes, with both continuous, dichotomous, and censored time to event variables (see details in 6.3.3 and 6.3.4).

Sensibility analyses will be performed to adjust on the time of participation of each patient (addition of the variation in length of participation of each patient in the model).

Cluster-adjusted linear regression will be used for continuous variables. Cluster-adjusted logistic regression will be used to compare proportions and cluster-adjusted survival analysis to compare time to event outcomes.

6.3.3 Analysis of the principal outcome

According to Rosendaal, calculation of the TTR should be estimated during at least 3 months. In the two groups, only INRv will be used to calculate TTR, included those performed to check INRc out of the target. We choose a 6-month follow-up period to have a more reliable TTR but with a minimal impact of other mortality causes.

To compare the TTR between a weekly monitoring strategy by INRc versus the usual monthly monitoring strategy by INRv in nursing home patients, we will use nested mixed linear regression model with a random effects term for the clusters to take account for clustering effect.

6.3.4 Analysis of secondary outcomes

A1 To compare the occurrence of venous thromboembolic events or haemorrhagic events under each of these two monitoring strategies, cluster-adjusted logistic regression will be used to compare cumulative incidence of first event during the 6 months of follow-up and cluster-adjusted proportional hazards model will be used to compare time to first event.

A2/A3 To compare the occurrence of venous thromboembolic events (A2) or haemorrhagic events (A3) under each of these two monitoring strategies, the chosen outcome is the number of events per patient. Multilevel adjusted Poisson model will be used.

B. To compare the TTR between a weekly monitoring strategy by INRc versus the usual monthly monitoring by INRv in two subgroups of patients: ≤90 and >90, we will use nested mixed linear regression model with a random effects term for the clusters to take account and we wil add the age (≤90 *vs* >90) and age*group interaction terms to the model.

As the study is not powered for this interaction analysis, the results will be treated with caution given the exploratory nature of these investigations

C. Monitoring conditions within each group will be described by means, standard deviations, or medians and interquartile intervals, according to the distribution of the variables.

D. To compare the cost of both monitoring strategies: the weekly INRc monitoring strategy vs the usual monthly monitoring strategy:

The decision tree methodology will be used to estimate the mean cost at six months. This tree will simply and graphically model patient clinical events. Indeed, the TTR is directly linked to medical events. The probabilities of each branch of the tree will be determined according to the occurrence of observed events and a cost will be assigned to each leaf of the tree.

10 000 Monte Carlo probabilistic simulations will be performed to assess the mean cost and the associated confidence interval. A sensitivity analysis will also be performed to evaluate the impact of the model parameter uncertainties on the results. A probabilistic sensitivity analysis will calculate the outcome of the decision tree over the range of all included variables with use of either the 95% confidence interval (95% CI) or the standard

deviation. To check the robustness of our results, we will conduct a series of two-way sensitivity analyses of the main parameters.

E. To assess the budget impact analysis in order to estimate the financial consequences of adopting the new intervention in France in this population:

A description of the calculations used to complete the BIA will be provided. Global costs between the two groups will be compared and presented in a table that shows the total and disaggregated costs for the time period reported in the BIA. Differences will be described as percentages. The analysis will be based on the methodology described in the updated guidance of good practice by ISPOR TASK FORCE (2014) and the guidelines published by French National Authority for Health (2016).

F. To assess, over the 6-month observation period, the concordance between INRc and INRv, we will take into account all the results of concurrent INRc and INRv in the experimental group. The intraclass correlation coefficient will be estimated via generalized mixed linear models to take into account intra-patient and intra-cluster measures.

6.3.5 Guess-the-group

Unenforceable.

6.3.6 Methods used to manage data that are missing, unused or invalid

Patients discharged from the protocol for reasons other than the occurrence of a major thromboembolic or haemorrhagic event (*i.e.* death from another cause, transfer to another institution, *etc*.) will be considered as unusable at that date. The main analysis will not take it into account.

The calculation of the sample size took into account these patients (see 3.5).

6.3.7 Choice of patients to be included in the analyses

All patients included in the study will also be included in analysis, which will be performed in intent-to-treat.

6.3.8 Level of significance

A type I error of 0.05 will be retained.

6.3.9 Statistical plan

The detailed statistical plan will be provided before data extraction and unblinding.

The decision to change the statistical methods set forth in this protocol shall be taken by the methodologist assigned to the study. Any change in the statistical method used to analyse the principal endpoint must be the subject of a protocol amendment. Any change in the statistical methods used to analyse the secondary endpoints must be notified in the study report.

7 Monitoring

7.1 Data and Safety Monitoring Board

Not applicable in category 2 Jardé law study.

7.1.1 Interim analyses

Not necessary.

7.2 Adjudication committee if necessary

An independent adjudication committee composed of a general practitioner, a haematologist or a cardiologist and a geriatrician will be established.

This adjudication committee will meet twice throughout the project: at the end of the follow-up of half of the included patients and at the end of the follow-up of the last included patient. It will only look at files that have had adverse events reported during the study.

7.3 Data monitoring

A sponsor-delegated CRA will regularly visit each of the study centres during the implementation of the trial. One or more visits will be carried out during the trial according to the rhythm of the inclusions and the duration of the study.

The reasons for these visits are:

- To verify that the protocol is being respected,
- To verify the consent forms,
- To verify serious adverse event reporting,
- To carry out quality control: to compare case report form data with source document data within each centre.

Those responsible for the quality control of this biomedical research trial and thereunto duly authorised by the sponsor have access to the individual data strictly necessary for quality control and are subject to professional secrecy.

All monitoring visits are accompanied by a written monitoring report (visit traceability).

7.4 Harms / Safety

According to the French code of Public Health, Art L. 1123-10:

"For all research involving humans, the investigator records the adverse events or the abnormal analysis results defined in the protocol as determinant for the safety evaluation, keeps a documentary record and notifies the sponsor.

The investigator informs the sponsor of all serious adverse events occurring in the participants, unless stated otherwise in the protocol.

The sponsor reports to the competent authority and, for research trials with healthy volunteers, to the General Manager of the Regional Health Agency, all relevant information relating to safety, in accordance with procedures defined by decree.

Without prejudice to Article L. 1123-9, and for any research involving the human person, when an unexpected serious adverse effect or a new development relevant to the research or product under research is likely to impair the safety of the included persons, the sponsor and the investigator take appropriate emergency safety measures.

For research trials outlined in sections 2 and 3 of Article L. 1121-1, the provisions of this article apply only in the absence of provisions relating to the safety applicable to each product or practice forming the object of the research. "

This research is interventional, prospective, comparative, superiority, multicentric, randomised by cluster, in closed cohort. The primary objective of this study is to compare the TTR between a weekly monitoring strategy y INRc versus the usual monthly monitoring strategy by INRv in nursing home patients.

It is thus a research involving humans which includes only minimal risks and constraints (2 ° of article L. 1121-1).

Consequently, any **serious adverse event occurring in a subject included in this research must be notified by the investigator** to the appropriate safety system:

- ✓ Incidents and risks of incidents involving an in vitro diagnostic medical device (IVIDD) used in the research must be reported to the national relevant vigilance centre.

Moreover we remind that:

- ✓ Any adverse effect likely to be due to the treatment administered or to its use must be declared to the Regional Center of Pharmacovigilance (CRPV).
- ✓ Any serious adverse event associated with the care must be reported by the investigator as part of the reporting obligation for serious adverse events related to care according to the procedures in effect in the institution.

When the event is reported to the appropriate safety system, the investigator must specify the inclusion of the patient in a clinical research protocol, specifying the references of the research.

8 Ethics and dissemination

8.1 Research ethics approval – sponsor obligations

Pursuant to Act No. 2004-806 of 9 August 2004 relating to public health policy and its implementing regulations, the sponsor agrees to perform all incumbent operations:

Insurance: The NUH, sponsor of the study, will obtain for the duration of the study an insurance covering its own liability and that of any actor involved in the realisation of the study, regardless of the nature of relationships between stakeholders and the sponsor.

Competent Authorities and Institutional review board ("*Comité de Protection des Personnes*"): The sponsor will inform the ANSM before starting the study. The research will start after favourable opinion from the CPP and information of the competent authorities.

Commission Nationale Informatique et Liberté (CNIL):

- MR001:

This study is part of the "MR001 Reference Methodology" which regulates the processing of personal data implemented in the context of research in the field of health requiring the collection of the consent of the person concerned, pursuant to the provisions of Articles 24-I, 25-II, 26-IV and 27-III of Law No. 78-17 of January 6th, 1978 amended on January 20th, 2017 in application of article 22 of law n° 2017-55.

The CHU of Nîmes, sponsor of the study, has undertaken to respect this reference methodology and received, on September 28th, 2016, the receipt of declaration of compliance with MR001 (Declaration number 1994798v0).

The data recorded during this research is subject to computerized processing at the CHU de Nîmes in compliance with the law "Informatique et Libertés" n° 78-17 of January 6, 1978 relating to information technology, files and freedoms amended by the law of June 20, 2018 relating to the protection of personal data in accordance with the GDPR (regulation (EU) 2016/679) in force since May 25, 2018.

- MR005:

This study is part of the "MR-005 reference methodology" published on June 7, 2018 at the CNIL which regulates the processing of data from the PMSI. The CHU of Nîmes, sponsor of the study, has undertaken to respect this reference methodology and received, on July 24th, 2018, the receipt of declaration of compliance with MR005 (Declaration number 2203389v0).

This study will be registered on the HDH data platform (Health Data Hub).

8.2 clinicaltrials.gov Statement

Before the first inclusion in the study, the study sponsor will obtain an NCT number issued by the www.clinicaltrials.gov website.

Throughout the study, the following events will trigger an update (within the next 30 days) of the clinicaltrials.gov declaration:

- CPP approval, ANSM information, or CNIL authorisation as appropriate, including substantial modifications, extensions or any other regulatory document that may affect the timing of the study or the content of the protocol.
- For each centre including patients, the date of first inclusion in the study.
- The date of the last inclusion in the study.
- The date of closure for any centre, should said closure occur before the inclusion of the last patient in the study.
- The date of the end of data collection needed to assess the main objective.
- The date of the last follow-up visit for the last person included in the study.
- If applicable, the date of early termination of the study (with justification).

In addition, the declaration will be updated at least every (<) 6 months.

8.3 Protocol amendments

Any substantial change, that is to say, any changes that might have a significant impact on persons' protection, the conditions of validity and the results of research, on the quality and safety of the interventions tested, on interpretation of scientific documents that support the conduct of research, or the modality of conduct, will be the subject of a written amendment that is submitted by the sponsor to the CPP and the competent authority for approval prior to being implemented.

Insubstantial changes, that is to say those that have no significant impact on any aspect of research whatsoever are transmitted to the CPP in order to inform the CPP of such changes.

All amendments to the protocol must be brought to the attention of all investigators involved in the research. Investigators are obliged to respect their content.

Any amendment that modifies the care of patients or the benefits, harms, risks and constraints of the research is the subject of a new briefing note and a new consent form which requires the same collecting procedures as mentioned above.

8.4 Consent

This is a protocol of an interventional research involving human persons at a cluster level.

8.4.1 Procedures for informing and obtaining consent from adult patients

When a patient meets the eligibility criteria, they will receive clear, comprehensible information adapted to their ability to understand the study (objectives, aims, duration of the research, expected benefits / constraints / foreseeable risks, constraints related to study, etc.) by an investigator (according to Article L1122-1). Respecting the principle of the autonomy of the person, the physician will give the information note (Appendix 9.1) and the explanations to the patient, rectify the errors of appreciation, resume the misunderstood data and help the patient, if needed, in their reflection and decision.

48 hours after the information appointment, the caregiver or the clinical study technician will call the patient and/or the trusted person/tutor/legal representative to find out whether they accept to participate and if so, to organise signing of the consent form (Appendix 9.1). The patient will be informed that they will be free to accept or refuse to participate in the study and may withdraw from the study at any time for any reason without incurring any responsibility. Whatever the reason, the refusal to participate will have no impact on the quality of the care that will continue to be given by the investigator, nor on the quality of the doctor-patient relationship.

The informed consent will be signed 48 hours after the information appointment. The reflection period between the presentation of the information note and the signature of the consent will then be of 48 hours.

In case of refusal to receive the experimental intervention, the patient will receive the control intervention, as usual, but will be analysed in interventional group.

8.4.2 Procedures for informing and obtaining consent from minors and their parents or guardians

Minors are excluded from this study. There are therefore no provisions concerning this group.

8.4.3 Procedures for informing and obtaining consent during emergency situations

Emergency situations have been excluded from this study. There are therefore no provisions for information and consent under emergency situations.

8.4.4 Procedures for informing and obtaining consent from adults under guardianship and their guardians or trusted-persons

According to Article L1122-1-1, when it is impossible for the person concerned to express consent in writing, he or she may be attested by the person of trust provided for in Article L. 1111-6, by a family member or, failing that, a relative of the person concerned, provided that person of trust, member or relative is independent of the investigator and the sponsor. The physician will give the information note (Appendix 9.1) and the explanations, rectify the errors of appreciation, resume the misunderstood data and help him/her, if needed, in their reflection and decision.

48 hours after the information appointment, the caregiver or the clinical study technician will call the trusted person/tutor/legal representative to find out whether they accept to participate and if so, to organise signing of the consent form (Appendix 9.1). He/she will be informed that they will be free to accept or refuse to participate in the study and may withdraw from the study at any time for any reason without incurring any responsibility. Whatever the reason, the refusal to participate will have no impact on the quality of the care that will continue to be given by the investigator to the patient, nor on the quality of the doctor-patient relationship.

Patients under tutorship or curatorship are not excluded. Their participation will be validated by their trusted-person/legal representative.

8.4.5 Procedures for informing and obtaining consent from adults under judicial protection

Persons under judicial protection have been excluded from this study. There are therefore no provisions concerning this group.

8.4.6 Additional consent or assent for ancillary studies

Unenforceable

8.5 Confidentiality

In accordance with article R.5120 of the French Public Health Code, the investigators, as well as any persons collaborating in the study, will respect medical confidentiality, especially as concerns the nature of the study, the persons participating in the study, and the obtained results.

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party without prior written approval of the sponsor.

The study monitor or other authorised representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

On all study-related documents, the patient will be identified using only a unique, 7-character identification number (C□□P□□□), and the first letter of his/her last name, the first letter of his/her first name, and his/her year of birth.

A patient identification list will be maintained by the investigator (and only the investigator).

The investigator will ensure that the anonymity of each person involved in the study is respected. No identifying information will be disclosed to the three parties other than those statutorily entitled to hold this information (and who are bound by professional secrecy).

8.5.1 General Data Protection Regulation (GDPR)

In accordance with the European data protection regulations, the Nîmes University hospital, as responsible for the processing of personal data and health data, must take the appropriate measures to inform the processing of this data and to enable patients to take advantage of it maintain control.

o Nîmes University Hospital, located at Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 04.66.68.42.36, drc@chu-nimes.fr, is brought to collect and keep in a file, computerised or paper, information on the health of the patient as part of the research.

o For this purpose, the research department of the CHU de Nîmes is involved in all matters relating to the protection of personal data.

o The data collected under the patient's consent in the context of the study are carried out in accordance with Articles 6.1.e, 6.1.f and Paragraphs i and j of Article 9.2 of the GDPR, i.e. the need to process data, particularly for scientific research purposes.

o Patients have the following rights to the data we collect for this study:

- the right to request information about the processing of data.
- the right to request the correction of data concerning them if they are inaccurate or incomplete. While we review claims, patients have the right to limit the processing of their data,

- the right to request that their data be transferred to them or to someone else in a commonly used format,
- the right to withdraw their consent or oppose the processing of their personal data, at any time, without having to justify their decision. No other data will then be collected after the withdrawal of their consent.
- If patients withdraw their consent or oppose the processing of their data, they may request the erasure of their previously collected data if there are no other legal requirements that require their use. Please note, however, that the data that has already been processed with the initial consent will be retained so as not to make it impossible or impossible to achieve the objectives of the research (RGPD Articles 17.3.c and 17.3.d).

8.6 Investigator obligations

Except in emergency situations requiring the establishing of specific therapeutic procedures, the investigator(s) agree(s) to comply with this protocol in all respects, especially with regard to obtaining consent and reporting and monitoring of serious adverse events.

The investigator agrees that the study will be conducted in accordance with Act No. 2004-806 of 9 August 2004 relating to public health policy and its implementing regulations, the Declaration of Helsinki, and Good Clinical Practice.

All data, all documents and reports may be subject to audits and regulatory inspections that cannot be opposed on the grounds of medical confidentiality.

All information collected is confidential and will not be disclosed. The investigator will ensure that the anonymity of each patient in the study is guaranteed. No identifying information of individuals will be disclosed to third parties other than those representing the Sponsor and the Ministry of Health, statutorily empowered to hold such information (and who are bound by professional secrecy).

8.7 Rationale for collecting ethnic information, if applicable

Unenforceable

8.8 Patient indemnity

Participants will not receive indemnity for their participation in this study.

8.9 Interdiction for persons to take part simultaneously in another trial and planned exclusion period following the trial

The patients must not participate in other interventional studies.

There is no exclusion period at the end of this study.

8.10 Declaration of interests

Nothing to declare

8.11 Access to data

Data management and statistical analysis is provided by the BESPIM. The conditions of transfer of all or part of the research database are decided by the research sponsor and are subject to a written contract.

8.12 Ancillary and post-trial care

The patients included in the trial will be followed for 6 months. Any emergencies will be managed by the investigator. Any patients who experience an adverse event (or not) will be followed up by the general practitioner until complete resolution of the complication. At the end of the trial, the medical follow-up will be carried out by the general practitioner of the patient.

8.13 Dissemination policy

8.13.1 Publication rules

All communication of results, either written or oral, must only be made with the prior agreement of the coordinating investigator and, if applicable, the research committee.

Articles must be made "open-access".

8.13.2 Communicating trial results

Conforming with the law n°2002-303 of 4th March 2002, patients must be informed at their request of the global research results.

8.13.3 Authorship eligibility guidelines

Authorship must follow the guidelines set by the International Committee of Medical Journal Editors (ICMJE).

The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals; Updated December 2013 (48).

8.13.4 Publication Guidelines

A medical writer is available at BESPIM to help with drafting and editing of the manuscript.

All publications, including conference abstracts, should follow the appropriate publication guidelines. The relevant primary and secondary guidelines are listed on the EQUATOR website (http://www.equator-network.org/). Manuscripts edited by BESPIM will undergo plagiarism detection using the iTHENTICATE software.

8.13.5 Choice of journal

Authors must avoid publication of any articles in "predatory journals".

8.13.6 Mention of the CHU Nîmes

For publication in French journals, the affiliation for all authors should be written in French, with the CHU abbreviated without spaces or full stops. Example: department of ..., Nîmes University Hospital, Univ Montpellier, Nimes, France

For publication in Anglophone journals, the affiliation of the authors should be in English with the CHU cited as follows: Department of..., CHU Nîmes, Univ Montpellier, Nîmes, France

The address for the corresponding author should be written in French to ensure delivery of any post.

When the Nîmes University Hospital is the study sponsor, author affiliation to the Nîmes University Hospital is obligatory and precedes other affiliations.

8.13.7 Public access to trial documents and/or results

Currently, the CHU Nîmes does not support public access to trial documents.

9 Appendages

9.1 Informed consent materials

9.1.1 For the patient

PATIENT INFORMATION NOTE

Study sponsor:

University Hospital of Nîmes

Place du Professeur Debré

30029 Nîmes Cedex 09

Evaluation of a weekly capillary INR monitoring strategy versus monthly venous INR monitoring in elderly patients in nursing homes: A multicenter randomized cluster trial

Version 2.0 of 12/01/2023

RCB-ID Number: 2022-A00516-37

Dear Madam, Sir,

Doctor ..... offers you the opportunity to participate in a clinical research study.

This information note is intended to inform you of the study in which we propose you to participate. If you don't understand certain words or things, don't hesitate to ask your doctor any questions you have.

Signing the consent form will attest to your final agreement to participate in the study.

PRESENTATION OF THE STUDY

In elderly patients, the full range of measures to be taken to prevent stroke represents a real clinical challenge. Vitamin K antagonists (VKAs) are prescribed for elderly patients suffering from atrial fibrillation, deep vein thrombosis, or those with a heart valve because they are at increased risk of stroke. However, monitoring VKAs is very complicated. In the event of underdosing, the embolic risks such as stroke, phlebitis and pulmonary embolism are amplified; and in the event of an overdose, the risk of bleeding is increased. In general, monitoring for VKAs is carried out on the basis of venous INR, a test carried out once a month from a blood test. That's the monitoring you have right now.

To improve the follow-up of patients on VKA, a second method has been developed: the capillary INR, a test carried out once a week directly at the patient's bedside, making it possible to obtain the value of the INR in real time and thus improve patient monitoring. This test is almost painless because it is performed by collecting a simple drop of blood from the patient's finger. The effectiveness of the method has already been demonstrated many times but never in elderly patients.

The aim of this study, in which we therefore invite you to participate, is to compare the usual strategy of monitoring VKA once a month by venous INR, to the weekly strategy by capillary INR monitoring VKA.

CONDUCT OF THE STUDY

The participating centres, i.e. the participating nursing homes, will be randomised into two groups:

- The interventional group: Centre where weekly monitoring by capillary INR will be applied.
- The control group: Centre continuing the usual management with venous INR.

Whether you belong to one or the other group depends on randomization and the group to which your nursing home will be affiliated.

All eligible patients from the same center will be informed and included in the study at the same time. At this stage, no establishment will know the group to which it will belong. The allocation of the nursing home to the control group or the experimental group will be done after the inclusion of all patients.

After reading this newsletter, you will have 48 hours to decide whether to participate in the study. If you agree, you will be presented with a consent form and the signature of the document will attest to your agreement to participate in the study.

The study will take place over six months.

Interventional group: For the purposes of the study, a venous INR and a capillary INR will be performed to ensure that the two tests give the same results. Then, when the congruence of the tests is ensured, the capillary INR will be carried out once a week, or even once every two weeks when the values obtained are good or, on the contrary, more frequently if the capillary INR is not good, or in the event of events such as a fall, fever, haemorrhage, etc. During the 6 months of the study, you will continue your management with monthly venous INR.

Control group: The treatment will be entirely identical to that usually performed by venous INR.

RESEARCH-SPECIFIC ACTS

Interventional group: Monitoring of your anticoagulants by capillary INR for 6 months in addition to monitoring by venous INR.

> The nurse will follow the instructions for performing the capillary INR: wash the patient's hands, insert a test strip into the device, massage the finger and hand to activate circulation, perform the capillary puncture of a 10µL drop of blood using the lancet. The drop of blood should be deposited on the strip less than 180s after the strip is inserted into the meter and less than 15 seconds after the beginning of the formation of the blood drop, the result is readable on the meter after 1 minute.

Control group: Usual management.

NUMBER OF PATIENTS INCLUDED

A total of 128 elderly people on VKA living in nursing homes will be recruited during this study, including 64 patients in the interventional group and 64 in the control group.

CONSTRAINTS & OBLIGATIONS

To participate in the study:

- You must have been on vitamin K antagonists for more than 6 months.
- You must be affiliated or a beneficiary of a health insurance scheme.
- You must have signed the consent form.
- You certify that you are not participating in any ongoing category 1 research.
- Your treating physician will be notified of your participation in the study.

EXPECTED BENEFIT(S)

Elderly patients treated with VKA require appropriate anticoagulant monitoring because the risks of bleeding and thromboembolism are high and difficult to control.

Capillary INR monitoring has the advantage of allowing better monitoring of VKA treatment, being rapid and being able to be carried out more frequently. This will reduce the risk of bleeding and thromboembolism, as demonstrated by our previous pilot study.

EXPECTED RISK(S)

The risks of participating in the study, for patients in the interventional group, are only: the feeling of slight pain during the hair INR test due to the removal of a small drop of blood from the finger.

INDEMNIFICATION

This study does not give rise to any compensation. Interventions specifically added to the usual care for the specific needs of the research will be fully covered.

RIGHTS AND GUARANTEES OF INDIVIDUALS

In accordance with European regulations on data protection, the NIMES University Hospital, as the person responsible for the processing of your personal data and health data, must take appropriate measures to inform you of the processing of this data and to allow you to retain control of it.

- The University Hospital of NÎMES, located Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 04.66.68.42.36, drc@chu-nimes.fr, is required to collect and store information on your health collected as part of the research in a computerized or paper file.
- To this end, the research department of the Nîmes University Hospital is involved in all questions relating to the protection of personal data. You can contact us with any questions at the following address:

  Directorate of Research, GHT and International Relations, Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 04.66.68.42.36; Fax: 04.66.68.34.00; email. drc@chu-nimes.fr

- The collection of data collected with your consent in the context of the study is carried out in accordance with Articles 6.1.e, 6.1.f and subparagraphs i and j of Article 9.2 of the GDPR, i.e. the need to process the data in particular for the purposes of scientific research

You have the following rights over the data we collect as part of this study:

- the right to request information about the processing of your data.
- the right to request the rectification of data concerning you if it is inaccurate or incomplete. While we are reviewing your request, you have the right to restrict the processing of your data,
- the right to request that your data be transferred to you or someone else in a commonly used format,
- the right to withdraw your consent or object to the processing of your personal data, at any time, without having to justify your decision. No further data will then be collected after your consent has been withdrawn.
- If you withdraw your consent or object to the processing of your data, you can request the erasure of your data already collected if there is no other legal requirement that requires its use. Please note, however, that your data that has already been processed with your initial consent will be kept so as not to make impossible or compromise the achievement of the research objectives (Articles 17.3.c and 17.3.d. of the GDPR).

Retention period: Research data will be kept for a period of thirty years from the end date of the study.

Recipients of personal data: Your health data is accessed by the healthcare team involved in your care pursuant to Article L. 1110-4 of the Public Health Code (CSP) as well as the clinical research team involved in the collection, quality control and analysis of the data.

If you wish, the overall results of this work will be communicated to you at its conclusion. You will be able to benefit from additional information about the research at any time and any new knowledge that may call into question your participation will be communicated to you.

In accordance with the law of 4 March 2002 on the rights of patients, you have the right to be accompanied by a trusted person for any medical act involving your consent.

You have the right to lodge a complaint with the Commission nationale de l'informatique et des libertés (CNIL): 3, place de Fontenoy – TSA 80715 – 75334 PARIS CEDEX 07 (telephone: 01.53.73.22.22).

In the event of material or non-material damage as a result of a breach of the above provisions relating to the protection of your data, you have the right to obtain compensation from the controller (or the processor if applicable) for the damage suffered. In particular, you can take legal action to obtain damages.

REGULATORY DATA

In accordance with the legislative and regulatory provisions, the University Hospital of Nîmes has subscribed under number 0101242214029 an insurance contract covering the Civil Liability of the Promoter of Interventional Research on the Human Person (RIPH) with HDI GLOBAL SE (Tour Opus 12, La Défense 9, 77 Esplanade du Gal de Gaulle – 92 914 PARIS LA DEFENSE CEDEX).

The terms of this protocol have been submitted to the examination of a Committee for the Protection of Persons (CPP) whose mission is to verify whether the conditions required for your protection and the respect of your rights are respected.

This committee issued a favorable opinion on June 09, 2022.

This protocol was declared to the competent authority (ANSM) on June 10, 2022.

You are completely free to accept or refuse to participate in this study. Following the reading of this information note, you will be given a 48-hour reflection period to allow you time to make your decision.

If you have any questions, don't hesitate to ask the doctor.

NAME AND CONTACT DETAILS

OF THE COORDINATING INVESTIGATOR

Dr David COSTA

Department of Biostatistics, Clinical Epidemiology, Public Health & Innovation in Methodology (BESPIM)

Nîmes University Hospital

Phone : 06.61.43.39.30

Rest assured that your participation is extremely valuable to us. We thank you in advance, Madam, Sir, for the help you are giving to medical research.

PATIENT CONSENT FORM

Study sponsor:
University Hospital of Nîmes
Place du Professeur Debré
30029 Nîmes Cedex 09

Evaluation of a weekly capillary INR monitoring strategy versus monthly venous INR monitoring in elderly patients in nursing homes: A multicenter randomized cluster trial

Version 2.0 of 12/01/2023

RCB-ID Number: 2022-A00516-37

Dear Madam, Sir,

Read the different parts of this document carefully. Signing this consent form will attest to your agreement to participate in this study. You must sign this document after reading, understanding and completing all the parts. This document is produced in three copies: one for the sponsor, one for the investigating doctor and one for you.

I, the undersigned..... (Surname, First name), born on ..... certify that I have read and understood the newsletter that was given to me and that I have had the opportunity to ask any questions I wanted.

☐ I freely agree to participate, under the conditions set out in the newsletter, in the above-mentioned research conducted by Dr. David COSTA.

Objection and withdrawal of consent

- I understand that my participation in this study is voluntary and that I can refuse it. If I wish, I will be **FREE AT ANY TIME DURING THE STUDY TO STOP MY PARTICIPATION** without having to justify myself. I will inform the principal investigator of the study, Dr. David Costa, in writing to the following address: BESPIM department, Nîmes University Hospital, Place du Professeur Debré, 30029 Nîmes Cedex 09.
- I understand that my decision to participate in this study does not relieve either the researchers or the host institution of their professional and legal obligations to me.
- I have taken note of my right to access and rectify personal information concerning me which is processed automatically. The right of access and rectification provided for by the "Informatique et Liberté" law can be exercised at any time by contacting the managers of the firm.

Acknowledgment of Advance Information

- The doctor informed me of the nature and goals of this research project, as well as how it was carried out and the possible benefits and risks of the study.
- In this regard, I have in my possession a newsletter (12/01/2023, version 2.0) that I have read and understood.
- I was able to ask all the questions I wanted about this project. I acknowledge that I had sufficient time to reflect between the newsletter and this consent and that I had the opportunity to discuss it with my doctor or my relatives, if I wished.
- In particular, I acknowledge that I have been given the right to be assisted by a trusted person of my choice.
- I acknowledge that I have been informed that the study may be discontinued at any time by decision of the sponsor or the authorities, that all measures will be taken in this case to ensure my safety and, if necessary, the continuation of my treatment, and that my personal participation may be suspended if I do not comply with the protocol.
- I know that I will be informed of any new facts that may call into question my consent to my participation in the study.

Acceptance of constraints

- I certify that I am affiliated or beneficiary of a health insurance scheme.
- I undertake to observe the constraints that have been explained and specified to me in the newsletter, both to minimize the risks and for the successful completion of the protocol.
- I formally certify that I am not currently involved in any category 1 intervention research (RIPH).
- I accept the prohibition that has been served on me from simultaneously participating in another research involving the human person (RIPH) category 1.

- I understand that concealing the truth can have detrimental consequences for my health. I therefore certify that I have answered sincerely all the questions that have been asked of me, in particular those relating to my state of health and my lifestyle.
- I undertake to respect the confidentiality rules applicable to the study, as they have been explained to me beforehand.
- I agree that my data may be used in future research exclusively for scientific purposes (in accordance with article L1122-1-2 relating to global consent).

Other Authorities

- As part of this study, all DATA AND INFORMATION concerning me will remain strictly CONFIDENTIAL. I only authorize their consultation by people designated by the investigators and possibly by a representative of the health authorities. I am informed that this clinical data collected will be subject to computerized processing authorized by the National Commission on Information Technology and Freedom.
- In accordance with the law of 4 March 2002, relating to patients' rights, I know that I have the possibility of being accompanied by a trusted person for any medical act involving my consent.

Date and signature of the patient

Date and signature of the investigator

9.1.2 For the legal representative

INFORMATION NOTE FOR THE LEGAL REPRESENTATIVE / CLOSE RELATIVE / GUARDIAN

Study sponsor:

University Hospital of Nîmes
Place du Professeur Debré
30029 Nîmes Cedex 09

Evaluation of a weekly capillary INR monitoring strategy versus monthly venous INR monitoring in elderly patients in nursing homes: A multicenter randomized cluster trial

Version 2.0 of 12/01/2023

RCB-ID Number: 2022-A00516-37

Dear Madam, Sir,

Doctor ..... would like to propose to your loved one..... participate in a clinical research study.

This information note is intended to inform you of the study in which we propose to participate. If you do not understand certain words or elements, do not hesitate to ask the doctor any questions you wish.

Signing the consent form will attest to your final agreement for your loved one to participate in the study.

PRESENTATION OF THE STUDY

In elderly patients, the full range of measures to be taken to prevent stroke represents a real clinical challenge. Vitamin K antagonists (VKAs) are prescribed for elderly patients suffering from atrial fibrillation, deep vein thrombosis, or heart valve carriers because they are at increased risk of stroke. However, monitoring VKAs is very complicated. In the event of underdosing, the risks of embolism such as stroke are amplified; And in the event of an overdose, the risk of bleeding is increased. In general, VKA surveillance is carried out on the basis of venous INR, a test carried out once a month in the laboratory using blood samples.

To improve the follow-up of patients on VKA, a second method has been developed: the capillary INR, a test carried out once a week directly at the patient's bedside, making it possible to obtain the INR value in real time and thus improve the monitoring of the patient's anticoagulants. This test is almost painless because it is performed by collecting a simple drop of blood from the patient's finger. The effectiveness of the method has already been demonstrated many times but never in elderly patients.

The aim of this study, in which we invite your loved one to participate, is to compare the usual strategy of monitoring VKA performed once a month, the venous INR, to the weekly capillary INR strategy of monitoring VKA.

CONDUCT OF THE STUDY

The participating centres, i.e. the participating nursing homes, will be randomised into two groups:

- The interventional group: Centre where weekly capillary INR monitoring will be applied in addition to monthly venous INR monitoring.
- The control group: Centre continuing the usual management with venous INR.

Whether your loved one belongs to one or the other group depends on randomization and the group to which the nursing home will be affiliated.

All eligible patients from the same center will be informed and included in the study at the same time. At this stage, no establishment will know the group to which it will belong. The allocation of the nursing home to the control group or the experimental group will be done after the inclusion of all patients.

After reading this newsletter, you will have 48 hours to decide whether your loved one will participate in the study. If you agree, you will be presented with a consent form and the signature of the document will attest to your agreement to participate in the study.

The study will take place over six months.

Interventional group: For the purposes of the study, a venous INR and a capillary INR will be performed to ensure that the two tests give the same results. Then, when the congruence of the tests is ensured, the capillary INR will be carried out once a week, or even once every two weeks when the values

obtained are good or, on the contrary, more frequently if the capillary INR is not good, or in the event of events such as a fall, fever, haemorrhage, etc.

Control group: The treatment will be entirely identical to that usually performed by venous INR.

RESEARCH-SPECIFIC ACTS

Interventional group: Weekly monitoring by capillary INR for 6 months.

Procedure that the nurse will follow to perform the capillary INR: wash the patient's hands, insert a test strip into the device, massage the finger and hand to activate circulation, perform the capillary puncture of a 10µL drop of blood using the lancet. The drop of blood should be deposited on the strip less than 180s after the strip is inserted into the meter and less than 15 seconds after the start of blood dropping formation. The result is readable on the reader after 1 minute.

Control group: Usual management with venous INR.

NUMBER OF PATIENTS INCLUDED

A total of 128 elderly people on VKA living in nursing homes will be recruited during this study, including 64 patients in the interventional group and 64 patients in the control group.

CONSTRAINTS & OBLIGATIONS

To allow your loved one to participate in the study:

- Your loved one must have been on vitamin K anti-vitamin K for more than 6 months.
- Your loved one must have been on vitamin K anti-vitamin K for more than 6 months.
- Your loved one must be affiliated or a beneficiary of a health insurance scheme.
- You must have signed the consent form.
- You certify that your loved one is not participating in any ongoing category 1 research.
- Your loved one's primary care physician will be notified of their participation in the study.

EXPECTED BENEFIT(S)

Elderly patients treated with VKA require appropriate anticoagulant monitoring because the risks of bleeding and thromboembolism are high and difficult to control.

Capillary INR monitoring has the advantage of allowing better monitoring of VKA treatment, being rapid and being able to be carried out more frequently. This will reduce the risk of bleeding and thromboembolism, as demonstrated by our pilot study.

EXPECTED RISK(S)

The risks that your loved one will incur to participate in the study, for patients in the interventional group, are only: the feeling of a slight pain during the hair INR test due to the removal of a drop of blood from the finger.

INDEMNIFICATION

This study does not give rise to any compensation.

Interventions specifically added to the usual care for the specific needs of the research will be fully covered.

RIGHTS AND GUARANTEES OF INDIVIDUALS

In accordance with European data protection regulations, the NIMES University Hospital, as the person responsible for the processing of personal data and health data, must take appropriate measures to inform you of the processing of this data and to allow you to retain control of it.

- The University Hospital of NÎMES, located Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 04.66.68.42.36, drc@chu-nimes.fr, is required to collect and store in a computerized or paper file information on your loved one's health collected as part of the research.
- To this end, the research department of the Nîmes University Hospital is involved in all questions relating to the protection of personal data. You can contact us with any questions at the following address:

  Directorate of Research, GHT and International Relations, Place du Professeur Debré, 30029 Nîmes Cedex 09; Tel: 04.66.68.42.36; Fax: 04.66.68.34.00; email. drc@chu-nimes.fr

- The collection of data collected with your consent in the context of the study is carried out in accordance with Articles 6.1.e, 6.1.f and subparagraphs i and j of Article 9.2 of the GDPR, i.e. the need to process the data in particular for the purposes of scientific research

You have the following rights over the data we collect as part of this study:

- the right to request information about data processing.
- the right to request the rectification of data concerning your loved one if it is inaccurate or incomplete. While we are reviewing your request, you have the right to restrict the processing of data,
- the right to request that your loved one's data be transferred to you or someone else in a commonly used format,
- the right to withdraw your consent or object to the processing of your loved one's personal data, at any time, without having to justify your decision. No further data will then be collected after your consent has been withdrawn.
- If you withdraw your consent or object to the processing of your loved one's data, you can request the deletion of the data already collected if there are no other legal requirements that require its use. Please note, however, that data that has already been processed with your initial consent will be stored so as not to make it impossible or compromise the achievement of the research objectives (Articles 17.3.c and 17.3.d. of the GDPR).

Retention period: Research data will be kept for a period of thirty years from the end date of the study.

Recipients of personal data: The healthcare team involved in the care provided pursuant to Article L. 1110-4 of the Public Health Code (CSP) and the clinical research team involved in the collection, quality control and analysis of the data have access to health data.

If you wish, the overall results of this work will be communicated to you at its conclusion. You will be able to benefit from additional information about the research at any time and any new knowledge that may call into question your participation will be communicated to you.

In accordance with the law of 4 March 2002 on the rights of patients, you have the right to accompany your loved one for any medical act involving your consent.

You have the right to lodge a complaint with the Commission nationale de l'informatique et des libertés (CNIL): 3, place de Fontenoy – TSA 80715 – 75334 PARIS CEDEX 07 (telephone: 01.53.73.22.22).

In the event of material or non-material damage as a result of a breach of the above provisions relating to the protection of your data, you have the right to obtain compensation from the controller (or the processor if applicable) for the damage suffered. In particular, you can take legal action to obtain damages.

REGULATORY DATA

In accordance with the legislative and regulatory provisions, the University Hospital of Nîmes has subscribed under number 0101242214029 an insurance contract covering the Civil Liability of the Promoter of Interventional Research on the Human Person (RIPH) with HDI GLOBAL SE (Tour Opus 12, La Défense 9, 77 Esplanade du Gal de Gaulle – 92 914 PARIS LA DEFENSE CEDEX).

The terms of this protocol have been submitted to the examination of a Committee for the Protection of Persons (CPP) whose mission is to verify whether the conditions required for your protection and the respect of your rights are respected.

This committee issued a favorable opinion on June 09, 2022.

This protocol was declared to the competent authority (ANSM) on June 10, 2022.

You are completely free to accept or refuse that your loved one participate in this study. Following the reading of this information note, you will be given a 48-hour reflection period to allow you time to make your decision.

If you have any questions, don't hesitate to ask the doctor.

NAME AND CONTACT DETAILS

OF THE PRINCIPAL INVESTIGATOR

Dr David COSTA

Department of Biostatistics, Clinical Epidemiology, Public Health & Innovation in Methodology (BESPIM)

Nîmes University Hospital

Phone : 06.61.43.39.30

Rest assured that your participation is extremely valuable to us. We thank you in advance, Madam, Sir, for the help you are giving to medical research.

KIN'S CONSENT FORM

Study sponsor:
University Hospital of Nîmes
Place du Professeur Debré
30029 Nîmes Cedex 09

Evaluation of a weekly capillary INR monitoring strategy versus monthly venous INR monitoring in elderly patients in nursing homes: A multicenter randomized cluster trial

Version 2.0 of 12/01/2023

RCB-ID Number: 2022-A00516-37

Dear Madam, Sir,

Read the different parts of this document carefully. Signing this consent form will attest to your agreement to participate for your loved one in this study. You must sign this document after reading, understanding and completing all the parts. This document is produced in three copies: one for the sponsor, one for the investigating doctor and one for you.

I, the undersigned..... (Surname, First name), born on ....., close to ..... (Surname, First name), certifies that I have read and understood the newsletter that was given to me and that I have had the opportunity to ask all the questions I wanted. Thus, I freely accept that my loved one participates, under the conditions defined in the newsletter, in the research designated above conducted by Dr. David COSTA.

Objection and withdrawal of consent

- I understand that participation in this study is voluntary and that I can refuse it. If I wish, I will be **FREE AT ANY TIME DURING THE STUDY TO STOP PARTICIPATING** without having to justify myself. I will inform the principal investigator of the study, Dr. David Costa, in writing to the following address: BESPIM department, Nîmes University Hospital, Place du Professeur Debré, 30029 Nîmes Cedex 09.

- I understand that my decision to have my loved one participate in this study does not relieve either the researchers or the host institution of their professional and legal obligations to my loved one.

- I have taken note of my right to access and rectify personal information concerning my loved one and which is processed automatically. The right of access and rectification provided for by the "Informatique et Liberté" law can be exercised at any time by contacting the managers of the firm.

Acknowledgment of Advance Information

- The doctor informed me of the nature and goals of this research project, as well as how it was carried out and the possible benefits and risks of the study.
- In this regard, I have in my possession a newsletter (12/01/2023, version 2.0) that I have read, and understood.
- I was able to ask all the questions I wanted about this project. I acknowledge that I have had sufficient time to reflect between the newsletter and this consent.
- I acknowledge that I have been informed that the study may be interrupted at any time by decision of the sponsor or the authorities, that all measures will be taken in this case to ensure the safety of my loved one and, if necessary, the continuation of the treatment.
- I know that I will be informed of any new facts that may call into question my consent to my loved one's participation in the study.

Acceptance of constraints

- I certify that my loved one is affiliated or beneficiary of a health insurance scheme.
- I undertake to observe the constraints that have been explained and specified to me in the newsletter, both to minimize the risks and for the successful completion of the protocol.
- I formally certify that my loved one is not currently participating in any category 1 intervention research (RIPH).
- I accept the prohibition that has been served on me to allow my loved one to participate simultaneously in another category 1 research involving the human person (RIPH).
- I understand that concealing the truth can have harmful consequences for the health of my loved one. I therefore certify that I have answered sincerely all the questions that have been put to me, in particular those relating to his state of health and his lifestyle.
- I undertake to respect the confidentiality rules applicable to the study, as they have been explained to me beforehand.
- I agree that my loved one's data may be used in subsequent research exclusively for scientific purposes (in accordance with article L1122-1-2 relating to global consent).

Other Authorities

- As part of this study, all DATA AND INFORMATION about my loved one will remain strictly CONFIDENTIAL. I only authorize their consultation by people designated by the investigators and possibly by a representative of the health authorities. I am informed that this clinical data collected will be subject to computerized processing authorized by the National Commission on Information Technology and Freedom.

Date and signature of the close	Date and signature of the investigator

9.2 Pre-analytical INR_v conditions checklist

Sterile citrated tube Sodium citrate 3.2%	☐
Needle diameter (19 to 23G)	☐
Time of turnstile ≤ 1 minute	☐
Tube transported in a vertical position	☐
Filling> 80%	☐
Transport at room temperature within 4 hours before possible freezing at -20°C for maximum 15 days	☐
Centrifugation of more than ten minutes at 1500G between 18 and 25°C	☐

9.3 Good sampling practice of INRv

The INR (International Normalized Ratio) is used to determine the effective dose for each patient. The INR "target" refers to the INR value to achieve in order to obtain a balanced treatment: for AF and DVT, the therapeutic zone is between 2 and 3 (INR target of 2.5) for cardiac valves or other indication between 2.5 and 3.5 (INR target of 3).

At the beginning of treatment, INR checks should be frequently performed until the INR target value is reached. VKA dose adjustment is carried out using a step-by-step approach, by controlling the INR every 2 to 4 days until two successive controls show stable INR values:

- If the target INR is not reached, the dose of VKA should be adjusted. The first INR check should be performed 3 days after dose adjustment and following INR checks every 2 to 4 days until the target INR is reached.
- When the INR target is reached and stable, the dosage of VKA should be maintained. The INR checks will be progressively spaced in a few weeks (maximum interval: one month).

Patient cares under VKA require care coordination. In particular, the biologist must know the procedure to quickly inform the pratictian of the patient and the patient in case results are out of the target area (1).

A reliable measurement of INRv requires quality sampling performed under conditions described (13,14):

- The needle diameter must be between 0.7 and 1 millimeter.
- The puncture must be performed with a tourniquet applied less than one minute.
- The blood sample must be collected in a citrated tube in 2nd position in the sample order.
- More than 80% filling of the tube volume is necessary.
- Blood samples must be transported in a vertical position to limit blood contact with the tube cap.
- Blood samples must be analysed within 6 hours after sampling.

9.4 BARC classification

Hemorrhagic events are classified according to the BARC (Bleeding Academic Research Consortium) classification that aimed to harmonize and create a universal definition of bleeding (46):

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of haemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a: Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleed). Any transfusion with overt bleeding

Type 3b Overt bleeding plus hemoglobin drop 5 g/dL* (provided hemoglobin drop is related to bleed)

Cardiac tamponade. Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid). Bleeding requiring intravenous vasoactive agents

Type 3c: Intracranial haemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal). Subcategories confirmed by autopsy or imaging or lumbar puncture. Intraocular bleed compromising vision

Type 4: CABG-related bleeding. Intracranial perioperative bleeding within 48 h. Reoperation after closure of sternotomy for the purpose of controlling bleeding. Transfusion of 5 U whole blood or packed red blood cells within a 48-h period†. Chest tube output 2L within a 24-h period

Type 5: fatal bleeding

Type 5a Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

9.5 References

1. Blas-Châtelain C, Chauvelier S, Foti P, Debure C, Hanon O. Risk factors of serious bleeding among ambulatory patients taking antivitamin K aged 75 and over. J Mal Vasc. 2014; 39(3):169-77.

2. Hugo GS, Figueiras-Graillet LM, Anguita M, Marín F, Bertomeu V, Roldán I, et al. Oral anticoagulation in octogenarians with atrial fibrillation. Int J Cardiol. 15 Nov 2016; 223:87-90.

3. Camm AJ, 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: an update of the 2010 ESC Guidelines for the management of atrial fibrillation developed with the special contribution of the European Heart Rhythm Association. Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol. Oct 2012; 14(10):1385-413.

4. Pourcel G, Meynié B, Bénier J, Dupont-Zacot E, Mouries R. Treatment with antivitamin K. URCAM Î Fr Rev Prat General Medicine. 2005; 19(690/691).

5. Blin P, Dureau-Pournin C, Abouelfath A, Lassalle R, Bénichou J, Cottin Y, et al. Benefit–risk of direct oral anticoagulants compared to vitamin K antagonists in non-valvular atrial fibrillation: ENGEL cohort of more than 100,000 patients from Sniiram. Rev Epidemiology Public Health. June 1, 2017; 65:S111.

6. HAS. Synthesis, care pathway guide, atrial fibrillation [Internet]. 2014 March. Available on: http://www.has-sante.fr/portail/jcms/c_1741768/fr/guide-parcours-de-soins-fibrillation-atriale

7. Bleeding during antithrombotic therapy in patients with atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. Arch Intern Med. 26 Feb 1996; 156(4):409-16.

8. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993; 69(3):236-9.

9. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 7 Oct 2016; 37(38):2893-962.

10. Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Eur Heart J. 9 Jan 2011; 32(18):2282-9.

11. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of Outcomes Among Patients Randomized to Warfarin Therapy According to Anticoagulant Control: Results From SPORTIF III and V. Arch Intern Med. 12 Feb 2007; 167(3):239-45.

12. Plichart M, Berrut G, Maubourguet N, Jeandel C, Emeriau JP, Ankri J, et al. Use of Vitamin K Antagonist Therapy in Geriatrics: A French National Survey from the French Society of Geriatrics and Gerontology (SFGG). Drugs Aging. Dec 2013; 30(12):1019-28.

13. Polack B, Schved JF, Boneu B. Preanalytical Recommendations of the 'Groupe d'Etude sur l'Hémostase et la Thrombose' (GEHT) for Venous Blood Testing in Hemostasis Laboratories. Pathophysiol Haemost Thromb. 2001; 31(1):61-8.

14. Ellouze R, Guermazi S. [Importance of preanalytical step in hemostasis]. Ann Biol Clin (Paris). August 2013; 71(4):401-7.

15. Chiron B, Le Reste JY, Mansourati J, Bensassi M, Claux F, Cadier S. Survey on the conditions for carrying out INR samples at home. Heads or tails? exercise. 2011; 22(95):4-9.

16. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 17 Sep 2009; 361(12):1139-51.

17. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med. 8 Sep 2011; 365(10):883-91.

18. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 15 Sep 2011; 365(11):981-92.

19. Romanelli RJ, Nolting L, Dolginsky M, Kym E, Orrico KB. Dabigatran Versus Warfarin for Atrial Fibrillation in Real-World Clinical Practice: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. March 2016;

9(2):126-34.

20. Strate LL, Ayanian JZ, Kotler G, Syngal S. Risk factors for mortality in lower intestinal bleeding. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. Sept 2008; 6(9):1004-10; Quiz 955-.

21. Amin A, Deitelzweig S, Jing Y, Makenbaeva D, Wiederkehr D, Lin J, et al. Estimation of the impact of warfarin's time-in-therapeutic range on stroke and major bleeding rates and its influence on the medical cost avoidance associated with novel oral anticoagulant use-learnings from ARISTOTLE, ROCKET-AF, and RE-LY trials. J Thromb Thrombolysis. August 1, 2014; 38(2):150-9.

22. HAS. Evaluation Report on Oral Anticoagulant Drugs [Internet]. 2018, Feb, p. 128. Report No.: 234. Available on: https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-02/rapport_reev_aco_cteval234_2018-02-09_15-38-37_999.pdf

23. HAS. Management strategy for protein-energy undernutrition in the elderly [Internet]. 2007, Apr, p. 159. Available on: https://www.has-sante.fr/portail/upload/docs/application/pdf/denutrition_personne_agee_2007_-_argumentaire.pdf

24. Heneghan C, Ward A, Perera R, Bankhead C, Fuller A, Stevens R, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. The Lancet. Feb 3, 2012; 379(9813):322-34.

25. Witt DM, Clark NP, Kaatz S, Schnurr T, Ansell JE. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016; 41:187-205.

26. Nusa D, Harvey I, Almansouri AY, Wright S, Neeman T, Ahmad O, et al. Assessment of point-of-care measurement of international normalised ratio using the CoaguChek XS Plus system in the setting of acute ischaemic stroke. Intern Med J. Nov 2013; 43(11):1205-9.

27. Karon BS, McBane RD, Chaudhry R, Beyer LK, Santrach PJ. Accuracy of Capillary Whole Blood International Normalized Ratio on the CoaguChek S, CoaguChek XS, and i-STAT 1 Point-of-Care Analyzers. Am J Clin Pathol. 7 Jan 2008; 130(1):88-92.

28. High Authority for Health. National Commission for the Evaluation of Medical Devices and Health Technologies, COAGUchecks XS, self-measurement device of the INR [Internet]. 2016, March, p. 27. Available on: https://www.has-sante.fr/portail/upload/docs/evamed/CEPP-4918_COAGUCHEK%20XS_08_mars_2016_(4918)_avis.pdf

29. HAS. evaluation of self-monitoring of INR in adult patients treated with VKA. [Internet]. 2008 Oct. Report No.: rapport_inr_2009-02-11_11-34-20_386. Available on: http://www.has-sante.fr/portail/upload/docs/application/pdf/2009-02/synthese_inr_1437.pdf

30. Chatap G, Karami A, Bendahmane M, Landre T, Giraud K, Ratiney R. Prospective validation study of a portable coagulometer for the monitoring of oral anticoagulation in a geriatric hospital. Rev. de Ger. 2013; (38):257-65.

31. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST. Feb 1, 2012; 141(2):e152S-e184S.

32. HAS. VKA overdose, risk situations and haemorrhagic accidents - Summary of recommendations. 2009; (420):17.

33. Cushman M, Lim W, A Zakai N. Clinical Practice Guide on Antithrombotic Drug Dosing and Management of Antithrombotic Drug- Associated Bleeding Complications in Adults - QUICK REFERENCE [Internet]. American Society of Hematology; 2014. Available on: http://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Reference.aspx

34. BC Guidelines. Warfarin therapy management [Internet]. 2015 Apr Available on: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/warfarinmgmt_2015_full.pdf

35. Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, et al. Anticoagulation Control and Prediction of Adverse Events in Patients With Atrial Fibrillation A Systematic Review. Circ Cardiovasc Qual Outcomes. Jan 11, 2008; 1(2):84-91.

36. Caulin C, Vittecoq D. Preventing drug iatrogenesis in elderly subjects [Internet]. AFSSAPS; 2005. Available at: http://ansm.sante.fr/var/ansm_site/storage/original/application/9641eb3f4a1e67ba18a6b8aecd3f1985.pdf

37. Philippe V. LA POLITIQUE DU MEDICAMENT. 2013, Dec, p. 125.

38. Aspinall SL, Zhao X, Handler SM, Stone RA, Kosmoski JC, Libby EA, et al. The Quality of Warfarin Prescribing

and Monitoring in Veterans Affairs Nursing Homes. J Am Geriatr Soc. Aug. 2010; 58(8):1475-80.

39. ANSM. anticoagulants in France in 2014: state of play, synthesis and surveillance [Internet]. 2014. Available on: http://ansm.sante.fr/var/ansm_site/storage/original/application/26ed375830c56499badf0014eb3bb81b.pdf

40. Stevanović J, Postma MJ, Le HH. Budget Impact of Increasing Market Share of Patient Self-Testing and Patient Self-Management in Anticoagulation. Value Health. June 1, 2016; 19(4):383-90.

41. Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, et al. Is self-monitoring an effective option for people receiving long-term vitamin K antagonist therapy? A systematic review and economic evaluation. BMJ Open [Internet]. 2015 Jun 25 [cited 2018 Jul 3]; 5(6). Available on: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4486963/

42. Weltgesundheitsorganisation, publisher. Primary health care: now more than ever. Geneva: World Health Organization; 2008. 119 p. (The world health report).

43. Saint-Lary O, Rougé-Bugat ME, Lognos B, Bayen M, Renard V. Development of research in primary care. Nov 2017; (#137).

44. White KL, Williams TF, Greenberg BG. The ecology of medical care. 1961. Bull N Y Acad Med. 1996; 73(1):187-212.

45. Maeseneer JMD, Driel ML van, Green LA, Weel C van. The need for research in primary care. The Lancet. 18 Oct 2003; 362(9392):1314-9.

9.6 Shuttle sheet

Patient's surname, first name	
Name and function of the sampler	
Date and Time of Sampling	
Indication of VKAs	
Type of VKA and dosage	
Tourniquet application time	
Type of tube used	
Needle Diameter	
Finned Units: Yes / No	
Direct drawdown: Yes / No	
Tube more than 80% full: Yes / No	
Identity of the biologist	
Laboratory Arrival Time	
Centrifuge Time	
To freeze or not	
PLC Reference / ISI	
Scan Time	
Venous INR Value	

9.7 Information letter to attending phisicians

INFORMATION NOTE FOR THE ATTENDING PHYSICIAN

Study sponsor:

University Hospital of Nîmes
Place du Professeur Debré
30029 Nîmes Cedex 09

Medical Policy Department

Strategy and Innovation

Directorate of Research, University Hospital and International Partnerships

Director: Anissa MEGZARI

Secretariat:

Tel.: 04.66.68.42.36

Fax: 04.66.68.34.00

Followed by:

Ms Sabrina NICOLAS

04.66.68.36.78

sabrina.nicolas@chu-nimes.fr

N/ref.: AM/ SN / – 19.

Evaluation of a weekly capillary INR monitoring strategy versus monthly venous INR monitoring in elderly patients in nursing homes: A multicenter randomized cluster trial

"INR-Cap" study

Version 0.1 - 30/07/2019

RCB-ID Number: 2022-A00516-37

Dear Madam, Sir,

Doctor ..... offered your patient..... (First name/LAST name) to participate in the study mentioned above.

This information note is intended to inform you of the study in which we propose to participate. If you have any questions, please do not hesitate to contact the doctor in charge of the study.

PRESENTATION OF THE STUDY

In elderly patients, the full range of measures to be taken to prevent stroke represents a real clinical challenge. Vitamin K antagonists (VKAs) are prescribed for elderly patients suffering from atrial fibrillation, deep vein thrombosis, or those with a heart valve because they are at increased risk of stroke. However, monitoring VKAs is very complicated. In the event of underdosing, the embolic risks such as stroke, phlebitis and pulmonary embolism are amplified; and in the event of an overdose, the risk of bleeding is increased. In general, monitoring for VKAs is carried out on the basis of venous INR, a test carried out once a month from a blood test. That's the monitoring you have right now.

To improve the follow-up of patients on VKA, a second method has been developed: the capillary INR, a test carried out once a week directly at the patient's bedside, making it possible to obtain the value of the INR in real time and thus improve patient monitoring. This test is almost painless because it is performed by collecting a simple drop of blood from the patient's finger. The effectiveness of the method has already been demonstrated many times but never in elderly patients.

The aim of the present study, in which we propose to your patient to participate, is to compare the usual strategy of monitoring VKA once a month by venous INR, to the weekly strategy by capillary INR monitoring of VKA.

CONDUCT OF THE STUDY

The participating centres, i.e. the participating nursing homes, will be randomised into two groups:

- The interventional group: Centre where weekly capillary INR monitoring will be applied in addition to monthly venous INR monitoring.
- The control group: Centre continuing the usual management with venous INR.

Belonging to one or the other group therefore depends on randomization and the group to which the nursing home will be affiliated.

All eligible patients from the same center will be informed and included in the study at the same time. At this stage, no establishment will know the group to which it will belong. The allocation of the nursing home to the control group or the experimental group will be done after the inclusion of all patients.

The study will take place over six months.

Interventional group: For the purposes of the study, a venous INR and a capillary INR will be performed to ensure that the two tests give the same results. Then, when the congruence of the tests is ensured, the capillary INR will be carried out once a week, or even once every two weeks when the values obtained are good or, on the contrary, more frequently if the capillary INR is not good, or in the event of events such as a fall, fever, haemorrhage, etc. A monthly venous INR will be performed, if it is off-target, the venous INR will be punctured upon return to the target.

Control group: The treatment will be entirely identical to that usually performed by venous INR.

RESEARCH-SPECIFIC ACTS

Interventional group: Monitoring of anticoagulants by capillary INR for 6 months in addition to management by venous INR.

> The nurse will follow the instructions for performing the capillary INR: wash the patient's hands, insert a test strip into the device, massage the finger and hand to activate circulation, perform the capillary puncture of a 10µL drop of blood using the lancet. The drop of blood should be deposited on the strip less than 180s after the strip is inserted into the meter and less than 15 seconds after the beginning of the formation of the blood drop, the result is readable on the meter after 1 minute.

Control group: Usual management.

NUMBER OF PATIENTS INCLUDED

A total of 128 elderly people on VKA living in nursing homes will be recruited during this study, including 64 patients in the interventional group and 64 in the control group.

CONSTRAINTS & OBLIGATIONS

- The patient must have been on vitamin K antagonists for more than 6 months.
- The patient must be affiliated or a beneficiary of a health insurance scheme.
- The patient must have signed the consent form.
- The patient must attest that they are not participating in any ongoing Category 1 research.
- Your treating physician will be notified of your participation in the study.

EXPECTED BENEFIT(S)

Elderly patients treated with VKA require appropriate anticoagulant monitoring because the risks of bleeding and thromboembolism are high and difficult to control.

Capillary INR monitoring has the advantage of allowing better monitoring of VKA treatment, being rapid and being able to be carried out more frequently. This will reduce the risk of bleeding and thromboembolism, as demonstrated by our previous pilot study.

EXPECTED RISK(S)

The risks for patients in the interventional group are only: the feeling of slight pain during the hair INR test due to the removal of a small drop of blood from the finger.

If you have any questions, don't hesitate to ask the doctor.

Name and contact information of the coordinating investigator

Dr David COSTA

Department of Biostatistics, Clinical Epidemiology, Public Health & Innovation in Methodology (BESPIM)

Nîmes University Hospital

Phone : 06.61.43.39.30

Rest assured that your participation is extremely valuable to us. We thank you in advance, Madam, Sir, for the help you are giving to medical research.