Assessment of the safety of Angioplasty procedures

SCRAP

2018/P02/283

NON-INTERVENTIONAL RESEARCH PROTOCOL INVOLVING THE HUMAN PERSON

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Sponsor
Hospital Group of La Rochelle Ré Aunis
Dr. Schweizer Street
17019 La Rochelle

Person who directs and monitors research:
Dr. Ludovic MEUNIER
Cardiology service
Hospital Group La Rochelle-Ré-Aunis
Dr. Schweitzer Street
17019 LA ROCHELLE

Center for Methodology and Data Management:
Clinical research unit
Hospital Group of La Rochelle Ré Aunis
Dr. Schweizer Street
17019 La Rochelle

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PROTOCOL UPDATE HISTORY

VERSION	DATE	REASON FOR UPDATE
1.0	26/12/2018	Initial version
2.0	02/11/2019	Request for information or modifications
3.0	02/20/2021	Amendment request for study extension

SUMMARY

ABREVIATIONS LIST

ARCClinical research associate
StrokeCerebrovascular accident
ANSMNational Agency for the Safety of Medicines and Health Products
CPPCommittee for the Protection of Persons
EMAEuropean Medicines Agency
MACEMajor Adverse Cardiac Events
TECClinical research technician

SUMMARY OF RESEARCH

PROMOTER	Hospital Group of La Rochelle Ré Aunis Dr. Schweizer Street 17019 La Rochelle
PERSON LEADING THE RESEARCH	Dr. Ludovic MEUNIER Cardiology service Hospital Group La Rochelle-Ré-Aunis
TITLE	**SAFETY EVALUATION OF ANGIOPLASTY INTERVENTIONS (SCRAP)**
RATIONALE/CONTEXT	Ischemic heart disease, or coronary heart disease, covers a set of pathologies due to insufficient oxygen supply to the myocardium due to the development of atherosclerosis in one or more coronary arteries. The use of active stents for the treatment of coronary stenosis is currently the standard treatment in almost all types of coronary lesions. In the percutaneous transluminal treatment of coronary lesions, angioplasty with balloons and bare stents has not shown satisfactory results in the past. The drug-eluting, so-called active balloon, could represent a new therapeutic option for the treatment of de novo lesions.
GOALS	To assess the safety of angioplasties performed in patients operated on at La Rochelle Hospital, the rate of major adverse cardiac events (MACE) will be determined and analyzed in the light of data from the literature.
RESEARCH SCHEME	non-interventional, prospective, monocentric research.
INCLUSION CRITERIA	• Patient treated for angioplasty, • Person affiliated or beneficiary of a social security scheme, • Informed about the study.
NON-INCLUSION CRITERIA	• language barrier, • Minor, • Pregnant woman, • Person under guardianship or curatorship, • person deprived of liberty, • Refusal to participate.
EVALUATION CRITERIA	The primary endpoint is a composite endpoint of major adverse cardiac events defined as death, nonfatal myocardial infarction (MI), nonfatal stroke (stroke), and target lesion revascularization (TLR) within 12 monthsthen at 36 monthsfollowing the intervention.
STUDY SIZE	The objective is to include more than 80% of patients over a period of 12 months, ie 1000 patients.
SEARCH DURATION	• Duration of the inclusion period: 12 months • Duration of follow-up per participant:36months (telephone contact at 12 monthsthen at 36 monthsfor MACE collection) • Total search time:48 month
STATISTICAL ANALYSIS OF DATA	The parameters collected are presented in tables containing descriptive and comparative statistics (total population; small vessel/large vessel subpopulations; stent[s]/stent[s] and active balloon[s]/active balloons subpopulations assets]). The MACE rate corresponds to the ratio of the number of patients who had one or more MACE to the total number of patients for whom the follow-up was carried out at 12 monthsthen to36month. The study of risk factors for MACE is carried out by bivariate analysis.
EXPECTED BENEFITS	The results of this study will make it possible to validate or not the algorithm of care applied to the hospital of La Rochelle. The results will be communicated to the Coronary Atheroma and Interventional Cardiology Group (GACI).

SCIENTIFIC RATIONALE AND GENERAL DESCRIPTION

CURRENT STATE OF KNOWLEDGE

Ischemic heart disease, or coronary heart disease, covers a set of pathologies due to insufficient oxygen supply to the myocardium due to the development of atherosclerosis in one or more coronary artery(ies). The use of active stents for the treatment of coronary stenosis is currently the standard treatment in almost all types of coronary lesions. In the percutaneous transluminal treatment of coronary artery lesions, balloon angioplasty with conventional balloons and drug-free eluting stents have not shown satisfactory results.(1)(2). Although some studies have shown balloon angioplasty and bare stent placement to be equally effective against restenosis(1)(2), a meta-analysis of 11 trials finds a rate of 25.8% for balloon angioplasty and 34.2% for bare-metal stents(3).

Thrombosis and in-stent restenosis, despite a decreasing incidence since the advent of first and then second generation active stents, remain frequent complications of angioplasty at around 5 to 15% depending on the series. (4.5). Indeed, the implantation of stents in the arterial wall leads to an inflammatory reaction around the mesh as well as the persistence of fibrinous deposits at the origin of a neointimal proliferation that is more thrombogenic than the native endothelium. (6). To this is added a phenomenon of neoatherosclerosis which appears later than on bare stents, most often 3 years from the date of implantation. On the other hand, very late stent thromboses, defined by the Academic Research Consortium as occurring more than one year after stent implantation, in fact require prolonged observation in order to take them into account.

The drug-eluting balloon, also called active balloon, or DCB (Drug Coated Balloon), was initially developed for the treatment of in-stent restenosis (4), and is currently considered the standard treatment for this pathology instead of in-stent active stenting. Since then, the active balloon has gradually been studied for the treatment of de novo lesions (5), particularly those of small vessels. The multicenter randomized BASKET-SMALL study on small de novo lesions (less than or equal to 2.5 mm in diameter) showed the non-inferiority of drug-eluting balloons compared to the active stent with regard to MACE up to 12 months, with similar event rates for both treatment groups(7).

Recently, pilot studies have demonstrated the feasibility of using drug-eluting balloons for the treatment of bifurcations(8), chronic occlusions(9), as well as calcified lesions after Rotablator(10). These studies have thus shown very promising and consistent results when the active balloon was used as an alternative therapy. The German consensus group has therefore recently developed recommendations for the treatment of small vessel disease using the drug-eluting balloon(11).The BASKET SMALL 2 study is the first study to have compared the effectiveness of the active balloon versus an active stent in the treatment of de novo lesions of small vessels, with a fairly long follow-up period of 3 years and in a sufficiently large workforce. (12).Other studies have been able to demonstrate good results at 6 months in terms of efficacy and safety of the active balloon on the treatment of de novo lesions, regardless of the caliber of the vessel treated. (13). However, data are lacking in the literature concerning the treatment

of de novo lesions by active balloon, with a sufficiently long follow-up period to take into account neo-atheromatosis and very late stent thrombosis, in a large sample.
The use of drug-eluting balloons in La Rochelle has gradually evolved from the in-stent indication, to de novo lesions of small vessels (≤ 2.5 mm), then to de novo lesions of large vessels. In addition to the treatment of long lesions on small caliber vessels, good immediate angiographic results are also obtained for the treatment of bifurcations (all types of Medina), for calcified lesions pretreated with Rotablator, as well as certain chronic occlusions.

RESEARCH ASSUMPTIONS

To assess the safety of angioplasties performed in patients operated on at La Rochelle Hospital, the rate of major adverse cardiac events (MACE) will be determined and analyzed in the light of data from the literature.

JUSTIFICATION OF METHODOLOGICAL CHOICES

The collection of data on MACE will be carried out by telephone follow-up at 12 monthsthen at 36 months. Major adverse cardiac events are defined as death, myocardial infarction, and ischemia-induced target lesion revascularization during the follow-up period.

EXPECTED BENEFITS

The results of this study will make it possible to validate or not the algorithm of care applied to the hospital of La Rochelle.
The results will be communicated to the Coronary Atheroma and Interventional Cardiology Group (GACI).

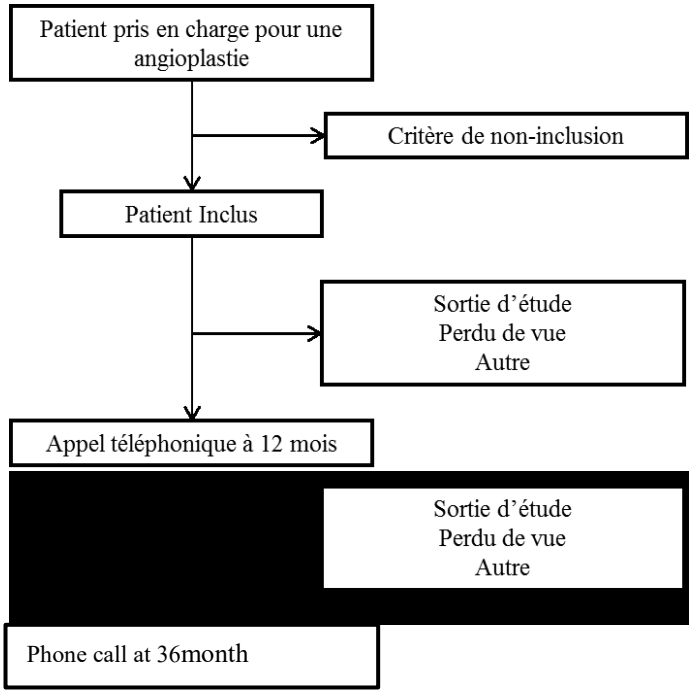
GOALS

1.1. PRIMARY OBJECTIVE

To assess the safety of angioplasties performed in patients operated on at La Rochelle Hospital, these will be referred to as 12 monthsthen at 36 monthsafter the operation to find out if any major adverse cardiac events (MACE) have occurred since their operation. The MACE rate will thus be determined.

RESEARCH DESIGN

This is non-interventional, cross-sectional, prospective, monocentric research.



ELIGIBILITY CRITERIA

1.2. INCLUSION CRITERIA

- Patient treated for angioplasty,
- Person affiliated or beneficiary of a social security scheme,
- Informed about the study.

NON-INCLUSION CRITERIA

- language barrier,
- Minor,
- Pregnant woman,
- Person under guardianship or curatorship,

- Persons deprived of liberty,
- Refusal to participate.

FEASIBILITY AND MODALITIES OF RECRUITMENT

Participants will be selected from the Cardiology department of the Saint Louis Hospital of the La Rochelle-Ré-Aunis Hospital Group.

PROCEDURES STUDIED

Patients referred for coronary angiography for revascularization are those diagnosed with acute coronary disease (Acute Coronary Syndrome with or without ST segment elevation) or chronic (silent myocardial ischemia, angina).

During coronary angiography, significant lesions are those for which the percentage of stenosis in relation to the reference diameter is ≥ 50-70%.
In case of angiographic doubt as to the significance of a lesion, an FFR (Fractional Flow Reserve) can be performed. A value less than or equal to 0.80 is thus in favor of a hemodynamically significant lesion.

Depending on the terrain, the number and the characteristics of the lesions, the patient is offered a strategy of surgical revascularization by bypass or interventional by angioplasty.
When the interventional strategy is chosen, the angioplasty of one or more lesions can be performed in one or more stages using stents (generally active) and/or active balloons.

The choice between stenting (active/naked) and active balloon is based on the following criteria:

- Active stenting:
    - hemodynamic instability, malignant ventricular hyperexcitability (VT, VF), plurivessel with altered LVEF,
    - extensive or sub-occlusive type C, D or E dissection or persistence of ≥ 50% stenosis after predilation.
- Active balloon: residual stenosis ≤ 30% and absence of extensive or sub-occlusive type C, D or E dissection after predilation(14), patient at risk of hemorrhage.
- Naked stenting: extensive or occlusive dissection after active balloon,

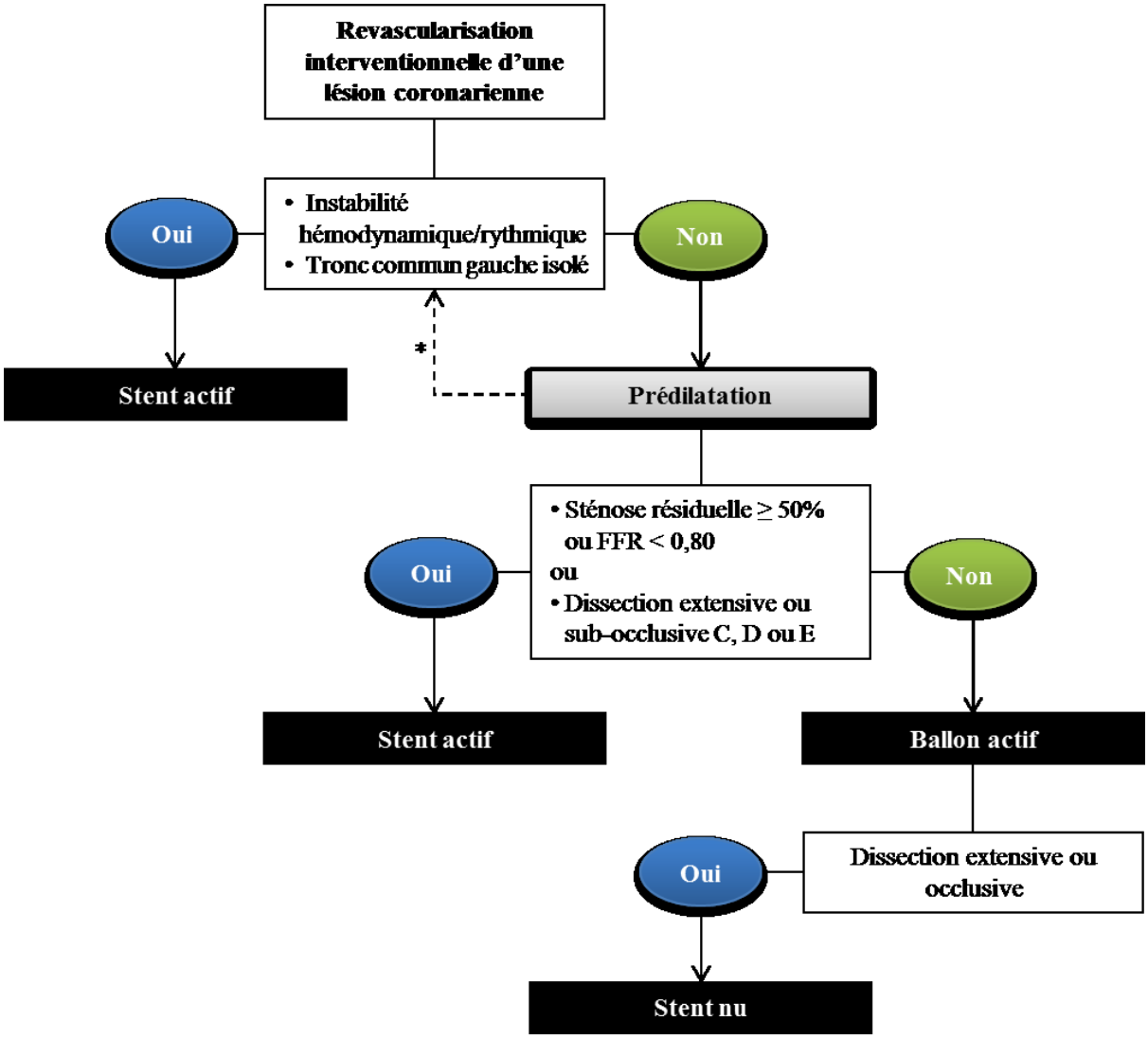


Figure 1: diagram of the strategy of revascularization by angioplasty.

* In case of haemodynamic/rhythmic instability; FFR: Fractional Flow Reserve

EVALUATION CRITERIA

The primary endpoint is a composite endpoint of major adverse cardiac events defined as death, nonfatal myocardial infarction (MI), nonfatal stroke (stroke), and target lesion revascularization (TLR) within 12 monthsthen 36 monthsfollowing the intervention.

PROCEDURE OF THE RESEARCH

RESEARCH TIMELINE

- Duration of the inclusion period: 12 months
- Duration of follow-up per participant:36months (telephone contact at 12 monthsthen at 36 monthsfor MACE collection)
- Total search time:48month

SUMMARY TABLE OF PARTICIPANT MONITORING

	Screening D-28 to D-1	Inclusion D0	Phone contact M12 +/- 30 days	Phone contact M36 +/- 30 days
Verification of eligibility criteria	X	X		
Presentation of the study	X	X		
Compendium of non-opposition		X		
MACE collection			X	X

INFORMATION OF DATA SUBJECTS

The doctor offers the patient to participate in this research and informs him:

- of the objective,
- of the computerized processing of the data concerning him which will be collected during this research and also specifies his rights of access, opposition and rectification to this data.

The doctor also checks the eligibility criteria. If the person agrees to participate, they give their consent orally and their non-objection is documented in their medical file. The participant may, at any time, oppose the use of his data, within the framework of the research.

The non-objection is collected before the patient leaves hospital.

FOLLOW-UP VISITS

Patients who have agreed to participate will be contacted one yearthen three yearsafter their intervention by telephone.

In case of MACE, the patient's cardiologist will be contacted for the detailed record of the event.

STATISTICAL ASPECTS

STUDY SIZE CALCULATION

In 2017, the La Rochelle cardiology department treated 1,252 patients for coronary pathologies. The objective is to include more than 80% of patients over a period of 12 months, ie 1000 patients.

1.3. STATISTICAL METHODS USED

The parameters collected are presented in tables with descriptive statistics for the total population and for the sub-populations defined by the size of the vessels (small vessels / large vessels) or the procedure used (active stent[s] / stent [s] and balloon[s] active[s] / balloon[s] active[s]), according to the following modalities:

- For quantitative variables: the mean and the standard deviation or the median, the minimum and the maximum
- For qualitative variables: the number, percentages and 95% confidence interval, for each of the modalities of the variable (excluding missing data in the denominator).

The MACE rate will correspond to the ratio of the number of patients having had one or more MACE to the total number of patients for whom the follow-up was carried out at 12 months.then at 36 months.

To compare the sub-populations, the analyzes test the null hypothesis of equality of means for the quantitative variables and of homogeneity of the populations for the qualitative variables:

- For the quantitative variables, after checking the equality of the variances and the normal distribution of the values, the Student test is used. In case of inequality of variances or non-Gaussian distribution, a non-parametric Mann-Whitney/Wilcoxon test is used.
- For qualitative variables, a chi-square test is carried out or a Fisher test in the case of small numbers.

The study of risk factors for MACE is carried out by bivariate analysis. Odds ratios and 95% confidence intervals are calculated.

ACCESS RIGHTS TO SOURCE DATA AND DOCUMENTS

ACCESS TO DATA

The acceptance of participation in the protocol implies that the people carrying out the research will make available the documents and individual data strictly necessary for the monitoring, quality control

and audit of the research, available to people with access to these documents in accordance with the laws and regulations in force.

SOURCE DATA

All information contained in original documents, or in authenticated copies of these documents, relating to clinical examinations, observations or other activities carried out in the context of research and necessary for the reconstitution and evaluation of the research. The documents in which source data is stored are called source documents.

Source documents:

- Hospital medical record
- Report of consultation of city cardiologists

DATA PRIVACY

In accordance with the legislative provisions in force, the persons having direct access to the source data will take all the necessary precautions to ensure the confidentiality of the information relating to the research, to the persons who lend themselves to it and in particular with regard to their identity as well as only to the results obtained. These people, in the same way as the people who direct and monitor the research, are subject to professional secrecy.

During the research or at its end, the data collected on the people who agree to it and transmitted to the promoter by the people who direct and monitor the research (or any other specialized contributors) will be codified. Under no circumstances should they clearly show the names of the persons concerned or their addresses.

The name of the patients will be coded by: Initial surname – initial first name – inclusion number (Example: Bertrand DUPOND, 65th inclusion BD65)

The promoter will ensure that each person who agrees to the research has been informed of access to the individual data concerning him and strictly necessary for the quality control of the research.

QUALITY CONTROL AND ASSURANCE

RESEARCH FOLLOW-UP

The follow-up of the research will be ensured by a health manager. He will be responsible, alongside the person directing and supervising the research, for:

- research logistics and monitoring,

- drawing up reports on its progress,
- verification of the update of the observation book (request for additional information, corrections, etc.).

He will work in accordance with standard operating procedures, in collaboration with the clinical research associate delegated by the promoter.

QUALITY CONTROL

A clinical research associate mandated by the sponsor visits the center on a regular basis, during the setting up of the research, one or more times during the research depending on the rhythm of inclusions and at the end of the research. During these visits, the following elements will be reviewed:

- compliance with the research protocol,
- quality of data collected in the case report: accuracy, missing data, consistency of data with source documents (medical records, appointment books, original laboratory results, etc., etc.).

Any visit will be the subject of a monitoring report in written form.

DATA MANAGMENT

CardioReport software will be used for data entry at inclusion. An extraction will create an Excel table to program and record the monitoring data at 12 monthsand at 36 monthsfor the census of MACE. The final database will be pseudonymised.

The person responsible for hosting and maintaining the database is the Groupe Hospitalier de la Rochelle Ré Aunis. The server hosting the data is located in the IT department.

Daily backups are performed on discs, the storage location is subject to access control and benefits from fire protection.

Authorization profiles define the functions or types of information accessible to a user. The logical access control is done by a password (8 characters minimum, 1 capital letter compulsory; validity: 2 months). A procedure defines the distribution of access control means to authorized persons, the allocation by the software administrator and specifies the written traceability of the request.

The shelf life is defined in the study protocol. The current archives are kept in the service until the results are published. Intermediate archives are kept according to legal provisions in the archive room dedicated to clinical research.

AUDITING AND INSPECTION

An audit may be carried out at any time by persons appointed by thepromoter andindependent of the people conducting the research. Its purpose is to verify the security of the participants and the respect of their rights, the respect of the applicable regulations and the reliability of the data.

An inspection can also be carried out by a competent authority (ANSM for France or EMA within the framework of a European test for example).

The audit, as well as the inspection, could apply to all stages of research, from the development of the protocol to the publication of the results and the classification of the data used or produced within the framework of the research.

Investigators agree to comply with the sponsor's requirements for an audit and the competent authority for an inspection of the research.

ETHICAL AND REGULATORY CONSIDERATIONS

COMPLIANCE WITH REFERENCE TEXTS

The promoter and the person(s) directing and supervising the research undertake to ensure that this research is carried out in accordance with law no. 2012-300 of March 5, 2012 relating to research. involving the human person and the declaration of Helsinki (which can be found in its integral version on the sitehttp://www.wma.net/en/30publications/10policies/b3/).

This research has received the favorable opinion of the Committee for the Protection of Persons (CPP) Sud-Est VI.

The data recorded during this research is subject to computerized processing at the Groupe Hospitalier de la Rochelle-Ré-Aunis in compliance with law n ° 78-17 of January 6, 1978 relating to data processing, files and freedoms amended by law 2004-801 of August 6, 2004.

This research is part of the “Reference Methodology” (MR-003). The La Rochelle-Ré-Aunis Hospital Group has signed a commitment to comply with this "Reference Methodology".

AMENDMENTS TO PROTOCOL

Any substantial modification, i.e. any modification likely to have a significant impact on the protection of persons, on the conditions of validity and on the results of the research, on the quality and safety of the products tested, on the interpretation of the scientific documents that support the progress of the

research or the methods of conducting it, is the subject of a written amendment which is submitted to the sponsor; the latter must obtain, prior to its implementation, a favorable opinion from the CPP.

Non-substantial modifications, ie those having no significant impact on any aspect of the research whatsoever, are communicated to the CPP for information.

All modifications are validated by the sponsor, and by all the research stakeholders concerned by the modification, before submission to the CPP. This validation may require the meeting of any committee set up for the research. .

All modifications to the protocol must be brought to the attention of all the people carrying out the research, who undertake to respect its content.

PRESERVATION OF DOCUMENTS AND DATA RELATING TO RESEARCH

The following documents will be archived by the service until the end of the period of practical usefulness. This indexed archive includes:

- Mail copies of the CPP notice
- The successive versions of the protocol (identified by the version number and the version date),
- The pseudonymised database,
- All appendices specific to the study,
- The final study report from the statistical analysis and quality control of the study (duplicate sent to the sponsor).
- Any audit certificates produced during the research

The database that gave rise to the statistical analysis must also be archived by the person in charge of the analysis (paper or electronic medium).
At the end of the period of practical usefulness, all the documents to be archived, as defined in the procedure for "classification and archiving of documents related to biomedical research" of the Groupe Hospitalier de la Rochelle Ré Aunis will be transferred to the archiving site dedicated to clinical research and will be placed under the responsibility of the Sponsor for 15 years after the end of the study in accordance with institutional practices.
No displacement or destruction can be carried out without the agreement of the Promoter. At the end of the 15 years, the promoter will be consulted for destruction. All data, documents and reports are subject to audit or inspection.

RULES RELATING TO PUBLICATION

SCIENTIFIC PAPERS

Any written or oral communication of the results of the research must receive the prior agreement of the person directing and supervising the research and, where applicable, of any committee set up for the research.

The publication of the main results mentions the name of the promoter, of all the people who included or followed patients in the research, of the methodologists, biostatisticians and data managers who participated in the research, of the members of the committee(s) set up(s) for the research and the possible participation of the laboratory name of the pharmaceutical laboratory / the source of funding. International rules for writing and publication will be taken into account (The Uniform Requirements for Manuscripts of the ICMJE, April 2010).

COMMUNICATION OF RESULTS TO PATIENTS

At their request, participants in the research are informed of the overall results of the latter.

TRANSFER OF DATA

The collection and management of data is provided by the Hospital Group of La Rochelle-Ré-Aunis. The conditions for the transfer of all or part of the research database are decided by the research sponsor and are the subject of a written contract.

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