A comparative study between a pre-hospital and an in-hospital circulatory support strategy (ECMO) in refractory cardiac arrest.

(APACAR2)

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1 PROTOCOL SUMMARY

Title: A comparative study between a pre-hospital and an in-hospital circulatory support strategy (ECMO) in refractory cardiac arrest.

Introduction and hypothesis:

Cardiac arrest (CA) or sudden death affects approximately 40,000 people in France. It is still a major cause of death in a young population. Management of CA is defined by international recommendations, detailed by learned societies in each country. It includes several links that are interconnected for its optimisation. This "survival chain" associates: early alert, early external cardiac massage, early defibrillation, early specialised intensive care and specific hospital management. Despite all these improvements, no progress, or little has been made in the survival of CA victims over the past few years in industrialised countries, and the survival rate in France is 3% to 5%.

Refractory cardiac arrest is defined as failure, after 30 minutes of specialised resuscitation. It used to be the standard to admit that there was no hope of spontaneous cardiac activity and satisfactory neurological recovery after this period, except in cases of CA with neuroprotection (intoxication, hypothermia).

External circulatory support such as "extracorporeal cardiopulmonary resuscitation" (ECPR) makes it possible to replace the circulatory activity of the myocardium and the respiratory activity of the lungs. The indications that are currently recognized in adults are:

- haemodynamic failure due to medical causes or after heart surgery
- respiratory failure (Acute Respiratory Distress Syndrome - ARDS) due to medical causes (infection, etc...) or post-surgery.

This technology was developed over the past 10 years, possibly as a result of several factors. The first is technological with miniaturisation and simplification of ECPR devices. This simplification is associated with an increase in the safety of use resulting from multi-setting monitoring built into ECPR devices.

The second factor is the extension of indications beyond cardiac surgery. In fact, medical intensive care teams are now accustomed to ECPR management without the intervention of cardiovascular surgeons. Specific training enables non-surgeon physicians to use this technique either in a hospital

setting with a cardiac surgery centre, or a network between a hospital without cardiac surgery and a tertiary care centre.

In in-hospital cardiac arrest (CA) some teams use ECPR with an improvement in the survival rate of 20% in comparison to standard resuscitation. This use demonstrates the possibility of neurological recovery independent from the recovery of spontaneous cardiac activity which can be differed.

These results encouraged the use of ECPR in cases of out-of-hospital refractory cardiac arrests. Patients who are victims of CA are resuscitated for 30 minutes on the spot where the CA occurs. They are then transferred to a specialised centre. The significant improvement in survival noted in in-hospital CAs was not observed in the French series of studies concerning out-of-hospital CAs. This survival is currently estimated at 4%. This difference can be partly explained by the difference in time between the beginning of cardiac massage and the implementation of circulatory support by ECMO ("low flow" period). This time period is directly correlated to survival. The French studies find an average period of approximately 120 minutes of low flow which corresponds to approximately 5% survival. This time period can be explained by the time required for the following:

- 30 minutes of specialised resuscitation
- placement on a stretcher
- transport to hospital
- ECMO implementation.

Since 2011 a strategy has been developed to shorten these time periods with the installation of the circulatory support system at the place where the cardiac arrest occurs. This strategy has proven its feasibility.

To demonstrate the superiority of this strategy in terms of survival, we would like to conduct a randomised comparative study of two strategies:1) ECPR implementation between the 20th minute to the 40th minute of CA, directly at the site of the CA, by emergency physicians and/or specifically trained resuscitators 2) optimised on-site resuscitation with secondary transfer to the hospital for the implementation of support. The purpose is to increase from 5% to 20% the survival of victims of out-of-hospital refractory cardiac arrests with a good neurological prognosis.

Main objective:

The hypothesis is that pre-hospital ECPR will result in survival for 20% of the patients, considering that the percentage of survival with in-hospital ECPR is less than 5%.

Main judgement criterion:

Survival with good neurological outcome (CPC 1 or 2) on discharge from intensive care or at 6 months

Secondary judgement criteria:

Success rate of the implementation of ECPR

ECPR implementation time

Immediate complications: haemorrhage, infection

Number of organ harvesting

The quality of survivors' neurological status according to the CPC neurological classification at D 28, 2 months and 1 year

Predictive indicators of the prognosis during cardiac arrest via cerebral and biological monitoring

Inclusion criteria:

Eligible patients have the following combination of criteria:

- Adults over 18 years of age and under 65 years of age
- **And** Refractory cardiac arrest (defined by the failure of professionals to resuscitate at the 20th minute of cardiac arrest with a minimum of 3 AED or equivalent analyse)
- **And** Beginning of external cardiac massage within the first 5 minutes after cardiac arrest (no flow < 5 min.) **with** persistant shockable rhythm ***or*** persistant of signs of life during resuscitation (any rhythm): spontaneous movement, absence of mydriasis and/or pupillary response, spontaneous breathing movements
- **And** Medical cause of the cardiac arrest
- **And** ETCO2 above 10 mm Hg at the time of inclusion
- **And** Absence of major co-morbidity.
- **And** ECPR team available and on-site before the 40th minute

Non-inclusion criteria:

– Children under 18 years of age

– Adults over 65 years of age

– Period of more than 5 minutes without cardiac massage after collapsing

– Known co-morbidity that compromises the prognosis for short or medium-term survival

– Cardiac arrest during transportation times

Methodology, type of study: This is a prospective randomised study of current care

Sample size (SS, power, risk): A total number of 105 patients in each group will make it possible to demonstrate at the alpha risk of 5% and a power of 1-β=90%, a significant difference in favour of early pre-hospital ECPR compared to the current practice with in-hospital ECPR.

Study procedure:

Baseline visit: patient inclusion

When a victim of cardiac arrest with strict "no flow" for less than 5 minutes is taken under care in an out-of hospital setting, a mobile ECPR team is rushed to the spot at the 10^{th} minute of cardiac arrest. The 2 physicians in this team verify the inclusion criteria. The patient is included when all the eligibility criteria are present, between the 20^{th} minute and the 40^{th} minutes of cardiac arrest. Treatment starts immediately after randomisation. The success rate and ECMO implementation time are noted and compared. The family is informed at inclusion or at intensive care arrival. The patient is informed as soon as possible, if he/she is alive.

Follow-up visit on discharge from intensive care, at day 28, at 2, 6 and 12 months:: These visits should evaluate the patient outcome. The CPC score and the number of transfusions and infections during hospitalisation are evaluated.

Duration of the study: 4 years

Participation period for one patient: 1 Year

Number of investigator sites: 4

Expected results: An increase of 5% to 20% of survival for victims of out-of-hospital refractory cardiac arrest, with a good neurological prognosis.

2 STATUS OF THE QUESTION

2.1 Circumstances surrounding the problem:

2.1.1 The limits of conventional resuscitation in cardiac arrests.

Sudden adult death, unexpected cardiac arrest (CA) most often related to cardiovascular causes, affects more than 40,000 people in France every year.

The prognosis of out-of-hospital sudden death is particularly sombre. Only 5 to 20% of the patients survive without neurological sequela. This prognosis can be partially improved by an efficient organisation of management that implements the concept of the "survival chain". An early alert by witnesses of the CA, carrying out the first interventions, cardiopulmonary resuscitation (CPR), defibrillation by the public or persons qualified in first-aid, followed by specialised resuscitation by a medical team (such as the ambulance service) increase the amount of survivors. The reduction in the time that passes before the first interventions (called the no-flow period) and the duration of resuscitation before return of spontaneous circulation (ROSC) called low-flow, are considered to be the primary predictive factors of survival in CA. (1)

Just recently, better knowledge of post-cardiac arrest syndrome (2) also contributed to an improvement in the prognosis and the quality of survival. The introduction of early angioplasty(3)(4) and the generalisation of therapeutic hypothermia(5)(6) now complete management for which coding is steadily improving through international and national recommendations that are updated every 5 years[1] (1). However, in order to show what it is capable of, this conventional management of CA requires spontaneous cardiac activity to be re-established as quickly as possible. Therefore, a return of spontaneous circulation (ROSC) must be obtained in the field in out-of-hospital sudden deaths.

Classically, in the absence of ROSC after 30 minutes of correctly administered resuscitation, the CA is considered to be refractory (7)(8)(9)and the treatment options are limited[8] (10). Just recently, it was shown that the chances of survival are non-existent after 16 minutes of resuscitation.(11) In most cases, resuscitation is discontinued and the patient is declared dead on the spot. The regulatory

inclusion of a physician on ambulance service teams relieves the difficulty of this decision. It is often simple to make and is medically indisputable when it is obvious that the prognostic factors are very unfavourable (notably, an extended no-flow period) and/or the conditions (advanced age, severe chronic disease, etc...) are not compatible with prolonged resuscitation. This decision is much more difficult when the prognostic factors are favourable and prolonged resuscitation efficiently provides spontaneous circulation (signs of the patient awaking during CPR). Under these circumstances, in France and several other European countries, the decision can be made to continue ECM and transport the refractory CA victim. It was made possible by the development of mechanical external cardiac massage devices such as Autopulse ®(12) and Lucas®(13)(14) which enable prolonged ECM during transport by the emergency service. However, this continuation of resuscitation can only be considered if it enables another subsequent treatment for the patient. Two options are possible. The patient can be declared dead and become a potential organ donor in the framework of an organ harvesting procedure in a patient after "cardiac death". This harvesting, which is highly organised according to regulations, can only be done in certain hospitals authorised by the French Biomedicine Agency.

Or, resuscitation can be prolonged by the use of extracorporeal circulatory support.

2.1.2. The progress of extracorporeal circulatory support and cardiac arrest

Circulatory support is a technique that has been in common use for many years now peri-operatively in cardiac surgery. One of its simplest forms, ECMO (extracorporeal membrane oxygenation) is being used more and more often outside of this field, notably in paediatrics and in the care of ARDS or refractory shock in adults. This technique has notably been widely introduced in general intensive care in the treatment of H1N1 malignant influenzas that affect young subjects(15). In parallel with this extension of the indications for ECMO, the technical development of equipment was a major factor. ECMO devices, which are particularly easy to use, miniaturised and energy autonomous, are available. They make it possible to use ECMO during inter-hospital transport by ambulance or

helicopter. In France, several teaching hospitals have therefore developed mobile teams called UMAC (mobile circulatory support unit) that enable the implementation of ECMO in intensive care units where there was none, and the transport of patients on circulatory and respiratory support to a reference centre. (16)

2.1.3. The implementation of ECMO in CA

It quickly became evident that the possibility of having artificial circulatory activity that enables efficient perfusion by oxygenated blood was important for CA victims whose heart had stopped beating. The term extracorporeal cardiopulmonary resuscitation (ECPR) has since emerged. The first research, conducted primarily during refractory CAs that occurred in the hospital setting, demonstrated the unexpected possibility for survival in patients who, without this option would be dead, and for whom resuscitation would have been stopped. In 2003 in Taiwan, Chen et al. noted a survival rate of almost 30% in a series of CAs that occurred in the hospital setting(17)(18). In Caen, France, the same phenomenon was noted: the survival of 8 out of 40 patients who benefited from ECPR following refractory CA(19). This technique proved to be highly adapted when the cause of the CA was potentially reversible. Mégarbane et al. noted the survival of 3 out of 12 victims of CA following acute intoxication with cardiotoxic drugs(20).

In international recommendations, circulatory support is still only recommended in paediatrics. However, these indisputable successes in adults led to an attempt to rationalise the use of therapeutic ECPR in France (21). The indications considered as possible include the existence of hypothermia, intoxication, signs of life during CPR, and CPR (low-flow) of less than 100 minutes.

The development of ECPR programmes for the treatment of refractory CA demonstrated a difference in prognosis between in-hospital and out-of-hospital CAs. In-hospital CAs quickly benefit from the implementation of ECPR. Out-of-hospital CA victims have late access to this possibility of resuscitation. In fact they require resuscitation of at least 30 minutes in the field to be considered as refractory, followed by transport under mechanical ECM until arrival at a centre with ECPR. Le

Guen et al. noted that in a series of patients who were victims of sudden death in Paris in out-of-hospital settings, only 2 out of 51 patients survived in good neurological condition(22). Most of these patients had extended low-flow periods before the implementation of ECPR. A negative correlation between the duration of resuscitation before ECPR and survival explains this poor prognostic result. In addition, resuscitation prolonged by mechanical ECM is burdened by its own morbidity as Agostinucci et al. emphasized(23). This negative influence before access to ECPR is also noted by Chen et al.(24) in the hospital setting. The prognosis rapidly decreases when resuscitation is prolonged: more than 40% survival if resuscitation lasts less than 30 minutes; 17% when it surpasses 60 minutes. This difference in survival between in-hospital and out-of-hospital CA is also noted in another series of French studies (Gay, AFAR abstract). The prognosis for out-of-hospital CA is even worse when it is accompanied by prolonged CPR. Morbidity is also higher among these patients. Cadarelli et al. included all the research and case histories published up until 2008 in a meta-analysis and demonstrated the harmful effect of prolonged CPR(25). In this analysis, the speed at which ECPR is implemented appears to be a prognostic factor similar to patients' age and the total duration of circulatory support. Therefore, ECPR that is started after more than 30 minutes of CPR results in a decrease in survival. Kilbaught et al.(26) emphasize that it is actually the time factor that makes the difference between in-hospital and out-of-hospital CAs. In their pre-hospital emergency system, very rapid transport of patients during CPR to start ECPR upon arrival in the emergency service is possible. With this strategy, they demonstrate that the difference in prognosis between in-hospital and out-of-hospital CAs is eliminated when the time for implementation of ECPR is comparable. As a result, ECPR is used earlier and earlier in hospitals in Japan with results currently being published that appear to be very positive for survival.

2.1.4 The concepts of pre-hospital ECPR

The analysis of the international literature shows that ECPR might be a management method that improves the survival of CA victims.

However, in the context of out-of-hospital sudden death in a medicalised emergency system and in the framework of French regulations, there are two limiting factors:

- the obligation for resuscitation for 30 minutes before categorically announcing that the CA is refractory and whether or not to choose another treatment option.
- the possibility to have access to ECPR within the closest time period to the 30 minutes of CPR, which appears to be an important threshold in determining the prognosis.

Pre-hospital ECPR, which is the basis of the research concept being proposed, includes arteriovenous cannulation and the implementation of the extracorporeal system (pump, oxygenator) in a non-healthcare setting. It is therefore different from the in-hospital transport of patients on ECPR since the preceding steps take place in a hospital. The implementation of ECPR in hospital studies can be rapid, approximately 20 minutes in the Japanese study series and according to our experience(27). ECPR for out-of-hospital refractory CAs was the subject of a few clinical cases, in children(28) and in sports events(29). Its feasibility by the ambulance service pre-hospital teams was confirmed in our last studies(30)(27).

The improvement in survival with early ECPR, close to a 30-minute period of CPR should also be demonstrated. It is only based on the extrapolation of the results of very fast transport and almost without specialised resuscitation of victims of sudden death close to a hospital with ECPR.

Confirmation of this concept is therefore of particular importance and in fact:

- it would provide the prospect of a new treatment possibility for patients whose chances for survival are extremely slim, because prolonged CPR is required to have access to a hospital ECPR. It is an essential step before conducting a multi-centre randomised study to demonstrate the beneficial effect on survival.

- it would make it possible to stress the pertinence of the French teams' approach in this field, notably in comparison to European countries (Germany, Spain, etc...) that already have a medicalised pre-hospital emergency system, or that are currently developing it, like Japan.
- finally, it might also result in a better determination of the place of therapeutic ECPR and as a result, clarify the indications for organ harvesting after "cardiac death" in victims of pre-hospital sudden death.

In brief, the objective of this project is to evaluate the advantage of pre-hospital ECPR in improving patient survival.

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3 RESEARCH OBJECTIVES

3.1 Main objective

Demonstration of an increase by 5% to 20% in survival of victims of out-of-hospital refractory cardiac arrest with a good neurological prognosis at 6 months evaluated by the CPC score.

3.2 Secondary objectives

To evaluate the complications of pre-hospital ECPR.

To evaluate the progression of patients admitted to the ICU.

To identify predictive factors of success of pre-hospital ECPR.

4 JUDGEMENT CRITERIA

4.1 Main judgement criterion

Patient survival with good neurological outcome (CPC 1 or 2) on discharge from the ICU or at 6 months.

4.2 Secondary judgement criteria

- The complications of pre-hospital ECMO are evaluated by indirect criteria. The criteria chosen are:

– Percentage of success with the implementation of ECPR. ECPR with an output of more than 2 litres per minute is considered to be successful.

– ECPR implementation time. The time period taken into account is the time period before incision - the initiation of ECPR

– The percentage of severe complications due to haemorrhage defined by more than 6 transfusions of packed red blood cells in the first 24 hours

– The percentage of infectious complications defined by the presence of a systemic inflammatory response associated with a presumed or identified infection during hospitalisation in the ICU.

- The progression of patients admitted to the ICU is evaluated by monitoring:

– With neurological assessment by the "Cerebral Performance Category" (CPC) score done on or in D 28, 2 months, and 1 year. (In conformance with the recommendations). This score is defined by:

o Level 1: Conscious and good cerebral performance, might have mild neurological or psychological deficit.

o Level 2: Conscious and moderate cerebral disability.

- Level 3: Conscious and severe cerebral disability.
- Level 4: Coma or vegetative state.
- Level 5: Brain death or demise

– For deceased patients, the number of patients progressing towards brain death, and the number of organs harvested.

- To identify predictive factors of success of pre-hospital ECMO.
  - The predictive factors are obtained by clinical and para-clinical data collection (implementation of cerebral monitoring by cerebral tissue saturation, and a pupillometer as well as measurement of venous blood lactates…)

5 POPULATION ELIGIBILITY CRITERIA

5.1 Inclusion criteria for ill subjects

Eligible patients have the following combination of criteria:

- Adults over 18 years of age and under 65 years of age
- And Refractory cardiac arrest (defined by the failure of professionals to resuscitate at the 20th minute of cardiac arrest with a minimum of 3 AED or equivalent analyse)
- And Beginning of external cardiac massage within the first 5 minutes after cardiac arrest (no flow < 5 min.) with persistant shockable rhythm ***or*** persistant signs of life during resuscitation: spontaneous movement, absence of mydriasis and/or pupillary response, spontaneous breathing movements
- And Medical cause of the cardiac arrest
- And ETCO2 above 10 mm Hg at the time of inclusion
- And Absence of major co-morbidity.
- And ECPR team available and on-site before the 40th minute

5.2 Non-inclusion criteria

The non-inclusion criteria are:

– Children under 18 years of age
– Adults over 65 years of age
– Period of more than 5 minutes without cardiac massage after collapsing
– Co-morbidity that compromises the prognosis for short or medium-term survival
– Cardiac arrest during transportation times

6 EXPERIMENTAL DESIGN

This is a multi-centre prospective superiority randomised study. The results are compared to the percentage of success of in-hospital use of ECMO. Due to the type of technology used, it is impossible to implement a blind.

7 NUMBER OF SUBJECTS INCLUDED

The hypothesis is that pre-hospital ECPR will result in success for 20% of the patients, considering that the percentage of survival with in-hospital use of ECMO is less than 5%. A total number of 105 patients per group will make it possible to demonstrate at the alpha risk of 5% and a power of 1-β=90%, a significant difference in favour of early pre-hospital ECPR compared to the current practice with in-hospital ECPR.

8 STATISTICAL ANALYSIS

8.1.1 Analysis of the main judgement criterion

The success rate of pre-hospital ECMO will be compared with the percentage of success of in-hospital ECMO by a Chi-squared test. An intermediary analysis will be done every 20 patients.

8.1.2 Analysis of the secondary judgement criteria

The identification of predictive factors of pre-hospital ECMO success will be done first by a univariate analysis using a chi-squared test (or a Fisher's exact test if the test application conditions are not verified) for the qualitative variables, and with a Student's test (or Wilcoxon if the test application conditions are not verified) for the quantitative variables.

Next, a multivariate analysis by logistic regression will enable the simultaneous study of factors associated with the pre-hospital success of ECPR by adjustment to the different potentially confounding variables. In the multivariate model only variables that are significant in univariate at the threshold p=0.20 will be used. The model variables will be selected by a backward stepwise method and tested by the likelihood ratio test. The association between the success of pre-hospital ECPR and the associated factors will be expressed in odds ratio (OR) and estimated with its confidence interval at 95%.

The tests will be bilateral and a level of significance $p<0.05$ will be considered as significant.

9 RESEARCH OUTLINE AND PROCEDURE

9.1 Recruitment method

This is a pragmatic study aimed at including all consecutive eligible patients. The investigators will seek the participation of all the victims of out-of-hospital cardiac arrest who are cared for and who present the required criteria (eligibility and non-eligibility). A record of potentially eligible patients will be kept updated in each participating site.

In practice, patients are included and randomised on the spot where the cardiac arrest occurs. The inclusion criteria are verified by the physician responsible for implementing ECPR on the spot.

9.2 Feasibility

At Necker, 40 patients per year benefit from ECPR for refractory cardiac arrest. The other investigator sites should quickly reach this rate of inclusion. It is reasonable to estimate a research period of 4 years.

9.3 Research procedure for each patient

Baseline visit: Patient recruitment and inclusion phase

When a victim of cardiac arrest with "no flow" for less than 5 minutes is taken under care in an out-of hospital setting, a mobile ECMO team is rushed to the spot at the 10^{th} minute. This team verifies the inclusion criteria. The patient is included and randomised when all the eligibility criteria are met as of the 20^{th} minute of cardiac arrest. Randomisation is done by drawing of lots from an envelope. In the pre-hospital ECMO group, treatment starts immediately. In the in-hospital ECMO group, medicalised resuscitation is continued and the patient is transferred to the hospital for the implementation of circulatory support. The ECPR success rate and implementation time are noted and compared. The family is informed at inclusion or at intensive care arrival. The patient is informed as soon as possible, if he/she is alive.

Follow-up visit on discharge from intensive care , at day 28, at 2, 6 and 12 months*:*

These visits should enable the evaluation of the patient outcome: survival, brain death or demise. A neurological exam evaluates the CPC score. The numbers of packed red blood cell transfusions in the first 24 hours and cases of sepsis over the course of hospitalisation are noted.

At 12 months, the physician will contact the patient to evaluate the patient outcome.

9.4 Scheduled participation period for each patient

The participation period is a maximum of 1 year.

9.5 Scheduled duration of the research

The recruitment period will last 36 months. The monitoring period up to the end of the study will last for 1 year for each patient included in the study. The total duration of the study will therefore be 4 years.

9.6 Methods for monitoring excluded patients

All withdrawals from the study should be documented and the investigator should specify the reason.

For patients considered to be lost to follow-up, the case report form should be filled out up to the last visit. The investigator will try his/her utmost to contact the patient, find out the reason for withdrawal from the trial and his/her health status. Patients who withdraw will not be re-included in the study. Their treatment number will not be reused. These patients will nevertheless, be monitored in a service not included in the protocol.

Lost to follow-up: we will consider a maximum of 5% of the patients in the entire cohort to be lost to follow-up.

10 DATA MANAGEMENT

10.1 Right to access source data and documents

10.1.1 Access to data

In accordance with GCPs:

- the sponsor is responsible for obtaining the permission of all parties involved in the research to guarantee direct access to all locations where the research will be carried out, to the source data, to the source documents and the reports, with the goal of quality control and audit by the sponsor
- the investigators will make available to those in charge of monitoring, quality control and audit relating to the research the documents and personal data strictly necessary for these controls, in accordance with the legislative and regulatory provisions in force.

10.1.2 Source documents

Source documents are defined as any original document or object that can prove the existence or accuracy of a piece of information or a fact recorded during the research. These documents will be kept for 15 years by the investigator or by the hospital in the case of a hospital medical file.

10.1.3 Data confidentiality

Those responsible for research quality control will take all necessary precautions to ensure the confidentiality of information about the research, the research subjects and in particular the identity of the subjects and the results obtained.

These individuals, as well as the investigators themselves, are subject to professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Penal Code).

During or after the research, the data collected about the research subjects and sent to the sponsor by the investigators (or any other specialised parties) will be made non-identifying.

Under no circumstances should the names and addresses of the subjects involved be shown.

The sponsor will ensure that each research subject has given permission in writing for access to personal information about him or her which is strictly necessary for the quality control of the research.

10.2 Data processing and storage of documents and data

10.2.1 Identification of the manager and the location(s) for data processing

The data management and the statistical analysis will be done by INSERM U970.

10.2.2 Data entry

Data entry will be carried out on electronic media via a web browser.

10.2.3 Data processing (CNIL, the French Data Protection Authority) in France

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

The processing of personal data for this research falls under the scope of the provisions of Articles 53 to 61 of the Law of 6 January 1978 relating to information technology, data files and privacy, modified by Law No. 0204-801 of 6 August 2004.

10.2.4 Archival

Specific documents for research relating to a medication for human use will be archived by the investigator and the sponsor for a period of 15 years after the end of the research.

10.3 Ownership of the data

AP-HP is the owner of the data, which cannot be used or disclosed to a third party without its prior approval.

11 ETHICAL AND LEGAL CONSIDERATIONS

The research will be supervised in line with the sponsor's standard operating procedures. The progress of research in investigational centres and the treatment of subjects will be conducted in line with the Declaration of Helsinki and current Good Clinical Practice.

11.1 Conditions for information of subjects

The ECPR Team will inform the family's subject in emergency at inclusion or at intensive care admission. If the patient is conscious at any time, he/she will be informed by the doctor in charge.

The information given by the subject will be noted in their medical records. The absence of opposition to the participation of the subject will be notified in his medical records by the investigator who collects it.

11.2 Request for an opinion from the Comité de Protection des Personnes (CPP, ethical review board)

The principal investigator obtains for this research prior to starting the research, the favourable opinion of the appropriate CPP (Ile de France II), within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

11.3 Request for the opinion of the CCTIRS (advisory committee on the processing of research information in the area of health) and request for authorisation from CNIL (French data protection authorities)

As the processing of personal data for this research does not fall under the scope of the MR 001 méthodologie de reference, the sponsor must obtain the opinion of the CCTIRS and the authorisation of the CNIL.

11.4 Modifications to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, prior to starting the research, a favourable opinion from the CPP within the scope of their respective authorities.

The information sheet can be revised if necessary, in particular if there is a substantial modification to the research.

Annexe 1

STUDY OUTLINE FOR EACH PATIENT SELECTED

Period	**Selection**		
Visit	**Out-of-hospital**	**Admission to the ICU**	**Discharge from the ICU**
Month	**D0**	**D0**	**Dn**
Inclusion - non-inclusion criteria, Information	**X**	**X**	
Information	**X**	**X**	
Inclusion	**X**		
Treatment: ECPR implementation	**X**		
Clinical exam	**X**		**X**
Neurological exam	**X**		**X**