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# BMJ Open

## The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery : a randomized, multicentre, double blind, study

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**The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery : a randomized, multicentre, double blind, study**

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**Key words:** surgery; glucocorticoid; dexamethasone; post-operative complications; pneumonia

## ABSTRACT

**Introduction** Postoperative complications are major healthcare problems and are associated with a reduced short-term and long-term survival after surgery. An excessive postoperative inflammatory response participates to the development of postoperative infection and mortality. The aim of the PACMAN study is to assess the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

**Methods and analysis:** The PACMAN is a multicentre, randomized, controlled, double blind, two-arms trial of 1222 high-risk patients aged 50 years of older undergoing major non-cardiac surgery at 32 acute care hospital in France. Patients are randomly assigned to dexamethasone (0,2mg.kg<sup>-1</sup> at the end of the surgical procedure, and at day+1, n=611) or to placebo (n=611). The primary outcome is a composite of predefined 14-day moderate or major pulmonary complications and mortality. Secondary outcomes are surgical complications, infections, organ failures, critical care-free days, length of hospital stay and all-cause mortality at 28 days.

**Ethics and dissemination:** The PACMAN trial protocol has been approved by the ethics committee of Sud Méditerranée V, and will be carried out according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The PACMAN trial is the first randomized controlled trial powered to investigate whether perioperative administration of corticosteroids in patients undergoing non-cardiac major surgery reduce postoperative complications. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

*Trial registration* number [clinicaltrials.gov](https://clinicaltrials.gov) NCT03218553

*Funding* This work is supported by a grant from the French Ministry of Health (PHRCN 2016, RC16\_0442)

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is a multicenter, randomized, controlled and double blind trial adequately powered to determine whether corticosteroid reduces postoperative complications in high risk patients undergoing major non-cardiac surgery.
- Treatment's benefits include reduced risk of postoperative infection, development of organ failure and reduced risk of mortality.
- Limitations due to the difficulty of sepsis diagnosis after major surgery are limited by the use of a placebo ensuring a double-blind evaluation of the primary outcome.
- This large study has the potential of changing international recommendations on the management of high risk patients undergoing major non-cardiac surgery.

## INTRODUCTION

More than 300 million major surgical procedures are undertaken worldwide each year [1]. For most patients, risks of surgery are low. However in an European international cohort, the mortality rate for patients undergoing non-cardiac surgery was higher than expected (4% of patients died before hospital discharge) [2]. It is interesting to consider that 10% of patients at risk of postoperative complications represent 80% of postoperative deaths [3]. It is also important to consider that patients who develop complications but survive until hospital discharge have usually reduced functional independence and long-term survival [4]. These data suggest that interventions to prevent complications and mortality should probably be undertaken early. One of the main targets to focus on is probably lung. Indeed, postoperative respiratory complications represent the most common perioperative complication after wound infections with an estimated incidence ranging from 2.0% to 5.6% for surgical procedures [4]. Respiratory failure after general anaesthesia and tracheal extubation has been shown to be one of the most meaningful factors associated with poor patient outcomes, leading to longer hospital stay [4]. Considering, the high volume of surgical procedures undertaken each year, the key message is that decreasing even a low rate of avoidable harm will be associated with a high cost saving for the society and many preventable deaths and complications for the patients.

Major surgery induces an inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein). The consequences of tissue surgical injuries are a release of danger-associated molecular patterns which initiate the production of pro-inflammatory mediators (cytokines, radical oxygen species) [5]. This inflammatory response is useful for tissue healing, but it is thought that an excessive response contributes to post-operative morbidity (such as infections and organ failures) and mortality. Glucocorticoids have thus been proposed to reduce the risk of complications in several medical conditions characterized by systemic inflammatory response.

In patients undergoing major cardiac surgery, corticosteroids reduce the risk of atrial fibrillation and the duration of mechanical ventilation<sup>17</sup>. In severe trauma patients, considering the potential immunostimulating effects of “low doses” corticosteroids [6], we have shown, in two multicentre, randomized, double blind placebo-controlled study on intubated trauma patients, that the use of an intravenous low-dose corticosteroids, compared with placebo, resulted in a decreased risk of hospital-acquired pneumonia [7,8]. Interestingly, apart from higher insulin consumption in patients receiving corticosteroids, no significant harm related to treatment was recorded in both studies.

Finally, the use of corticotherapy to enhance recovery after major non cardiac surgery is not recommended. The objective of the PACMAN study is to ascertain whether or not the administration of early corticosteroid with standard care compared with standard care alone

1 prevents respiratory complications and reduces mortality in high-risk patients undergoing major  
2 surgery. We are reporting the version 4 of the protocol (2<sup>nd</sup> September 2017). This manuscript has  
3 been submitted for publication on the 30<sup>th</sup> of November 2017, before the inclusion of the first  
4 patient in the study.  
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## Methods and Design

### *Hypothesis*

High-risk patients treated with short course of corticosteroid have reduced morbidity and mortality rates compared to those receiving standard care alone after major non-cardiac surgery.

### *Research Questions*

1. Does short-course of moderate doses of dexamethasone prevent death and/or post-operative respiratory complications after major non-cardiac surgery in high-risk patients ?
2. Does short-course of moderate doses of dexamethasone reduce the duration of hospitalization after major non-cardiac surgery in high-risk patients ?
3. Does short-course of moderate doses of dexamethasone prevent delayed skin healing ?

### *Design*

The Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) study is a multicenter, randomized, double blind, parallel-group, controlled trial (Figure 1).

### *Ethic*

The Institutional Review Board of Sud Méditerranée V (France) approved the study protocol (June 2017). Patients provide written consent for participation. The PACMAN trial is conducted in accordance with the declaration of Helsinki and is registered on June 2017 at <http://clinicaltrials.gov/> with trial registration NCT03218553.

### *Setting*

The study involved 33 French hospitals, each centre caring for more than 200 patients undergoing major surgery each year.

### *Study population*

Investigators screen consecutive high-risk patients undergoing major non-cardiac surgery. Patients older than 50 years and scheduled for a major surgery (> 90 minutes and performed under general anesthesia) of the abdomen, pelvis, thorax, face/neck, vascular surgery are eligible provided that they have one or more of the following risk factors : age > 65 years, presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less), medical history of stroke, moderate to severe renal impairment (clearance of creatinine  $\leq$  30 ml/L), active smoking, averaged observed blood losses over 500 ml or emergency surgery. These risk factors have been adapted from the systematic review for the preoperative pulmonary risk

1 stratification for non-cardiothoracic surgery published by the American College of Physicians [9]  
2 and from the guidelines for the management of severe perioperative bleeding of the European  
3 Society of Anesthesiology [10]. Exclusions criteria are: allergy to the intravenous formulation of  
4 dexamethasone, treatment with systemic corticosteroids at a dose > 5 mg.day<sup>-1</sup> of equivalent  
5 prednisolone in the previous 3 months, uncontrolled psychotic disorder (acute or chronic)  
6 chronic renal failure (clearance of creatinine < 10 ml/min), life expectancy of less than 1 month,  
7 preoperative shock (defined by the need for continuous infusion of vasoactive drugs  
8 (norepinephrine, epinephrine or dobutamine), acute pulmonary edema in the last 7 days, active  
9 bacterial or viral infection, pregnant women, breastfeeding women, minors, Adults under  
10 guardianship or trusteeship.

### 11 ***Treatment Allocation***

12 Patients are randomized in a 1:1 ratio and stratified according to cancer (yes/no) and according to  
13 the type of surgical procedure (thoracic surgery or not). Randomisation is made by a computerized  
14 number generator list provided by a statistician not involved in the determination of eligibility or in  
15 the assessment of outcomes. All assignments are made through a dedicated, pass-word protected,  
16 SSL-encrypted website. Patients are randomized in the first 24 prior to surgery to dexamethasone  
17 (intervention group) or to placebo (control group).

### 18 ***Masking protocol***

19 Randomized patients are given a number corresponding to a «PACMAN treatment pack» that  
20 contains: 4 x 10 mg vial of dexamethasone or placebo, and a sheet for schedule administration.

### 21 ***Procedures***

22 At the end of the surgery (< 2 hours after skin closure), and before study drug administration, the  
23 blood level of c-reactive protein (CRP) is measured (Figure 1). Then, patients randomized to either  
24 intravenous infusion of dexamethasone (0.2 mg.kg<sup>-1</sup> of real body-weight immediately within the 2  
25 hours after the end of the surgery, and at day+1) or injection of placebo receive treatment (Figure  
26 1). The blood level of CRP is measured at day+1 and day+2 after surgery. The treatment is  
27 administrated independently of the CRP levels.

### 28 ***Standard of care***

29 According to recent recommendations and publications, clinicians are prompted to realise adequate  
30 timing of antimicrobial prophylaxis [11], to apply a protective ventilation strategy (low tidal  
31 volume and Positive End Expiratory Pressure) during surgery [12], to closely monitor and treat  
32 peroperative hypovolemia and hypotension [13,14] and to early stop sedation at the end of the  
33

1 surgery [15]. Decisions of post-operative admission to intensive care unit and of prophylactic  
2 application of non-invasive ventilation will follow local standard of cares.  
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#### 4 ***Protocol drop-out***

5 For patients developing an allergic reaction to the study treatment, the second injection will  
6 not be performed and the appropriate treatment of the allergic reaction will be provided. Patients  
7 with allergic reaction to dexamethasone will be kept in analysis and remain analysis with the  
8 intervention group. Clinicians can use glucocorticoid during the first 7 days of the study only in  
9 case of formal indication of steroid (rescue treatment). Patients treated with out-of-protocol  
10 glucocorticoid will be kept in analysis and remain analysis with their attributed group.  
11

#### 12 ***Study end points***

13 The primary outcome is a composite outcome (all-cause mortality and major postoperative  
14 complications) within 14 days after surgery, at least one item among the following: postoperative  
15 sepsis, Postoperative pulmonary complication (postoperative pneumonia, need for invasive  
16 ventilation and/or noninvasive ventilation for respiratory failure) and all-cause mortality.  
17

18 Secondary outcomes are all-cause mortality at 28 days, duration of invasive mechanical  
19 ventilation, duration of non-invasive mechanical ventilation, hospital free-days at 28 days, surgical  
20 complications according to the Clavien-Dindo classification within 28 days, unplanned admission  
21 or readmission to intensive care units (within 28 days following randomization), organ failures  
22 within 14 days after surgery, Sequential Organ Failure Assessment (SOFA) at day+1 and day+3,  
23 proportion of patients who experienced adverse events, especially hyperglycaemia, healing  
24 impairment at day +14 after surgery.  
25

#### 26 ***Follow-up Data***

27 The following variables are collected: demographics, American Society of Anesthesiology (ASA)  
28 score, pre-operative medical optimization, per-surgery management (drugs, mechanical ventilation,  
29 durations of procedure, fluid infusion, bleeding, post-operative analgesia), infections, organ  
30 failures, blood levels of CRP, healing, post-operative complications, length of ventilator support,  
31 and ICU hospitalisation and death at day 28 are recorded.  
32

#### 33 ***Data Collection and Checking***

34 Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or  
35 clinical personnel under the supervision of the study site investigators. From the eCRFs the trial  
36 database will be established.  
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#### 38 ***Study Monitoring***

39 The study will be monitored on behalf of the promotor (Nantes University Hospital). Site staff will  
40 be available to facilitate the monitoring visits and ensure that all required documentation is  
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available for review. Study initiation visits are carried out at all sites before recruitment starts at that site. During regular monitoring visits realized throughout the duration of the trial, an independent research assistant will carry out Source Data Verification of trial data, verify informed consent forms and ensure the completeness of the Investigator Site Files.

### ***Study Oversight***

Study sponsor is the Nantes University Hospital (5 allée de l'île Gloriette, 44000 Nantes, drcnantes@chu-nantes.fr). Experienced research staff will monitor the study for quality, the integrity of data in all the participating centers. Serious adverse events and unexpected related or possibly related serious events are reported blinded to the promotor within respectively 24 hours or 7 days. An independent data and safety monitoring board (DSMB) is appointed by the sponsor. The DSMB is made up of 4 individuals with no connection to the research, including three clinician specializing in the management of ICU patients and corticotherapy in ICU, and a methodologist/biostatistician. Before the first inclusion, and every 300 inclusions, the DSMB looks over the ethics in accordance with the Declaration of Helsinki, monitors patient safety and reviews safety issues as the study progresses. The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of serious adverse reactions.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research. Trial recruitment can be stopped by the promotor on the advice of the DSMB in case of safety concern.

### ***Roles of the sponsor and of the funder***

The sponsor and the funder have no role in the design or conduct of the study, the data analysis, the writing of the manuscript or in the decision to submit the manuscript.

### ***Statistical consideration***

All analyses will be performed with the use of SAS software (version 9.4, NC, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines. Analyzes will be conducted, first, on data from the modified intention-to-treat (modified-ITT) population, second, in the intention-to-treat (ITT) population as well as in the per-protocol population. The criteria for including patients in the modified-ITT and in the per-protocol populations, respectively, are provided below.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired *t* test or the Mann-Whitney *U* test when appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Categorical data will be presented as exact numbers and percentages.

### ***Number of patients***

The rate of the primary endpoint in the control group is expected to reach 20% [12,16]. Assuming a 20% rate in the control group and 14% in the dexamethasone group, A total of 1222 patients are needed to detect this difference between the two groups with a 5% type I error and a power of 80% in a two-sided test.

### ***Pre-Planned primary analysis***

For the primary analysis, data will be analysed with the use of logistic regression adjusted for stratification factors (cancer and thoracic procedure).

The effects of the treatment will be investigated in ITT, in modified-ITT and in per-protocol populations. **In the ITT analyse**, all randomized patients will be kept in analysis. In the **modified-ITT analyse**, all randomized patients will be kept in analysis except those who would not have been eligible for randomization according to the inclusion/non-inclusion criteria or those who have not received any injection of the experimental treatment (dexamethasone or placebo). In the **per-protocol analyse**, all randomized patients will be kept in analysis except patients having one or more major protocol violations defined as those who would not be eligible for randomization according to inclusion/non-inclusion criteria; or those who accidentally would have received the wrong intervention (Dexamethasone or placebo); or those in whom surgical intervention could not have been done (for example, intra-abdominal extensive cancer); or those who have withdrawn consent; those who would have received out-of-protocol glucocorticoids.

### ***Planned sub-group analyses:***

- Strates of randomization (cancer yes/no, thoracic procedure yes/no)
- According to the level of CRP measured at the end of the surgical procedure immediately before the first injection of the studied treatment (< 50, 50-150 or > 150 mg/mL).
- In diabetic and non-diabetic patients.

No interim efficacy analyze will be performed so that no adjustment is required to the final p-value to allow for the multiple testing. The DSMB will only analyse safety data and can make recommendation for adjustment of the number of patients to be included to ensure the statistical power of the mITT analysis.

### ***Method for missing data***

There should not be missing data for the primary outcome measure and the missing data rate

1 should be low for the other outcomes as well. Missing data will be described by treatment arm.  
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3 According to the rate of missing data (over 5%) sensitivity analyses will be performed using  
4 multiple imputation methods as well as worst case scenario (missing data considered as the most  
5 unfavourable case) and maximum bias scenario (missing data considered as the most favourable or  
6 unfavourable case in the placebo and experimental arms respectively).  
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### 9 ***Data Sharing statement***

10 The principle investigator will have access to the final trial data set. Data sharing: patient level data  
11 and/or full dataset and/or statistical code will be available upon request to the corresponding author.  
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13 Consent for the data sharing was not obtained but the presented data are anonymised and risk of  
14 identification is low and the potential benefits of sharing these data outweigh the potential harms.  
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## 21 **DISCUSSION**

22  
23 The PACMAN trial is the first randomized controlled study powered to investigate short-  
24 course of moderate dose of dexamethasone in patients undergoing major non-cardiac surgery.  
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27 Several trials have investigated the benefits of administering corticosteroids in patients  
28 undergoing major surgery. However, there is yet no agreement on the beneficial effects of  
29 corticosteroids in alleviating surgical stress. This disagreement probably stems from the variability  
30 in the drugs used, their dosage and administration schedule, and the surgical procedures in different  
31 studies. Also the fear of side effects induced by a possible immunosuppression (infections,  
32 postoperative wound complications, anastomotic leakage) explains the extreme variability of  
33 behaviour from one centre to another and among patients and physicians. These considerations  
34 prevented the performance of a large scale randomized study despite evidences that corticosteroids  
35 could enhance outcome and even decrease the rate of infections after non-cardiac major surgery  
36 (see above). Before general recommendations for perioperative corticosteroids administration can  
37 be made, obviously conclusive safety studies must be available. So far, there seem to be no safety  
38 issues [17-19] related to a single preoperative dose of corticosteroids including specific studies on  
39 wound healing [20,21]. The consequences of perioperative use of corticosteroids for glucose  
40 homeostasis need further evaluation, but so far the transitory increased hyperglycemic response has  
41 not been related to increased postoperative complications [22].  
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51 We will include patients considered as high risk of post-operative respiratory complications  
52 according to American and European recommendations [9] [10]. Risk factors of pulmonary  
53 complications are either related to the surgery, or to the medical history of the patients. We decided  
54 to not limit the PACMAN study to a specific type of surgery but to include all sort of surgery  
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1 provided that the expected duration of the procedure exceeds 90 minutes. This strategy maximises  
2 recruitment rates and improves the generalisation of results. We acknowledge that the clinical risk  
3 factors of postoperative respiratory complications are inconstantly used in clinical practice, which  
4 can limit the applicability to the study results. However, preoperative optimization by nutritional  
5 support, respiratory physiotherapy or smoking cessation are recommended in patients presenting  
6 such risk factors [9]. The selection of high risk patients will result in a high incidence rate of the  
7 primary endpoint, which will result in a study of high clinical relevance and statistical power.  
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10 We selected a composite outcome as the primary criteria. The use of mortality as a primary  
11 endpoint is never used in perioperative studies because the risk of death is low and the statistical  
12 power would be low. Respiratory complications are particularly frequent and serious after major  
13 surgery and we have recently proposed that glucocorticoid prevent the development of  
14 inflammation-related immunosuppression [6], and decrease the risk of pneumonia after severe  
15 trauma [7,8]. Finally, mortality is not competitive with the primary criteria since the outcome all  
16 cause of death is included in the composite primary outcome.  
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19 For the primary statistical analysis of the primary outcome, we will use a modified intention  
20 to treat analysis including patients fulfilling all the inclusion criteria and who have received at least  
21 one injection of the experimental treatment. This strategy has recently been used in randomized  
22 clinical trials evaluating peri-procedure treatments [14,23], because the time between the  
23 randomization, which is realized before the procedure, and the administration of the study  
24 treatment, which is realized during or after the procedure, expose the study to a high risk of  
25 included patients not receiving the allocated treatment (e.g. cancelled or delayed surgery or  
26 perioperative complications). In this setting, we strongly believe that the mITT is more accurate to  
27 the medical field than the ITT. However, the exclusion of patients in the mITT analysis can  
28 theoretically decrease the statistical power of the study. Thus, the DSMB will have access to the  
29 number of patients excluded from the mITT analysis, and if necessary the DMSB will have the  
30 responsibility to propose an increase of the number of patients to be included to guarantee the study  
31 power. Finally, the intention-to-treat analysis will be reported in the final version of the manuscript.  
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### 34 ***Trial status***

35 The trial has already achieved many milestones. The trial is sponsored by the French ministry  
36 of health (PHRCN 2016\_0442). Insurance for non-negligent harm has been provided by University  
37 Hospital of Nantes (France). Research ethics committee approval was obtained in September 2019  
38 (Comité de Protection des Personnes Sud Méditerranée V). The French Agency for the safety of  
39 medicines and medical devices authorized the study in September 2017 (#170245RS-21). The study  
40 is registered with the American registry of trials (<https://clinicaltrials.gov/> NCT03218553). The  
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1 current emphasis is on opening the recruitment infra-structures, which is ongoing, and in  
2 developing the monitoring infrastructure. No patient has yet been included, and expected starting  
3 point of the study is December 2017.  
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6  
7 The principle investigator (KA), the scientific expert (EF), the statistician (FF) and the study  
8 coordinator (AR) will write the first draft of the manuscript. All the co-authors (investigators who  
9 had realized not less than 30 inclusions) will append and approve the final manuscript before the  
10 submission. No professional writer will be used.  
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13  
14 In conclusion, the PACMAN trial is an investigator-initiated randomized controlled trial  
15 powered to test the hypothesis that the short-course of moderate doses of dexamethasone in patients  
16 undergoing major non-cardiac surgery decreases the risk of post-operative complications. The  
17 results of the PACMAN Trial will be relevant to the wide number of clinicians interested in  
18 perioperative medicine.  
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#### 24 **ACKNOWLEDGMENT**

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26 participating centres for their involvement in this important study.  
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#### 29 **AUTHORS' CONTRIBUTIONS**

30 KA, EF, FF and AR conceived the study, coordinated its design and drafted the manuscript. AR and  
31 KA wrote the manuscript. EF and FF read and were involved in critical appraisal and revision of the  
32 manuscript. FF provided statistical expertise. All authors approved the final manuscript prior to  
33 submission.  
34  
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#### 36 **COMPETING INTERESTS**

37 No competing interests  
38  
39

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41 This study is an investigator-initiated trial, funded by a grant from the French Ministry of Health.  
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43  
44

#### 45 **DATA SHARING STATEMENT**

46 The principal investigator will have access to the trial data set. Patient level data and/or full dataset  
47 and/or statistical code will be available on request to the corresponding author. Consent was not  
48 obtained, but the presented data are anonymised and risk of identification is low and the potential  
49 benefits of sharing these data outweigh the potential harms.  
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### List of abbreviations

DSMB: Data and Safety Monitoring Board, ICU: Intensive Care Unit, ITT: Intention-to-treat.

### Competing interests

The authors declare that they have no competing interests.

### Figure 1: Flow chart.

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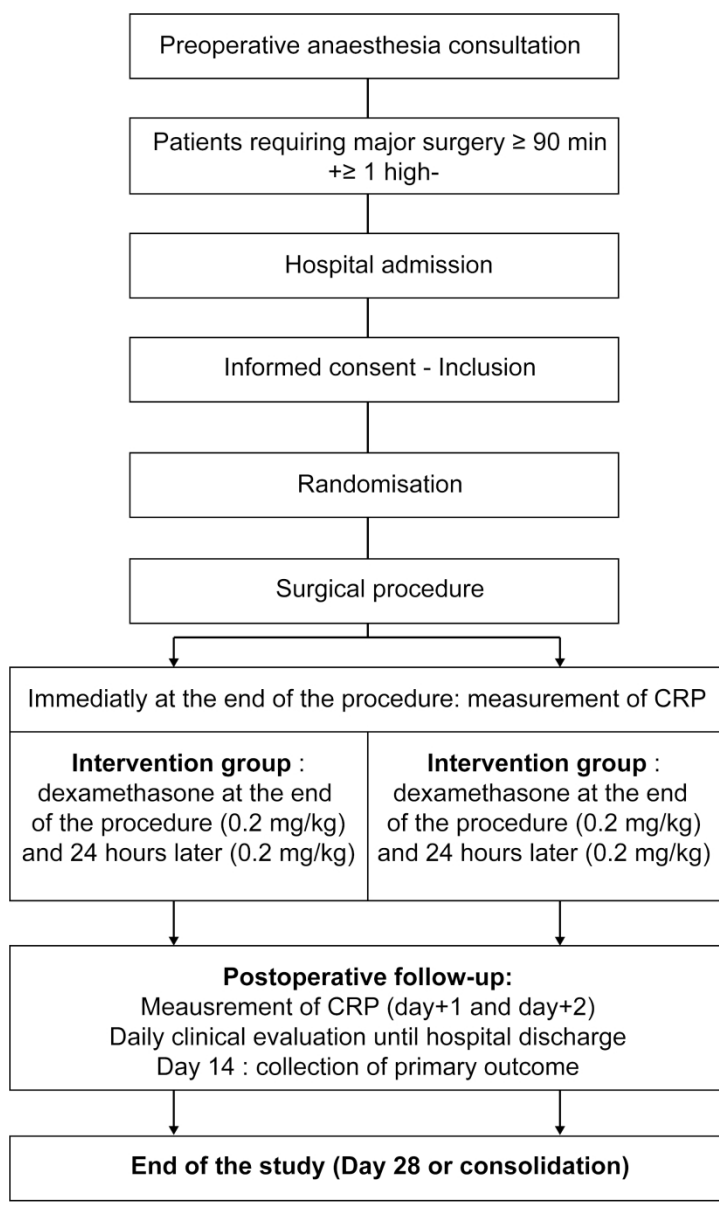


Figure 1

173x289mm (300 x 300 DPI)

# BMJ Open

## The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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<b>Primary Subject Heading</b>:	Anaesthesia
Secondary Subject Heading:	Infectious diseases
Keywords:	SURGERY, glucocorticoid, dexamethasone, post-operative complications, pneumonia

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Manuscripts

**The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study**

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**Key words:** surgery; glucocorticoid; dexamethasone; post-operative complications; pneumonia

## ABSTRACT

**Introduction** Postoperative complications are major healthcare problems and are associated with a reduced short-term and long-term survival after surgery. An excessive postoperative inflammatory response participates to the development of postoperative infection and mortality. The aim of the PACMAN study is to assess the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

**Methods and analysis:** The PACMAN is a multicentre, randomized, controlled, double blind, superiority, two-arms trial of 1222 high-risk patients aged 50 years of older undergoing major non-cardiac surgery at 32 acute care hospital in France. Patients are randomly assigned to dexamethasone (0,2mg.kg<sup>-1</sup> at the end of the surgical procedure, and at day+1, n=611) or to placebo (n=611). The primary outcome is a composite of predefined 14-day major pulmonary complications and mortality. Secondary outcomes are surgical complications, infections, organ failures, critical care-free days, length of hospital stay and all-cause mortality at 28 days.

**Ethics and dissemination:** The PACMAN trial protocol has been approved by the ethics committee of Sud Méditerranée V, and will be carried out according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The PACMAN trial is the first randomized controlled trial powered to investigate whether perioperative administration of corticosteroids in patients undergoing non-cardiac major surgery reduce postoperative complications. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

*Trial registration* number [clinicaltrials.gov](https://clinicaltrials.gov) NCT03218553

*Funding* This work is supported by a grant from the French Ministry of Health (PHRCN 2016, RC16\_0442)

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is a multicenter, randomized, controlled and double blind trial adequately powered to determine whether corticosteroid reduces postoperative complications in high risk patients undergoing major non-cardiac surgery.
- Treatment's benefits include reduced risk of postoperative infection, development of organ failure and reduced risk of mortality.
- Limitations due to the difficulty of sepsis diagnosis after major surgery are limited by the use of a placebo ensuring a double-blind evaluation of the primary outcome.
- This large study has the potential of changing international recommendations on the management of high risk patients undergoing major non-cardiac surgery.



## INTRODUCTION

More than 300 million major surgical procedures are undertaken worldwide each year [1]. For most patients, risks of surgery are low. However in an European international cohort, the mortality rate for patients undergoing non-cardiac surgery was higher than expected (4% of patients died before hospital discharge) [2]. It is interesting to consider that 10% of patients at risk of postoperative complications represent 80% of postoperative deaths [3]. It is also important to consider that patients who develop complications but survive until hospital discharge have usually reduced functional independence and long-term survival [4]. These data suggest that interventions to prevent complications and mortality should probably be undertaken early. One of the main targets to focus on is probably lung. Indeed, postoperative respiratory complications represent the most common perioperative complication after wound infections with an estimated incidence ranging from 2.0% to 5.6% for surgical procedures [4]. Respiratory failure after general anaesthesia and tracheal extubation has been shown to be one of the most meaningful factors associated with poor patient outcomes, leading to longer hospital stay [4]. Considering, the high volume of surgical procedures undertaken each year, the key message is that decreasing even a low rate of avoidable harm will be associated with a high cost saving for the society and many preventable deaths and complications for the patients.

Major surgery induces an inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein). The consequences of tissue surgical injuries are a release of danger-associated molecular patterns which initiate the production of pro-inflammatory mediators (cytokines, radical oxygen species) [5]. This inflammatory response is useful for tissue healing, but it is thought that an excessive response contributes to post-operative morbidity (such as infections and organ failures) and mortality. Glucocorticoids have thus been proposed to reduce the risk of complications in several medical conditions characterized by systemic inflammatory response.

In patients undergoing major cardiac surgery, corticosteroids were associated with reduction in length of intensive care unit stay [6], but a beneficial effect on the risk of mortality is uncertain [7]. In severe trauma patients, considering the potential immunostimulating effects of “low doses” corticosteroids [8], we have shown, in two multicentre, randomized, double blind placebo-controlled study on intubated trauma patients, that the use of an intravenous low-dose corticosteroids, compared with placebo, resulted in a decreased risk of hospital-acquired pneumonia [9,10]. Interestingly, apart from higher insulin consumption in patients receiving corticosteroids, no significant harm related to treatment was recorded in both studies. In major non-cardiac surgery, a recent meta-analysis concluded that perioperative administration of glucocorticoids is safe, but proofs are lacking to demonstrate clinically important benefits [11]. The

1 objective of the PACMAN study is to ascertain whether or not the administration of early  
2 corticosteroid with standard care compared with standard care alone prevents respiratory  
3 complications and reduces mortality in high-risk patients undergoing major surgery. We are  
4 reporting the version 4 of the protocol (2<sup>nd</sup> September 2017). This manuscript has been submitted  
5 for publication on the 30<sup>th</sup> of November 2017, before the inclusion of the first patient in the study.  
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For peer review only

## Methods and Design

### *Hypothesis*

High-risk patients treated with short course of corticosteroid have reduced morbidity and mortality rates compared to those receiving standard care alone after major non-cardiac surgery.

### *Research Questions*

1. Does short-course of moderate doses of dexamethasone prevent death and/or post-operative respiratory complications after major non-cardiac surgery in high-risk patients ?
2. Does short-course of moderate doses of dexamethasone reduce the duration of hospitalization after major non-cardiac surgery in high-risk patients ?
3. Does short-course of moderate doses of dexamethasone prevent delayed skin healing ?

### *Design*

The Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) study is a multicenter, randomized, double blind, parallel-group, superiority, controlled trial (Figure 1).

### *Ethic*

The Institutional Review Board of Sud Méditerranée V (France) approved the study protocol (June 2017). Patients provide written consent for participation. The PACMAN trial is conducted in accordance with the declaration of Helsinki and is registered on June 2017 at <http://clinicaltrials.gov/> with trial registration NCT03218553.

### *Setting*

The study involved 33 French hospitals, each centre caring for more than 200 patients undergoing major surgery each year.

### *Study population*

Investigators screen consecutive high-risk patients undergoing major non-cardiac surgery. Patients older than 50 years and scheduled for a major surgery (> 90 minutes and performed under general anesthesia) of the abdomen, pelvis, thorax, face/neck, vascular surgery are eligible provided that they have one or more of the following risk factors : age > 65 years, presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less), medical history of stroke, moderate to severe renal impairment (clearance of creatinine  $\leq$  30 ml/L), active smoking, averaged observed blood losses over 500 ml or emergency surgery. These risk factors have been adapted from the systematic review for the preoperative pulmonary risk

1 stratification for non-cardiothoracic surgery published by the American College of Physicians [12]  
2 and from the guidelines for the management of severe perioperative bleeding of the European  
3 Society of Anesthesiology [13]. Exclusions criteria are: allergy to the intravenous formulation of  
4 dexamethasone, treatment with systemic corticosteroids at a dose  $> 5 \text{ mg}\cdot\text{day}^{-1}$  of equivalent  
5 prednisolone in the previous 3 months, uncontrolled psychotic disorder (acute or chronic)  
6 chronic renal failure (clearance of creatinine  $< 10 \text{ ml/min}$ ), life expectancy of less than 1 month,  
7 preoperative shock (defined by the need for continuous infusion of vasoactive drugs  
8 (norepinephrine, epinephrine or dobutamine), acute pulmonary edema in the last 7 days, active  
9 bacterial or viral infection, pregnant women, breastfeeding women, minors, Adults under  
10 guardianship or trusteeship.

### 11 ***Identification and information of patients***

12 All consecutive adult patients requiring surgery with an expected duration  $\geq 90$  minutes will be  
13 assessed for eligibility. During the anesthesia consultation or in the operating room in case of  
14 emergency surgery, local investigators (anesthesiologists and/or surgeons) will verify inclusion and  
15 exclusion criteria. Investigators will invite the patients to participate to the study. Patients will be  
16 informed in complete and faithful terms and in understandable language of the objectives and  
17 constraints of the study, the potential risks, the required observation and safety measures, and their  
18 right to refuse to participate in the study or to revoke their consent at any time. All information  
19 appears in an information notice and consent form given to the patient. Written informed consent  
20 will be obtained by the investigator. All these documents are approved by the competent Ethics  
21 Committee. Two original copies will be co-signed by both the investigator and the patient and the  
22 parents. The second copy is to be kept in the patient's medical record.

### 23 ***Treatment Allocation***

24 Patients are randomized in a 1:1 ratio and stratified according to cancer (yes/no) and according to  
25 the type of surgical procedure (thoracic surgery or not). Randomisation is made by a computerized  
26 number generator list provided by a statistician not involved in the determination of eligibility or in  
27 the assessment of outcomes. All assignments are made through a dedicated, pass-word protected,  
28 SSL-encrypted website. Patients are randomized in the first 24 prior to surgery to dexamethasone  
29 (intervention group) or to placebo (control group).

### 30 ***Masking protocol***

31 Randomized patients are given a number corresponding to a «PACMAN treatment pack» that  
32 contains: 4 x 10 mg vial of dexamethasone or placebo, and a sheet for schedule administration.

### 33 ***Procedures***

1 At the end of the surgery (< 2 hours after skin closure), and before study drug administration, the  
2 blood level of c-reactive protein (CRP) is measured (Figure 1). Then, patients randomized to either  
3 slow intravenous infusion of dexamethasone (0.2 mg.kg<sup>-1</sup> of real body-weight within the 2 hours  
4 after the end of the surgery, and at day+1) or injection of placebo receive treatment (Figure 1). The  
5 blood level of CRP is measured at day+1 and day+2 after surgery. The treatment is administrated  
6 slowly (over 15 to 30 minutes) independently of the CRP levels.  
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### 11 ***Standard of care***

12 According to recent recommendations and publications, clinicians are prompted to realise adequate  
13 timing of antimicrobial prophylaxis [14], to apply a protective ventilation strategy (low tidal  
14 volume and Positive End Expiratory Pressure) during surgery [15], to closely monitor and treat  
15 perioperative hypovolemia and hypotension [16,17] and to early stop sedation at the end of the  
16 surgery [18]. Decisions of post-operative admission to intensive care unit and of prophylactic  
17 application of non-invasive ventilation will follow local standard of cares. Prophylactic  
18 administration of glucocorticoid for postoperative nausea and vomiting or postoperative oedema is  
19 not permitted. Clinicians can use glucocorticoid during the first 7 days of the study only in case of  
20 formal indication of steroid such as stridor (rescue therapy).  
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### 27 ***Protocol drop-out***

28 For patients developing an allergic reaction to the study treatment, the second injection will  
29 not be performed and the appropriate treatment of the allergic reaction will be provided. Patients  
30 with allergic reaction to dexamethasone will be kept in analysis and remain analysis with the  
31 intervention group. Patients treated with out-of-protocol glucocorticoid will be kept in analysis and  
32 remain analysis with their attributed group.  
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### 37 ***Study end points***

38 The primary outcome is a composite outcome (all-cause mortality and major postoperative  
39 complications) within 14 days after surgery, at least one item among the following: postoperative  
40 sepsis, Postoperative pulmonary complication (postoperative pneumonia, need for invasive  
41 ventilation and/or noninvasive ventilation for respiratory failure) and all-cause mortality. The rates  
42 of patients discharged before day 14, and evaluated between day 14 and day 28, will be reported.  
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47 Secondary outcomes are all-cause mortality at 28 days, duration of invasive mechanical  
48 ventilation, duration of non-invasive mechanical ventilation, hospital free-days at 28 days, surgical  
49 complications according to the Clavien-Dindo classification within 28 days, unplanned admission  
50 or readmission to intensive care units (within 28 days following randomization), organ failures  
51 within 14 days after surgery, Sequential Organ Failure Assessment (SOFA) at day+1 and day+3,  
52 proportion of patients who experienced adverse events, especially hyperglycaemia, healing  
53 impairment, anastomotic leakage at day +14 after surgery.  
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### ***Follow-up Data***

The following variables are collected: demographics, American Society of Anesthesiology (ASA) score, pre-operative medical optimization, per-surgery management (drugs, mechanical ventilation, durations of procedure, fluid infusion, bleeding, post-operative analgesia), infections, organ failures, blood levels of CRP, healing, post-operative complications (including anastomotic leakage), length of ventilator support, and ICU hospitalisation and death at day 28 are recorded.

### ***Data Collection and Checking***

Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or clinical personnel under the supervision of the study site investigators. From the eCRFs the trial database will be established.

### ***Study Monitoring***

The study will be monitored on behalf of the promotor (Nantes University Hospital). Site staff will be available to facilitate the monitoring visits and ensure that all required documentation is available for review. Study initiation visits are carried out at all sites before recruitment starts at that site. During regular monitoring visits realized throughout the duration of the trial, an independent research assistant will carry out Source Data Verification of trial data, verify informed consent forms and ensure the completeness of the Investigator Site Files.

### ***Study Oversight***

Study sponsor is the Nantes University Hospital (5 allée de l'île Gloriette, 44000 Nantes, drc-nantes@chu-nantes.fr). Experienced research staff will monitor the study for quality, the integrity of data in all the participating centers. Serious adverse events and unexpected related or possibly related serious events are reported blinded to the promotor within respectively 24 hours or 7 days. An independent data and safety monitoring board (DSMB) is appointed by the sponsor. The DSMB is made up of 4 individuals with no connection to the research, including three clinician specializing in the management of ICU patients and corticotherapy in ICU, and a methodologist/biostatistician. Before the first inclusion, and every 300 inclusions, the DSMB looks over the ethics in accordance with the Declaration of Helsinki, monitors patient safety and reviews safety issues as the study progresses. The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions

- to permanently terminate the research in light of serious adverse reactions.
- to recommend increasing the total number of patients to be included to ensure the study power in case of high number of exclusions in the per-protocol analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research. Trial recruitment can be stopped by the promotor on the advice of the DSMB in case of safety concern.

### ***Roles of the sponsor and of the funder***

The sponsor and the funder have no role in the design or conduct of the study, the data analysis, the writing of the manuscript or in the decision to submit the manuscript.

### ***Statistical consideration***

All analyses will be performed with the use of SAS software (version 9.4, NC, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines. Analyzes will be conducted, first, on data from the modified intention-to-treat (modified-ITT) population, second, in the intention-to-treat (ITT) population as well as in the per-protocol population. The criteria for including patients in the modified-ITT and in the per-protocol populations, respectively, are provided below.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired *t* test or the Mann-Whitney *U* test when appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Categorical data will be presented as exact numbers and percentages.

### ***Number of patients***

The rate of the primary endpoint in the control group is expected to reach 20% [15,19]. Assuming a 20% rate in the control group and 14% in the dexamethasone group, A total of 1222 patients are needed to detect this difference between the two groups with a 5% type I error and a power of 80% in a two-sided test.

### ***Pre-Planned primary analysis***

For the primary analysis, data will be analysed with the use of logistic regression adjusted for stratification factors (cancer and thoracic procedure).

The effects of the treatment will be investigated in ITT, in modified-ITT and in per-protocol populations. **In the ITT analyse**, all randomized patients will be kept in analysis. **In the modified-ITT analyse**, all randomized patients will be kept in analysis except those who would not have been eligible for randomization according to the inclusion/non-inclusion criteria or those who have not received any injection of the experimental treatment (dexamethasone or placebo). **In the per-protocol analyse**, all randomized patients will be kept in analysis except patients having one or

more major protocol violations defined as those who would not be eligible for randomization according to inclusion/non-inclusion criteria; or those who accidentally would have received the wrong intervention (Dexamethasone or placebo); or those in whom surgical intervention could not have been done (for example, intra-abdominal extensive cancer); or those who have withdrawn consent; those who would have received out-of-protocol glucocorticoids.

***Pre-specified sub-group analyses:***

- Strates of randomization (cancer yes/no, thoracic procedure yes/no)
- Medical history of corticosteroid in the preceding 3 months (yes/no)
- Emergency *vs* scheduled surgery
- According to the level of CRP measured at the end of the surgical procedure immediately before the first injection of the studied treatment (< 50, 50-150 or > 150 mg/mL).
- According to the surgery (abdomen, pelvis, thorax, face/neck or vascular surgery)
- In diabetic and non-diabetic patients.

No interim efficacy analyze will be performed so that no adjustment is required to the final p-value to allow for the multiple testing. The DSMB will only analyse safety data and can make recommendation for adjustment of the number of patients to be included to ensure the statistical power of the mITT analysis.

***Method for missing data***

There should not be missing data for the primary outcome measure and the missing data rate should be low for the other outcomes as well. Missing data will be described by treatment arm. According to the rate of missing data (over 5%) sensitivity analyses will be performed using multiple imputation methods as well as worst case scenario (missing data considered as the most unfavourable case) and maximum bias scenario (missing data considered as the most favourable or unfavourable case in the placebo and experimental arms respectively).

***Data Sharing statement***

The principle investigator will have access to the final trial data set. Data sharing: patient level data and/or full dataset and/or statistical code will be available upon request to the corresponding author. Consent for the data sharing was not obtained but the presented data are anonymised and risk of identification is low and the potential benefits of sharing these data outweigh the potential harms.

***Patient and Public Involvement statement***

The development of the research question and outcome measures was informed by patients' priorities, which is notably the prevention of post-operative complications. Patients were not involved neither in the design of the study. Patients were involved neither in the recruitment nor in the conduct of the study. Results of the study will be disseminated to study participants upon personal request to the study coordinator. For this randomised clinical trial, the burden of the



1 intervention was assessed by an institutional review board, notably composed of representative of  
2 patient associations.  
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## 8 **DISCUSSION**

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10 The PACMAN trial is a nationwide randomized controlled study powered to investigate  
11 short-course of moderate dose of dexamethasone in patients undergoing major non-cardiac surgery.  
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14 Several trials have investigated the benefits of administering corticosteroids in patients  
15 undergoing major surgery. However, there is yet no agreement on the beneficial effects of  
16 corticosteroids in alleviating surgical stress. This disagreement probably stems from the variability  
17 in the drugs used, their dosage and administration schedule, and the surgical procedures in different  
18 studies. Also the fear of side effects induced by a possible immunosuppression (infections,  
19 postoperative wound complications, anastomotic leakage) explains the extreme variability of  
20 behaviour from one centre to another and among patients and physicians. These considerations  
21 prevented the performance of a large scale randomized study despite evidences that corticosteroids  
22 could enhance outcome and even decrease the rate of infections after non-cardiac major surgery  
23 (see above). Before general recommendations for perioperative corticosteroids administration can  
24 be made, obviously conclusive safety studies must be available. So far, there seem to be no safety  
25 issues [20-22] related to a single preoperative dose of corticosteroids including specific studies on  
26 wound healing [23,24]. The consequences of perioperative use of corticosteroids for glucose  
27 homeostasis need further evaluation, but so far the transitory increased hyperglycemic response has  
28 not been related to increased postoperative complications [25]. To reach definitive conclusion on  
29 the effects of glucocorticoids on the risk of post-operative infections, we are eagerly awaiting the  
30 results from the PADDI randomized clinical trial which is investigating the effects of low dose of  
31 dexamethasone on surgical site infection, and from the PACMAN trial whose primary outcome is a  
32 composite outcome made of death and respiratory infections.  
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45 While perioperative glucocorticoids are widely administrated, the latest meta-analyses found  
46 that we are lacking power to detect differences in complications [11], and that no definitive  
47 conclusions can be made regarding clinically important benefice [7]. While the PADDI study is a  
48 non-inferiority trial designed to test the safety of dexamethasone in an unselected population, we  
49 have designed the PACMAN trial to investigate the potential benefits of the treatment in a surgical  
50 population with high risk of post-operative respiratory complications according to American and  
51 European recommendations [12,13]. Risk factors of pulmonary complications are either related to  
52 the surgery, or to the medical history of the patients. The external validity of the PACMAN results  
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1 to unselected patients should be cautious in case of increased risks of the side-effects recorded as  
2 secondary outcomes.  
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5 We decided to not limit the PACMAN study to a specific type of surgery but to include all  
6 sort of surgery provided that the expected duration of the procedure exceeds 90 minutes. This  
7 strategy maximises recruitment rates and improves the generalisation of results. We acknowledge  
8 that the clinical risk factors of postoperative respiratory complications are inconstantly used in  
9 clinical practice, which can limit the applicability to the study results. However, preoperative  
10 optimization by nutritional support, respiratory physiotherapy or smoking cessation are  
11 recommended in patients presenting such risk factors [12]. The selection of high risk patients will  
12 result in a high incidence rate of the primary endpoint, which will result in a study of high clinical  
13 relevance and statistical power.  
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19 A wide range of doses of dexamethasone has been tested in surgical or critically ill patients :  
20 from low (4-8 mg/day [11,26]), to high doses (1-2 mg/kg [6,27]). The PACMAN trial is designed to  
21 investigate the effects of dexamethasone on the risk of major respiratory complications, notably  
22 pneumonia, and we thus decided to evaluate the effects of moderate doses as proposed in the latest  
23 recommendations and meta-analysis for the treatment with steroids of in patients with pneumonia  
24 [28,29]. The timing of administration is also critical to consider. We decided to initiate the study  
25 treatment during the post-operative inflammatory response, rather than before the surgery, because  
26 glucocorticoids induce the apoptosis of immune cells in absence of inflammation but are stimulate  
27 immunity when administrated during an inflammatory response [30,31].  
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37 We selected a composite outcome as the primary criteria. The use of mortality as a primary  
38 endpoint is never used in perioperative studies because the risk of death is low and the statistical  
39 power would be low. Respiratory complications are particularly frequent and serious after major  
40 surgery and we have recently proposed that glucocorticoid prevent the development of  
41 inflammation-related immunosuppression [8], and decrease the risk of pneumonia after severe  
42 trauma [9,10]. Finally, mortality is not competitive with the primary criteria since the outcome all  
43 cause of death is included in the composite primary outcome.  
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49 For the primary statistical analysis of the primary outcome, we will use a modified intention  
50 to treat analysis including patients fulfilling all the inclusion criteria and who have received at least  
51 one injection of the experimental treatment. This strategy has recently been used in randomized  
52 clinical trials evaluating peri-procedure treatments [17,32], because the time between the  
53 randomization, which is realized before the procedure, and the administration of the study  
54 treatment, which is realized during or after the procedure, expose the study to a high risk of  
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1 included patients not receiving the allocated treatment (e.g. cancelled or delayed surgery or  
2 perioperative complications). In this setting, we strongly believe that the mITT is more accurate to  
3 the medical field than the ITT. However, the exclusion of patients in the mITT analysis can  
4 theoretically decrease the statistical power of the study. Thus, the DSMB will have access to the  
5 number of patients excluded from the mITT analysis, and if necessary the DSMB will have the  
6 responsibility to propose an increase of the number of patients to be included to guarantee the study  
7 power. Finally, the intention-to-treat analysis will be reported in the final version of the manuscript.  
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### 13 ***Trial status***

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15 The trial has already achieved many milestones. The trial is sponsored by the French ministry  
16 of health (PHRCN 2016\_0442). Insurance for non-negligent harm has been provided by University  
17 Hospital of Nantes (France). Research ethics committee approval was obtained in September 2019  
18 (Comité de Protection des Personnes Sud Méditerranée V). The French Agency for the safety of  
19 medicines and medical devices authorized the study in September 2017 (#170245RS-21). The study  
20 is registered with the American registry of trials (<https://clinicaltrials.gov/> NCT03218553). The  
21 current emphasis is on opening the recruitment infra-structures, which is ongoing, and in  
22 developing the monitoring infrastructure. No patient has yet been included, and expected starting  
23 point of the study is December 2017.  
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27 The principle investigator (KA), the scientific expert (EF), the statistician (FF) and the study  
28 coordinator (AR) will write the first draft of the manuscript. All the co-authors (investigators who  
29 had realized not less than 30 inclusions) will append and approve the final manuscript before the  
30 submission. No professional writer will be used.  
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34 In conclusion, the PACMAN trial is an investigator-initiated randomized controlled trial  
35 powered to test the hypothesis that the short-course of moderate doses of dexamethasone in patients  
36 undergoing major non-cardiac surgery decreases the risk of post-operative complications. The  
37 results of the PACMAN Trial will be relevant to the wide number of clinicians interested in  
38 perioperative medicine.  
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### 48 **ACKNOWLEDGMENT**

49 We thank patients and relatives, patient advisers, physicians, nursing staff and clinical research  
50 associates of the participating centres for their involvement in this important study.  
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### 53 **AUTHORS' CONTRIBUTIONS**

54 KA, EF, FF and AR conceived the study, coordinated its design and drafted the manuscript. AR and  
55 KA wrote the manuscript. EF and FF read and were involved in critical appraisal and revision of the  
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1 manuscript. FF provided statistical expertise. All authors approved the final manuscript prior to  
2 submission.  
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#### 4 **COMPETING INTERESTS**

5 No competing interests  
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#### 8 **SOURCE OF FUNDING**

9 This study is an investigator-initiated trial, funded by a grant from the French Ministry of Health.  
10 Grant Number PHRCN 2016\_0442  
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#### 13 **DATA SHARING STATEMENT**

14 The principal investigator will have access to the trial data set. Patient level data and/or full dataset  
15 and/or statistical code will be available on request to the corresponding author. Consent was not  
16 obtained, but the presented data are anonymised and risk of identification is low and the potential  
17 benefits of sharing these data outweigh the potential harms.  
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### 33 List of abbreviations

34 DSMB: Data and Safety Monitoring Board, ICU: Intensive Care Unit, ITT: Intention-to-treat.

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### 37 Competing interests

38 The authors declare that they have no competing interests.

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### 45 Figure 1: Flow chart.

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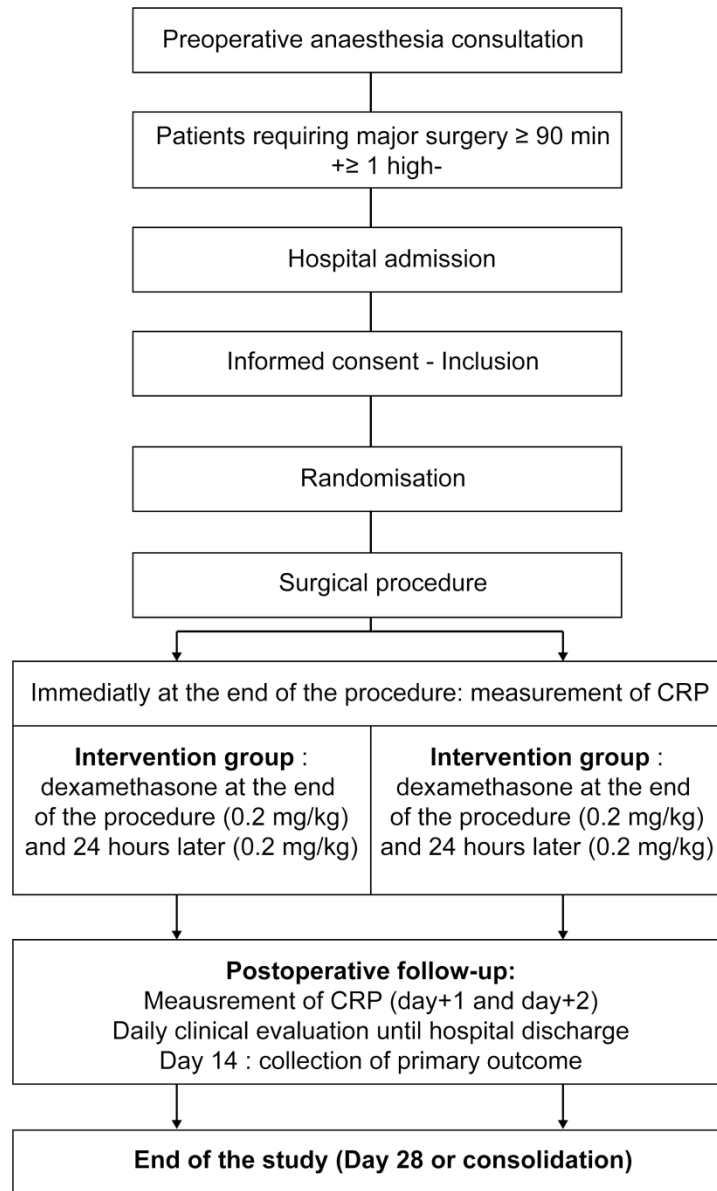


Figure 1

173x289mm (300 x 300 DPI)



# BMJ Open

## The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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Manuscripts

1  
2 **The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and**  
3 **mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority**  
4 **study**  
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50 **Key words:** surgery; glucocorticoid; dexamethasone; post-operative complications; pneumonia  
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## ABSTRACT

**Introduction** Postoperative complications are major healthcare problems and are associated with a reduced short-term and long-term survival after surgery. An excessive postoperative inflammatory response participates to the development of postoperative infection and mortality. The aim of the PACMAN study is to assess the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

**Methods and analysis:** The PACMAN is a multicentre, randomized, controlled, double blind, superiority, two-arms trial of 1222 high-risk patients aged 50 years of older undergoing major non-cardiac surgery at 32 acute care hospital in France. Patients are randomly assigned to dexamethasone (0,2mg.kg-1 at the end of the surgical procedure, and at day+1, n=611) or to placebo (n=611). The primary outcome is a composite of predefined 14-day major pulmonary complications and mortality. Secondary outcomes are surgical complications, infections, organ failures, critical care-free days, length of hospital stay and all-cause mortality at 28 days.

**Ethics and dissemination:** The PACMAN trial protocol has been approved by the ethics committee of Sud Méditerranée V, and will be carried out according to the Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The PACMAN trial is a randomized controlled trial powered to investigate whether perioperative administration of corticosteroids in patients undergoing non-cardiac major surgery reduce postoperative complications. The results of this study will be disseminated through presentation at scientific conferences and publication in peer-reviewed journals.

*Trial registration* number [clinicaltrials.gov NCT03218553](https://clinicaltrials.gov/ct2/show/study/NCT03218553)

*Funding* This work is supported by a grant from the French Ministry of Health (PHRCN 2016, RC16\_0442)

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is a multicenter, randomized, controlled and double blind trial adequately powered to determine whether corticosteroid reduces postoperative complications in high risk patients undergoing major non-cardiac surgery.
- Potential treatment's benefits include reduced risk of postoperative infection, development of organ failure and reduced risk of mortality.
- Limitations due to the difficulty of sepsis diagnosis after major surgery are limited by the use of a placebo ensuring a double-blind evaluation of the primary outcome.
- This large study has the potential of changing international recommendations on the management of high risk patients undergoing major non-cardiac surgery.

## INTRODUCTION

More than 300 million major surgical procedures are undertaken worldwide each year [1]. For most patients, risks of surgery are low. However in an European international cohort, the mortality rate for patients undergoing non-cardiac surgery was higher than expected (4% of patients died before hospital discharge) [2]. It is interesting to consider that 10% of patients at risk of postoperative complications represent 80% of postoperative deaths [3]. It is also important to consider that patients who develop complications but survive until hospital discharge have usually reduced functional independence and long-term survival [4]. These data suggest that interventions to prevent complications and mortality should probably be undertaken early. One of the main targets to focus on is probably lung. Indeed, postoperative respiratory complications represent the most common perioperative complication after wound infections with an estimated incidence ranging from 2.0% to 5.6% for surgical procedures [4]. Respiratory failure after general anaesthesia and tracheal extubation has been shown to be one of the most meaningful factors associated with poor patient outcomes, leading to longer hospital stay [4]. Considering, the high volume of surgical procedures undertaken each year, the key message is that decreasing even a low rate of avoidable harm will be associated with a high cost saving for the society and many preventable deaths and complications for the patients.

Major surgery induces an inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein). The consequences of tissue surgical injuries are a release of danger-associated molecular patterns which initiate the production of pro-inflammatory mediators (cytokines, radical oxygen species) [5]. This inflammatory response is useful for tissue healing, but it is thought that an excessive response contributes to post-operative morbidity (such as infections and organ failures) and mortality. Glucocorticoids have thus been proposed to reduce the risk of complications in several medical conditions characterized by systemic inflammatory response.

In patients undergoing major cardiac surgery, corticosteroids were associated with reduction in length of intensive care unit stay [6], but no difference in 30 day mortality or major morbidity in was found [7]. In severe trauma patients, considering the potential immunostimulating effects of “low doses” corticosteroids [8], we have shown, in two multicentre, randomized, double blind placebo-controlled study on intubated trauma patients, that the use of an intravenous low-dose corticosteroids, compared with placebo, resulted in a decreased risk of hospital- acquired pneumonia [9,10]. Interestingly, apart from higher insulin consumption in patients receiving corticosteroids, no significant

1  
2 harm related to treatment was recorded in both studies. In major non-cardiac surgery, a recent meta-  
3 analysis concluded that proofs are lacking to demonstrate clinically important benefits with  
4 perioperative administration of glucocorticoids, and that safety has not been sufficiently investigated to  
5 rule out any clinically important side effects [11]. The objective of the PACMAN study is to ascertain  
6 whether or not the administration of early corticosteroid with standard care compared with standard  
7 care alone prevents respiratory complications and reduces mortality in high-risk patients undergoing  
8 major surgery. We are reporting the version 4 of the protocol (2<sup>nd</sup> September 2017). This manuscript  
9 has been submitted for publication on the 30<sup>th</sup> of November 2017, before the inclusion of the first  
10 patient in the study.  
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## Methods and Design

### *Hypothesis*

High-risk patients treated with short course of corticosteroid have reduced morbidity and mortality rates compared to those receiving standard care alone after major non-cardiac surgery.

### *Research Questions*

1. Does short-course of moderate doses of dexamethasone prevent death and/or post-operative respiratory complications after major non-cardiac surgery in high-risk patients ?
2. Does short-course of moderate doses of dexamethasone reduce the duration of hospitalization after major non-cardiac surgery in high-risk patients ?
3. Does short-course of moderate doses of dexamethasone prevent delayed skin healing ?

### *Design*

The Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) study is a multicenter, randomized, double blind, parallel-group, superiority, controlled trial (Figure 1).

### *Ethic*

The Institutional Review Board of Sud Méditerranée V (France) approved the study protocol (June 2017). Patients provide written consent for participation. The PACMAN trial is conducted in accordance with the declaration of Helsinki and is registered on June 2017 at <http://clinicaltrials.gov/> with trial registration NCT03218553.

### *Setting*

The study involved 33 French hospitals, each centre caring for more than 200 patients undergoing major surgery each year.

### *Study population*

Investigators screen consecutive high-risk patients undergoing major non-cardiac surgery. Patients older than 50 years and scheduled for a major surgery (> 90 minutes and performed under general anesthesia) of the abdomen, pelvis, thorax, face/neck, vascular surgery are eligible provided that they have one or more of the following risk factors : age > 65 years, presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less), medical



1 history of stroke, moderate to severe renal impairment (clearance of creatinine  $\leq$  30 ml/L), active  
2 smoking, averaged observed blood losses over 500 ml or emergency surgery. These risk factors have  
3 been adapted from the systematic review for the preoperative pulmonary risk stratification for non-  
4 cardiothoracic surgery published by the American College of Physicians [12] and from the guidelines  
5 for the management of severe perioperative bleeding of the European Society of Anesthesiology [13].  
6 Exclusions criteria are: allergy to the intravenous formulation of dexamethasone, treatment with  
7 systemic corticosteroids at a dose  $>$  5 mg.day<sup>-1</sup> of equivalent prednisolone in the previous 3 months,  
8 uncontrolled psychotic disorder (acute or chronic) chronic renal failure (clearance of creatinine  $<$  10  
9 ml/min), life expectancy of less than 1 month, preoperative shock (defined by the need for continuous  
10 infusion of vasoactive drugs (norepinephrine, epinephrine or dobutamine), acute pulmonary edema in  
11 the last 7 days, active bacterial or viral infection, pregnant women, breastfeeding women, minors,  
12 Adults under guardianship or trusteeship.

### 23 ***Identification and information of patients***

24 All consecutive adult patients requiring surgery with an expected duration  $\geq$  90 minutes will be  
25 assessed for eligibility. During the anesthesia consultation or in the operating room in case of  
26 emergency surgery, local investigators (anesthesiologists and/or surgeons) will verify inclusion and  
27 exclusion criteria. Investigators will invite the patients to participate to the study. Patients will be  
28 informed in complete and faithful terms and in understandable language of the objectives and  
29 constraints of the study, the potential risks, the required observation and safety measures, and their  
30 right to refuse to participate in the study or to revoke their consent at any time. All information appears  
31 in an information notice and consent form given to the patient. Written informed consent will be  
32 obtained by the investigator. All these documents are approved by the competent Ethics Committee.  
33 Two original copies will be co-signed by both the investigator and the patient and the parents. The  
34 second copy is to be kept in the patient's medical record.

### 44 ***Treatment Allocation***

45 Patients are randomized in a 1:1 ratio and stratified according to cancer (yes/no) and according to the  
46 type of surgical procedure (thoracic surgery or not). Randomisation is made by a computerized number  
47 generator list provided by a statistician not involved in the determination of eligibility or in the  
48 assessment of outcomes. All assignments are made through a dedicated, pass-word protected, SSL-  
49 encrypted website. Patients are randomized in the first 24 prior to surgery to dexamethasone  
50 (intervention group) or to placebo (control group).

### ***Masking protocol***

Randomized patients are given a number corresponding to a «PACMAN treatment pack» that contains: 4 x 10 mg vial of dexamethasone or placebo, and a sheet for schedule administration.

### ***Procedures***

At the end of the surgery (< 2 hours after skin closure), and before study drug administration, the blood level of c-reactive protein (CRP) is measured (Figure 1). Then, patients randomized to either slow intravenous infusion of dexamethasone (0.2 mg.kg<sup>-1</sup> of real body-weight within the 2 hours after the end of the surgery, and at day+1) or injection of placebo receive treatment (Figure 1). The blood level of CRP is measured at day+1 and day+2 after surgery. The treatment is administrated slowly (over 15 to 30 minutes) independently of the CRP levels.

### ***Standard of care***

According to recent recommendations and publications, clinicians are prompted to realise adequate timing of antimicrobial prophylaxis [14], to apply a protective ventilation strategy (low tidal volume and Positive End Expiratory Pressure) during surgery [15], to closely monitor and treat perioperative hypovolemia and hypotension [16,17] and to early stop sedation at the end of the surgery [18]. Decisions of post-operative admission to intensive care unit and of prophylactic application of non-invasive ventilation will follow local standard of cares. Prophylactic administration of glucocorticoid for postoperative nausea and vomiting or postoperative oedema is not permitted. Clinicians can use glucocorticoid during the first 7 days of the study only in case of formal indication of steroid such as stridor (rescue therapy).

### ***Protocol drop-out***

For patients developing an allergic reaction to the study treatment, the second injection will not be performed and the appropriate treatment of the allergic reaction will be provided. Patients with allergic reaction to dexamethasone will be kept in analysis and remain analysis with the intervention group. Patients treated with out-of-protocol glucocorticoid will be kept in analysis and remain analysis with their attributed group.

### ***Study end points***

The primary outcome is a composite outcome (all-cause mortality and major postoperative complications) within 14 days after surgery, at least one item among the following: postoperative sepsis, Postoperative pulmonary complication (postoperative pneumonia, need for invasive ventilation and/or noninvasive ventilation for respiratory failure) and all-cause mortality.

1  
2 The diagnosis of pneumonia will be retained according to European guidelines i.e. association  
3 48 hours after admission of at least 2 signs (body temperature > 38°C; leukocytosis >12 000/mL, or  
4 leukopenia <4000/mL; purulent pulmonary secretions) with the appearance of a new infiltrate or  
5 change in an existing infiltrate on chest x-ray and a bacterial documentation (blood or respiratory fluid  
6 analysis) [19,20].  
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10 The rates of patients discharged before day 14, and evaluated between day 14 and day 28, will  
11 be reported. Secondary outcomes are all-cause mortality at 28 days, duration of invasive mechanical  
12 ventilation, duration of non-invasive mechanical ventilation, hospital free-days at 28 days, surgical  
13 complications according to the Clavien-Dindo classification within 28 days, unplanned admission or  
14 readmission to intensive care units (within 28 days following randomization), organ failures within 14  
15 days after surgery, Sequential Organ Failure Assessment (SOFA) at day+1 and day+3, proportion of  
16 patients who experienced adverse events, especially hyperglycaemia, healing impairment, anastomotic  
17 leakage at day +14 after surgery.  
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#### 24 ***Follow-up Data***

25 The following variables are collected: demographics, American Society of Anesthesiology (ASA)  
26 score, pre-operative medical optimization, per-surgery management (drugs, mechanical ventilation,  
27 durations of procedure, fluid infusion, bleeding, post-operative analgesia), infections, organ failures,  
28 blood levels of CRP, healing, post-operative complications (including anastomotic leakage), length of  
29 ventilator support, and ICU hospitalisation and death at day 28 are recorded.  
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#### 35 ***Data Collection and Checking***

36 Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or  
37 clinical personnel under the supervision of the study site investigators. From the eCRFs the trial  
38 database will be established.  
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#### 43 ***Study Monitoring***

44 The study will be monitored on behalf of the promotor (Nantes University Hospital). Site staff will be  
45 available to facilitate the monitoring visits and ensure that all required documentation is available for  
46 review. Study initiation visits are carried out at all sites before recruitment starts at that site. During  
47 regular monitoring visits realized throughout the duration of the trial, an independent research assistant  
48 will carry out Source Data Verification of trial data, verify informed consent forms and ensure the  
49 completeness of the Investigator Site Files.  
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#### 55 ***Study Oversight***

Study sponsor is the Nantes University Hospital (5 allée de l'île Gloriette, 44000 Nantes, drcnantes@chu-nantes.fr). Experienced research staff will monitor the study for quality, the integrity of data in all the participating centers. Serious adverse events and unexpected related or possibly related serious events are reported blinded to the promotor within respectively 24 hours or 7 days. An independent data and safety monitoring board (DSMB) is appointed by the sponsor. The DSMB is made up of 4 individuals with no connection to the research, including three clinician specializing in the management of ICU patients and corticotherapy in ICU, and a methodologist/biostatistician. Before the first inclusion, and every 300 inclusions, the DSMB looks over the ethics in accordance with the Declaration of Helsinki, monitors patient safety and reviews safety issues as the study progresses. The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of serious adverse reactions.
- to recommend increasing the total number of patients to be included to ensure the study power in case of high number of exclusions in the per-protocol analysis.

The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-assessment of the benefit-risk ratio during the research. Trial recruitment can be stopped by the promotor on the advice of the DSMB in case of safety concern.

### ***Roles of the sponsor and of the funder***

The sponsor and the funder have no role in the design or conduct of the study, the data analysis, the writing of the manuscript or in the decision to submit the manuscript.

### ***Statistical consideration***

All analyses will be performed with the use of SAS software (version 9.4, NC, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines. Analyzes will be conducted, first, on data from the modified intention-to-treat (modified-ITT) population, second, in the intention-to-treat (ITT) population as well as in the per-protocol population. The criteria for including patients in the modified-ITT and in the per-protocol populations, respectively, are provided below.

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2 Continuous variables will be presented as mean and standard deviations (as median and quartiles,  
3 otherwise) and will be compared with the use of the unpaired  $t$  test or the Mann-Whitney  $U$  test when  
4 appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to  
5 assess homoscedasticity. Categorical data will be presented as exact numbers and percentages.  
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### 8 *Number of patients*

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10 The rate of the primary endpoint in the control group is expected to reach 20% [15,21]. Assuming a  
11 20% rate in the control group and 14% in the dexamethasone group, A total of 1222 patients are needed  
12 to detect this difference between the two groups with a 5% type I error and a power of 80% in a two-  
13 sided test.  
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### 16 *Pre-Planned primary analysis*

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18 For the primary analysis, data will be analysed with the use of logistic regression adjusted for  
19 stratification factors (cancer and thoracic procedure).  
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23 The effects of the treatment will be investigated in ITT, in modified-ITT and in per-protocol  
24 populations. **In the ITT analyse**, all randomized patients will be kept in analysis. In the **modified-ITT**  
25 **analyse**, all randomized patients will be kept in analysis except those who would not have been eligible  
26 for randomization according to the inclusion/non-inclusion criteria or those who have not received any  
27 injection of the experimental treatment (dexamethasone or placebo). In the **per-protocol analyse**, all  
28 randomized patients will be kept in analysis except patients having one or more major protocol  
29 violations defined as those who would not be eligible for randomization according to inclusion/non-  
30 inclusion criteria; or those who accidentally would have received the wrong intervention  
31 (Dexamethasone or placebo); or those in whom surgical intervention could not have been done (for  
32 example, intra-abdominal extensive cancer); or those who have withdrawn consent; those who would  
33 have received out-of-protocol glucocorticoids.  
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### 41 *Pre-specified exploratory sub-group analyses:*

- 42 - Strates of randomization (cancer yes/no, thoracic procedure yes/no)
- 43 - Medical history of corticosteroid in the preceding 3 months (yes/no)
- 44 - Emergency vs scheduled surgery
- 45 - According to the level of CRP measured at the end of the surgical procedure immediately before the
- 46 first injection of the studied treatment (< 50, 50-150 or > 150 mg/mL).
- 47 - According to the surgery (abdomen, pelvis, thorax, face/neck or vascular surgery)
- 48 - In diabetic and non-diabetic patients.

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50 No interim efficacy analyze will be performed so that no adjustment is required to the final p-value  
51 to allow for the multiple testing. The DSMB will only analyse safety data and can make  
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2 recommendation for adjustment of the number of patients to be included to ensure the statistical power  
3 of the mITT analysis.  
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#### 5 ***Method for missing data***

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7 There should not be missing data for the primary outcome measure and the missing data rate  
8 should be low for the other outcomes as well. Missing data will be described by treatment arm.  
9 According to the rate of missing data (over 5%) sensitivity analyses will be performed using multiple  
10 imputation methods as well as worst case scenario (missing data considered as the most unfavourable  
11 case) and maximum bias scenario (missing data considered as the most favourable or unfavourable case  
12 in the placebo and experimental arms respectively).  
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#### 15 ***Data Sharing statement***

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17 The principle investigator will have access to the final trial data set. Data sharing: patient level data  
18 and/or full dataset and/or statistical code will be available upon request to the corresponding author.  
19 Consent for the data sharing was not obtained but the presented data are anonymised and risk of  
20 identification is low and the potential benefits of sharing these data outweigh the potential harms.  
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#### 23 ***Patient and Public Involvement statement***

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25 The development of the research question and outcome measures was informed by patients' priorities,  
26 which is notably the prevention of post-operative complications. Patients were not involved neither in  
27 the design of the study. Patients were involved neither in the recruitment nor in the conduct of the  
28 study. Results of the study will be disseminated to study participants upon personal request to the study  
29 coordinator. For this randomised clinical trial, the burden of the intervention was assessed by an  
30 institutional review board, notably composed of representative of patient associations.  
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## 41 **DISCUSSION**

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43 The PACMAN trial is a nationwide randomized controlled study powered to investigate short-  
44 course of moderate dose of dexamethasone in patients undergoing major non-cardiac surgery.  
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48 Several trials have investigated the benefits of administering corticosteroids in patients undergoing  
49 major surgery. However, there is yet no agreement on the beneficial effects of corticosteroids in  
50 alleviating surgical stress. This disagreement probably stems from the variability in the drugs used,  
51 their dosage and administration schedule, and the surgical procedures in different studies. Also the fear  
52 of side effects induced by a possible immunosuppression (infections, postoperative wound  
53 complications, anastomotic leakage) explains the extreme variability of behaviour from one centre to  
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1 another and among patients and physicians. These considerations prevented the performance of a large  
2 scale randomized study despite evidences that corticosteroids could enhance outcome and even  
3 decrease the rate of infections after non-cardiac major surgery (see above). Before general  
4 recommendations for perioperative corticosteroids administration can be made, obviously conclusive  
5 safety studies must be available. So far, there seem to be no safety issues [22-24] related to a single  
6 preoperative dose of corticosteroids including specific studies on wound healing [25,26]. The  
7 consequences of perioperative use of corticosteroids for glucose homeostasis need further evaluation,  
8 but so far the transitory increased hyperglycemic response has not been related to increased  
9 postoperative complications [27]. To reach definitive conclusion on the effects of glucocorticoids on  
10 the risk of post-operative infections, we are eagerly awaiting the results from the PADDI randomized  
11 clinical trial which is investigating the effects of low dose of dexamethasone on surgical site infection,  
12 and from the PACMAN trial whose primary outcome is a composite outcome made of death and  
13 respiratory infections.

14 While perioperative glucocorticoids are widely administrated, the latest meta-analyses found that  
15 we are lacking power to detect differences in complications [11], and that no definitive conclusions can  
16 be made regarding clinically important benefice [7]. While the PADDI study is a non-inferiority trial  
17 designed to test the safety of dexamethasone in an unselected population, we have designed the  
18 PACMAN trial to investigate the potential benefits of the treatment in a surgical population with high  
19 risk of post-operative respiratory complications according to American and European recommendations  
20 [12,13]. Risk factors of pulmonary complications are either related to the surgery, or to the medical  
21 history of the patients. The external validity of the PACMAN results to unselected patients should be  
22 cautious in case of increased risks of the side-effects recorded as secondary outcomes.

23 We decided to not limit the PACMAN study to a specific type of surgery but to include all sort  
24 of surgery provided that the expected duration of the procedure exceeds 90 minutes. This strategy  
25 maximises recruitment rates and improves the generalisation of results. We acknowledge that the  
26 clinical risk factors of postoperative respiratory complications are inconstantly used in clinical practice,  
27 which can limit the applicability to the study results. However, preoperative optimization by nutritional  
28 support, respiratory physiotherapy or smoking cessation are recommended in patients presenting such  
29 risk factors [12]. The selection of high risk patients will result in a high incidence rate of the primary  
30 endpoint, which will result in a study of high clinical relevance and statistical power.

31 A wide range of doses of dexamethasone has been tested in surgical or critically ill patients : from  
32 low (4-8 mg/day [11,28]), to high doses (1-2 mg/kg [6,29]). The PACMAN trial is designed to  
33 investigate the effects of dexamethasone on the risk of major respiratory complications, notably

1 pneumonia, and we thus decided to evaluate the effects of moderate doses as proposed in the latest  
2 recommendations and meta-analysis for the treatment with steroids of in patients with pneumonia  
3 [30,31]. The timing of administration is also critical to consider. We decided to initiate the study  
4 treatment during the post-operative inflammatory response, rather than before the surgery, because  
5 glucocorticoids induce the apoptosis of immune cells in absence of inflammation but are stimulate  
6 immunity when administrated during an inflammatory response [32,33].

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12 We selected a composite outcome as the primary criteria. The use of mortality as a primary  
13 endpoint is never used in perioperative studies because the risk of death is low and the statistical power  
14 would be low. Respiratory complications are particularly frequent and serious after major surgery and  
15 we have recently proposed that glucocorticoid prevent the development of inflammation-related  
16 immunosuppression [8], and decrease the risk of pneumonia after severe trauma [9,10]. Finally,  
17 mortality is not competitive with the primary criteria since the outcome all cause of death is included in  
18 the composite primary outcome.

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24 For the primary statistical analysis of the primary outcome, we will use a modified intention to  
25 treat analysis including patients fulfilling all the inclusion criteria and who have received at least one  
26 injection of the experimental treatment. This strategy has recently been used in randomized clinical  
27 trials evaluating peri-procedure treatments [17,34], because the time between the randomization, which  
28 is realized before the procedure, and the administration of the study treatment, which is realized during  
29 or after the procedure, expose the study to a high risk of included patients not receiving the allocated  
30 treatment (e.g. cancelled or delayed surgery or perioperative complications). In this setting, we strongly  
31 believe that the mITT is more accurate to the medical field than the ITT. However, the exclusion of  
32 patients in the mITT analysis can theoretically decrease the statistical power of the study. Thus, the  
33 DSMB will have access to the number of patients excluded from the miTT analysis, and if necessary  
34 the DMSB will have the responsibility to propose an increase of the number of patients to be included  
35 to guarantee the study power. Finally, the intention-to-treat analysis will be reported in the final version  
36 of the manuscript.

### 37 38 39 40 41 42 43 44 45 46 47 ***Trial status***

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50 The trial has already achieved many milestones. The trial is sponsored by the French ministry of  
51 health (PHRCN 2016\_0442). Insurance for non-negligent harm has been provided by University  
52 Hospital of Nantes (France). Research ethics committee approval was obtained in September 2019  
53 (Comité de Protection des Personnes Sud Méditerranée V). The French Agency for the safety of  
54 medicines and medical devices authorized the study in September 2017 (#170245RS-21). The study is



1 registered with the American registry of trials ([https://clinicaltrials.gov/ NCT03218553](https://clinicaltrials.gov/NCT03218553)). The current  
2 emphasis is on opening the recruitment infra-structures, which is ongoing, and in developing the  
3 monitoring infrastructure. No patient has yet been included, and expected starting point of the study is  
4 December 2017.  
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9 The principle investigator (KA), the scientific expert (EF), the statistician (FF) and the study  
10 coordinator (AR) will write the first draft of the manuscript. All the co-authors (investigators who had  
11 realized not less than 30 inclusions) will append and approve the final manuscript before the  
12 submission. No professional writer will be used.  
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17 In conclusion, the PACMAN trial is an investigator-initiated randomized controlled trial  
18 powered to test the hypothesis that the short-course of moderate doses of dexamethasone in patients  
19 undergoing major non-cardiac surgery decreases the risk of post-operative complications. The results  
20 of the PACMAN Trial will be relevant to the wide number of clinicians interested in perioperative  
21 medicine.  
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30 associates of the participating centres for their involvement in this important study.  
31  
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## 33 **AUTHORS' CONTRIBUTIONS**

34 KA, EF, FF and AR conceived the study, coordinated its design and drafted the manuscript. AR and  
35 KA wrote the manuscript. EF and FF read and were involved in critical appraisal and revision of the  
36 manuscript. FF provided statistical expertise. All authors approved the final manuscript prior to  
37 submission.  
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## 41 **COMPETING INTERESTS**

42 No competing interests  
43  
44

## 45 **SOURCE OF FUNDING**

46 This study is an investigator-initiated trial, funded by a grant from the French Ministry of Health. Grant  
47 Number PHRCN 2016\_0442  
48  
49

## 50 **DATA SHARING STATEMENT**

51 The principal investigator will have access to the trial data set. Patient level data and/or full dataset  
52 and/or statistical code will be available on request to the corresponding author. Consent was not  
53 obtained, but the presented data are anonymised and risk of identification is low and the potential  
54 benefits of sharing these data outweigh the potential harms.  
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For peer review only

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1  
2 **List of abbreviations**

3 DSMB: Data and Safety Monitoring Board, ICU: Intensive Care Unit, ITT: Intention-to-treat.  
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7 **Competing interests**

8 The authors declare that they have no competing interests.  
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14 **Figure 1: Flow chart.**  
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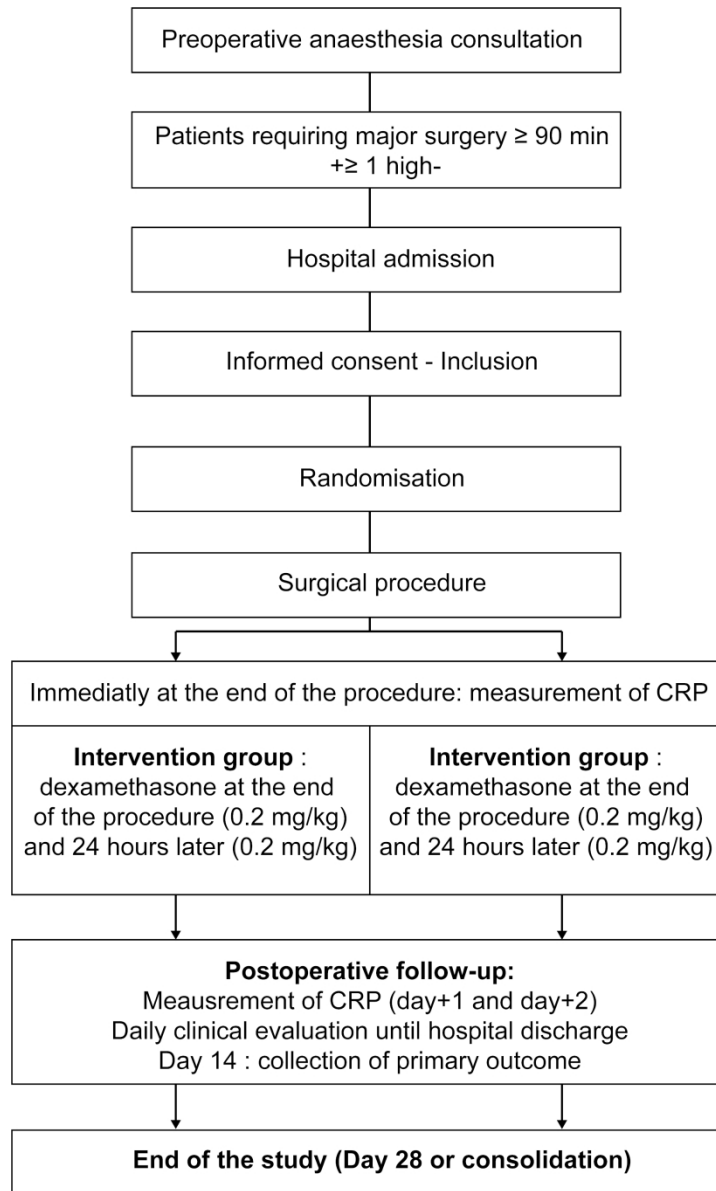


Figure 1

173x289mm (300 x 300 DPI)

# BMJ Open

## The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study

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<b>Primary Subject Heading</b>:	Anaesthesia
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Keywords:	SURGERY, glucocorticoid, dexamethasone, post-operative complications, pneumonia

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**The PACMAN trial protocol – Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac major surgery: a randomized, multicentre, double blind, superiority study**

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40 **Key words:** surgery; glucocorticoid; dexamethasone; post-operative complications; pneumonia  
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## 1 2 1 3 2 **ABSTRACT**

4  
5 3 **Introduction** Postoperative complications are major healthcare problems and are associated with a  
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8 4 reduced short-term and long-term survival after surgery. An excessive postoperative inflammatory  
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10 5 response participates to the development of postoperative infection and mortality. The aim of the  
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12 6 PACMAN study is to assess the effectiveness of perioperative administration of corticosteroid to  
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14 7 reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.

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17 8 **Methods and analysis:** The PACMAN is a multicentre, randomized, controlled, double blind,  
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19 9 superiority, two-arm trial of 1222 high-risk patients aged 50 years or older undergoing major non-  
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21 10 cardiac surgery at 32 acute care hospital in France. Patients are randomly assigned to  
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23 11 dexamethasone (0,2mg.kg<sup>-1</sup> at the end of the surgical procedure, and at day+1, n=611) or to placebo  
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25 12 (n=611). The primary outcome is a composite of predefined 14-day major pulmonary complications  
26  
27 13 and mortality. Secondary outcomes are surgical complications, infections, organ failures, critical  
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29 14 care-free days, length of hospital stay and all-cause mortality at 28 days.

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33 15 **Ethics and dissemination:** The PACMAN trial protocol has been approved by the ethics  
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35 16 committee of Sud Méditerranée V, and will be carried out according to the Good Clinical Practice  
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37 17 guidelines and the principles of the Declaration of Helsinki. The PACMAN trial is a randomized  
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39 18 controlled trial powered to investigate whether perioperative administration of corticosteroids in  
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41 19 patients undergoing non-cardiac major surgery reduce postoperative complications. The results of  
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43 20 this study will be disseminated through presentation at scientific conferences and publication in  
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45 21 peer-reviewed journals.

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49 22 *Trial registration* number [clinicaltrials.gov](http://clinicaltrials.gov) NCT03218553

50  
51 23 *Funding* This work is supported by a grant from the French Ministry of Health (PHRCN 2016,  
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53 24 RC16\_0442)

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study is a multicenter, randomized, controlled and double blind trial adequately powered to determine whether corticosteroid reduces postoperative complications in high risk patients undergoing major non-cardiac surgery.
- Potential treatment's benefits include reduced risk of postoperative infection, development of organ failure and reduced risk of mortality.
- Limitations due to the difficulty of sepsis diagnosis after major surgery are limited by the use of a placebo ensuring a double-blind evaluation of the primary outcome.
- This large study has the potential of changing international recommendations on the management of high risk patients undergoing major non-cardiac surgery.

## INTRODUCTION

More than 300 million major surgical procedures are undertaken worldwide each year [1]. For most patients, risks of surgery are low. However in an European international cohort, the mortality rate for patients undergoing non-cardiac surgery was higher than expected (4% of patients died before hospital discharge) [2]. It is interesting to consider that 10% of patients at risk of postoperative complications represent 80% of postoperative deaths [3]. It is also important to consider that patients who develop complications but survive until hospital discharge have usually reduced functional independence and long-term survival [4]. These data suggest that interventions to prevent complications and mortality should probably be undertaken early. One of the main targets to focus on is probably lung. Indeed, postoperative respiratory complications represent the most common perioperative complication after wound infections with an estimated incidence ranging from 2.0% to 5.6% for surgical procedures [4]. Respiratory failure after general anaesthesia and tracheal extubation has been shown to be one of the most meaningful factors associated with poor patient outcomes, leading to longer hospital stay [4]. Considering, the high volume of surgical procedures undertaken each year, the key message is that decreasing even a low rate of avoidable harm will be associated with a high cost saving for the society and many preventable deaths and complications for the patients.

Major surgery induces an inflammatory response characterized by activation of platelets, neutrophils, monocytes, macrophages, cascades (coagulation, fibrinolytic, and kallikrein). The consequences of tissue surgical injuries are a release of danger-associated molecular patterns which initiate the production of pro-inflammatory mediators (cytokines, radical oxygen species) [5]. This inflammatory response is useful for tissue healing, but it is thought that an excessive response contributes to post-operative morbidity (such as infections and organ failures) and mortality. Glucocorticoids have thus been proposed to reduce the risk of complications in several medical conditions characterized by systemic inflammatory response.

In patients undergoing major cardiac surgery, corticosteroids were associated with reduction in length of intensive care unit stay [6], but no difference in 30 day mortality or major morbidity in was found [7]. In severe trauma patients, considering the potential immunostimulating effects of “low doses” corticosteroids [8], we have shown, in two multicentre, randomized, double blind placebo-controlled study on intubated trauma patients, that the use of an intravenous low-dose corticosteroids, compared with placebo, resulted in a decreased risk of hospital-acquired pneumonia [9,10]. Interestingly, apart from higher insulin consumption in patients receiving corticosteroids, no significant harm related to treatment was recorded in both studies. In major non-cardiac surgery, a recent meta-analysis concluded that proofs are lacking to demonstrate clinically

1  
2 1 important benefits with perioperative administration of glucocorticoids, and that safety has not been  
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4 2 sufficiently investigated to rule out any clinically important side effects [11]. The objective of the  
5  
6 3 PACMAN study is to ascertain whether or not the administration of early corticosteroid with  
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8 4 standard care compared with standard care alone prevents respiratory complications and reduces  
9  
10 5 mortality in high-risk patients undergoing major surgery. We are reporting the version 4 of the  
11  
12 6 protocol (2<sup>nd</sup> September 2017). This manuscript has been submitted for publication on the 30<sup>th</sup> of  
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14 7 November 2017, before the inclusion of the first patient in the study.  
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For peer review only

## Methods and Design

### *Hypothesis*

High-risk patients treated with short course of corticosteroid have reduced morbidity and mortality rates compared to those receiving standard care alone after major non-cardiac surgery.

### *Research Questions*

1. Does short-course of moderate doses of dexamethasone prevent death and/or post-operative respiratory complications after major non-cardiac surgery in high-risk patients ?
2. Does short-course of moderate doses of dexamethasone reduce the duration of hospitalization after major non-cardiac surgery in high-risk patients ?
3. Does short-course of moderate doses of dexamethasone prevent delayed skin healing ?

### *Design*

The Perioperative Administration of Corticotherapy on Morbidity and mortality After Non-cardiac surgery (PACMAN) study is a multicenter, randomized, double blind, parallel-group, superiority, controlled trial (Figure 1). KA and AR wrote the first draft of the protocol. FF was responsible of the statistical plan. EF extensively revised the protocol. All the authors approved the final version.

### *Ethic approval*

The Institutional Review Board of Sud Méditerranée V (France) approved the study protocol (June 2017, version 4). Patients provide written consent for participation (see supplementary file). The PACMAN trial is conducted in accordance with the declaration of Helsinki and is registered on June 2017 at <http://clinicaltrials.gov/> with trial registration NCT03218553.

### *Setting*

The study involved 33 French hospitals, each centre caring for more than 200 patients undergoing major surgery each year.

### *Study population*

Investigators screen consecutive high-risk patients undergoing major non-cardiac surgery. Patients older than 50 years and scheduled for a major surgery (> 90 minutes and performed under general anesthesia) of the abdomen, pelvis, thorax, face/neck, vascular surgery are eligible provided that they have one or more of the following risk factors : age > 65 years, presence of a defined risk factor for cardiac or respiratory disease (exercise tolerance equivalent to 6 metabolic equivalents or less), medical history of stroke, moderate to severe renal impairment (clearance of creatinine  $\leq$  30

1 mll/L), active smoking, averaged observed blood losses over 500 ml or emergency surgery. These  
2 risk factors have been adapted from the systematic review for the preoperative pulmonary risk  
3 stratification for non-cardiothoracic surgery published by the American College of Physicians [12]  
4 and from the guidelines for the management of severe perioperative bleeding of the European  
5 Society of Anesthesiology [13]. Exclusions criteria are: allergy to the intravenous formulation of  
6 dexamethasone, treatment with systemic corticosteroids at a dose  $> 5 \text{ mg}\cdot\text{day}^{-1}$  of equivalent  
7 prednisolone in the previous 3 months, uncontrolled psychotic disorder (acute or chronic)  
8 chronic renal failure (clearance of creatinine  $< 10 \text{ ml/min}$ ), life expectancy of less than 1 month,  
9 preoperative shock (defined by the need for continuous infusion of vasoactive drugs  
10 (norepinephrine, epinephrine or dobutamine), acute pulmonary edema in the last 7 days, active  
11 bacterial or viral infection, pregnant women, breastfeeding women, minors, Adults under  
12 guardianship or trusteeship.

### 13 ***Identification and information of patients***

14 All consecutive adult patients requiring surgery with an expected duration  $\geq 90$  minutes will be  
15 assessed for eligibility. During the anesthesia consultation or in the operating room in case of  
16 emergency surgery, local investigators (anesthesiologists and/or surgeons) will verify inclusion and  
17 exclusion criteria. Investigators will invite the patients to participate to the study. Patients will be  
18 informed in complete and faithful terms and in understandable language of the objectives and  
19 constraints of the study, the potential risks, the required observation and safety measures, and their  
20 right to refuse to participate in the study or to revoke their consent at any time. All information  
21 appears in an information notice and consent form given to the patient. Written informed consent  
22 will be obtained by the investigator. All these documents are approved by the competent Ethics  
23 Committee. Two original copies will be co-signed by both the investigator and the patient and the  
24 parents. The second copy is to be kept in the patient's medical record.

### 25 ***Treatment Allocation***

26 Patients are randomized in a 1:1 ratio and stratified according to cancer (yes/no) and according to  
27 the type of surgical procedure (thoracic surgery or not). Randomisation is made by a computerized  
28 number generator list provided by a statistician not involved in the determination of eligibility or in  
29 the assessment of outcomes. All assignments are made through a dedicated, pass-word protected,  
30 SSL-encrypted website. Patients are randomized in the first 24 prior to surgery to dexamethasone  
31 (intervention group) or to placebo (control group).

### 32 ***Masking protocol***

33 Randomized patients are given a number corresponding to a «PACMAN treatment pack» that  
34 contains: 4 x 10 mg vial of dexamethasone or , and a sheet for schedule administration.



## **Procedures**

At the end of the surgery (< 2 hours after skin closure), and before study drug administration, the blood level of c-reactive protein (CRP) is measured (Figure 1). Then, patients randomized to either slow intravenous infusion of dexamethasone (0.2 mg.kg<sup>-1</sup> of real body-weight within the 2 hours after the end of the surgery, and at day+1) or injection of placebo receive treatment (Figure 1). The blood level of CRP is measured at day+1 and day+2 after surgery. The treatment is administrated slowly (over 15 to 30 minutes) independently of the CRP levels.

## **Standard of care**

According to recent recommendations and publications, clinicians are prompted to realise adequate timing of antimicrobial prophylaxis [14], to apply a protective ventilation strategy (low tidal volume and Positive End Expiratory Pressure) during surgery [15], to closely monitor and treat peroperative hypovolemia and hypotension [16,17] and to early stop sedation at the end of the surgery [18]. Decisions of post-operative admission to intensive care unit and of prophylactic application of non-invasive ventilation will follow local standard of cares. Prophylactic administration of glucocorticoid for postoperative nausea and vomiting or postoperative oedema is not permitted. Clinicians can use glucocorticoid during the first 7 days of the study only in case of formal indication of steroid such as stridor (rescue therapy).

## **Protocol drop-out**

For patients developing an allergic reaction to the study treatment, the second injection will not be performed and the appropriate treatment of the allergic reaction will be provided. Patients with allergic reaction to dexamethasone will be kept in analysis and remain analysis with the intervention group. Patients treated with out-of-protocol glucocorticoid will be kept in analysis and remain analysis with their attributed group. No procedure for revealing a participant's allocated intervention during the trial is planned.

## **Study end points**

The primary outcome is a composite outcome (all-cause mortality and major postoperative complications) within 14 days after surgery, at least one item among the following: postoperative sepsis, Postoperative pulmonary complication (postoperative pneumonia, need for invasive ventilation and/or noninvasive ventilation for respiratory failure) and all-cause mortality.

The diagnosis of pneumonia will be retained according to European guidelines i.e. association 48 hours after admission of at least 2 signs (body temperature > 38°C; leukocytosis >12 000/mL, or leukopenia <4000/mL; purulent pulmonary secretions) with the appearance of a new infiltrate or change in an existing infiltrate on chest x-ray and a bacterial documentation (blood or respiratory fluid analysis) [19,20].

1  
2 1 The rates of patients discharged before day 14, and evaluated between day 14 and day 28,  
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4 2 will be reported. Secondary outcomes are all-cause mortality at 28 days, duration of invasive  
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6 3 mechanical ventilation, duration of non-invasive mechanical ventilation, hospital free-days at 28  
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8 4 days, surgical complications according to the Clavien-Dindo classification within 28 days,  
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10 5 unplanned admission or readmission to intensive care units (within 28 days following  
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12 6 randomization), organ failures within 14 days after surgery, Sequential Organ Failure Assessment  
13  
14 7 (SOFA) at day+1 and day+3, proportion of patients who experienced adverse events, especially  
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16 8 hyperglycaemia, healing impairment, anastomotic leakage at day +14 after surgery.

### 16 9 ***Follow-up Data***

17 10 The following variables are collected: demographics, American Society of Anesthesiology (ASA)  
18 11 score, pre-operative medical optimization, per-surgery management (drugs, mechanical ventilation,  
19 12 durations of procedure, fluid infusion, bleeding, post-operative analgesia), infections, organ  
20 13 failures, blood levels of CRP, healing, post-operative complications (including anastomotic  
21 14 leakage), length of ventilator support, and ICU hospitalisation and death at day 28 are recorded.

### 26 15 ***Data Collection and Checking***

27 16 Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or  
28 17 clinical personnel under the supervision of the study site investigators. From the eCRFs the trial  
29 18 database will be established.

### 34 19 ***Study Monitoring***

35 20 The study will be monitored on behalf of the promotor (Nantes University Hospital). Site staff will  
36 21 be available to facilitate the monitoring visits and ensure that all required documentation is  
37 22 available for review. Study initiation visits are carried out at all sites before recruitment starts at that  
38 23 site. During regular monitoring visits realized throughout the duration of the trial, an independent  
39 24 research assistant will carry out Source Data Verification of trial data, verify informed consent  
40 25 forms and ensure the completeness of the Investigator Site Files.

### 47 26 ***Study Oversight***

48 27 Study sponsor is the Nantes University Hospital (5 allée de l'île Gloriette, 44000 Nantes, drc-  
49 28 nantes@chu-nantes.fr). Experienced research staff will monitor the study for quality, the integrity  
50 29 of data in all the participating centers. Serious adverse events and unexpected related or possibly  
51 30 related serious events are reported blinded to the promotor within respectively 24 hours or 7 days.  
52 31 An independent data and safety monitoring board (DSMB) is appointed by the sponsor. The DSMB  
53 32 is made up of 4 individuals with no connection to the research, including three clinician specializing  
54 33 in the management of ICU patients and corticotherapy in ICU, and a methodologist/biostatistician.

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2 1 Before the first inclusion, and every 600 inclusions, the DSMB looks over the ethics in accordance  
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4 2 with the Declaration of Helsinki, monitors patient safety and reviews safety issues as the study  
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6 3 progresses. The DSMB makes recommendations to the sponsor about the continuation,  
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8 4 modification or termination of the research. The recommendations that the DSMB can make are:

- 9 5 - to continue the research with no modifications
- 10  
11 6 - to continue the research with a modification to the protocol and/or to the  
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13 7 monitoring of subjects
- 14  
15 8 - to temporarily halt inclusions
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17 9 - to permanently terminate the research in light of serious adverse reactions.
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19 10 - to recommend increasing the total number of patients to be included to ensure the study  
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21 11 power in case of high number of exclusions in the per-protocol analysis.

22 12 The DSMB has a consultative role in advising the sponsor on safety issues such as tolerance and re-  
23  
24 13 assessment of the benefit-risk ratio during the research. Trial recruitment can be stopped by the  
25  
26 14 promotor on the advice of the DSMB in case of safety concern.

### 27 15 ***Roles of the sponsor and of the funder***

28 16 The sponsor and the funder have no role in the design or conduct of the study, the data analysis, the  
29  
30 17 writing of the manuscript or in the decision to submit the manuscript.

### 31 18 ***Statistical consideration***

32 19 All analyses will be performed with the use of SAS software (version 9.4, NC, USA) before  
33  
34 20 the breaking of the randomization code, according to International Conference on Harmonization-  
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36 21 Good Clinical Practice guidelines. Analyzes will be conducted, first, on data from the modified  
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38 22 intention-to-treat (modified-ITT) population, second, in the intention-to-treat (ITT) population as  
39  
40 23 well as in the per-protocol population. The criteria for including patients in the modified-ITT and in  
41  
42 24 the per-protocol populations, respectively, are provided below.

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44 25 Continuous variables will be presented as mean and standard deviations (as median and  
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46 26 quartiles, otherwise) and will be compared with the use of the unpaired *t* test or the Mann-Whitney  
47  
48 27 *U* test when appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-  
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50 28 Snedecor test to assess homoscedasticity. Categorical data will be presented as exact numbers and  
51  
52 29 percentages.

### 53 30 ***Number of patients***

54 31 The rate of the primary endpoint in the control group is expected to reach 20% [15,21]. Assuming a  
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56 32 20% rate in the control group and 14% in the dexamethasone group, A total of 1222 patients are  
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58 33 needed to detect this difference between the two groups with a 5% type I error and a power of 80%  
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60 34 in a two-sided test.

### 35 35 ***Pre-Planned primary analysis***

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2 1 For the primary analysis, data will be analysed with the use of logistic regression adjusted  
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4 2 for stratification factors (cancer and thoracic procedure).

5 3 The effects of the treatment will be investigated in ITT, in modified-ITT and in per-protocol  
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7 4 populations. **In the ITT analyse**, all randomized patients will be kept in analysis. In the **modified-**  
8  
9 5 **ITT analyse**, all randomized patients will be kept in analysis except those who would not have  
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11 6 been eligible for randomization according to the inclusion/non-inclusion criteria or those who have  
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13 7 not received any injection of the experimental treatment (dexamethasone or placebo). In the **per-**  
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15 8 **protocol analyse**, all randomized patients will be kept in analysis except patients having one or  
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17 9 more major protocol violations defined as those who would not be eligible for randomization  
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19 10 according to inclusion/non-inclusion criteria; or those who accidentally would have received the  
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21 11 wrong intervention (Dexamethasone or placebo); or those in whom surgical intervention could not  
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23 12 have been done (for example, intra-abdominal extensive cancer); or those who have withdrawn  
24  
25 13 consent; those who would have received out-of-protocol glucocorticoids.

#### 24 14 ***Pre-specified exploratory sub-group analyses:***

- 26 15 - Strates of randomization (cancer yes/no, thoracic procedure yes/no)
- 27 16 - Medical history of corticosteroid in the preceding 3 months (yes/no)
- 28 17 - Emergency *vs* scheduled surgery
- 29 18 - According to the level of CRP measured at the end of the surgical procedure immediately before  
30 19 the first injection of the studied treatment (< 50, 50-150 or > 150 mg/mL).
- 31 20 - According to the surgery (abdomen, pelvis, thorax, face/neck or vascular surgery)
- 32 21 - In diabetic and non-diabetic patients.

33 22 No interim efficacy analyze will be performed so that no adjustment is required to the final p-  
34 23 value to allow for the multiple testing. The DSMB will only analyse safety data and can make  
35 24 recommendation for adjustment of the number of patients to be included to ensure the statistical  
36 25 power of the mITT analysis. Important protocol modifications will be disseminate by the promoters  
37 26 to all the relevant parties.

#### 38 27 ***Method for missing data***

39 28 There should not be missing data for the primary outcome measure and the missing data rate  
40 29 should be low for the other outcomes as well. Missing data will be described by treatment arm.  
41 30 According to the rate of missing data (over 5%) sensitivity analyses will be performed using  
42 31 multiple imputation methods as well as worst case scenario (missing data considered as the most  
43 32 unfavourable case) and maximum bias scenario (missing data considered as the most favourable or  
44 33 unfavourable case in the placebo and experimental arms respectively).

#### 45 34 ***Data Sharing statement***

1 The principle investigator will have access to the final trial data set. Data sharing: patient level data  
2 and/or full dataset and/or statistical code will be available upon request to the corresponding author.  
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### ***Patient and Public Involvement statement***

6 The development of the research question and outcome measures was informed by patients'  
7 priorities, which is notably the prevention of post-operative complications. Patients were not  
8 involved neither in the design of the study. Patients were involved neither in the recruitment nor in  
9 the conduct of the study. Results of the study will be disseminated to study participants upon  
10 personal request to the study coordinator. For this randomised clinical trial, the burden of the  
11 intervention was assessed by an institutional review board, notably composed of representative of  
12 patient associations.

## **DISCUSSION**

16 The PACMAN trial is a nationwide randomized controlled study powered to investigate  
17 short-course of moderate dose of dexamethasone in patients undergoing major non-cardiac surgery.

18 Several trials have investigated the benefits of administering corticosteroids in patients  
19 undergoing major surgery. However, there is yet no agreement on the beneficial effects of  
20 corticosteroids in alleviating surgical stress. This disagreement probably stems from the variability  
21 in the drugs used, their dosage and administration schedule, and the surgical procedures in different  
22 studies. Also the fear of side effects induced by a possible immunosuppression (infections,  
23 postoperative wound complications, anastomotic leakage) explains the extreme variability of  
24 behaviour from one centre to another and among patients and physicians. These considerations  
25 prevented the performance of a large scale randomized study despite evidences that corticosteroids  
26 could enhance outcome and even decrease the rate of infections after non-cardiac major surgery  
27 (see above). Before general recommendations for perioperative corticosteroids administration can  
28 be made, obviously conclusive safety studies must be available. So far, there seem to be no safety  
29 issues [22-24] related to a single preoperative dose of corticosteroids including specific studies on  
30 wound healing [25,26]. The consequences of perioperative use of corticosteroids for glucose  
31 homeostasis need further evaluation, but so far the transitory increased hyperglycemic response has  
32 not been related to increased postoperative complications [27]. To reach definitive conclusion on  
33 the effects of glucocorticoids on the risk of post-operative infections, we are eagerly awaiting the  
34 results from the PADDI randomized clinical trial which is investigating the effects of low dose of

1  
2 1 dexamethasone on surgical site infection, and from the PACMAN trial whose primary outcome is a  
3  
4 2 composite outcome made of death and respiratory infections.

5 3 While perioperative glucocorticoids are widely administrated, the latest meta-analyses found  
6 4 that we are lacking power to detect differences in complications [11], and that no definitive  
7 5 conclusions can be made regarding clinically important benefice [7]. While the PADDI study is a  
8 6 non-inferiority trial designed to test the safety of dexamethasone in an unselected population, we  
9 7 have designed the PACMAN trial to investigate the potential benefits of the treatment in a surgical  
10 8 population with high risk of post-operative respiratory complications according to American and  
11 9 European recommendations [12,13]. Risk factors of pulmonary complications are either related to  
12 10 the surgery, or to the medical history of the patients. The external validity of the PACMAN results  
13 11 to unselected patients should be cautious in case of increased risks of the side-effects recorded as  
14 12 secondary outcomes.

15 13 We decided to not limit the PACMAN study to a specific type of surgery but to include all  
16 14 sort of surgery provided that the expected duration of the procedure exceeds 90 minutes. This  
17 15 strategy maximises recruitment rates and improves the generalisation of results. We acknowledge  
18 16 that the clinical risk factors of postoperative respiratory complications are inconstantly used in  
19 17 clinical practice, which can limit the applicability to the study results. However, preoperative  
20 18 optimization by nutritional support, respiratory physiotherapy or smoking cessation are  
21 19 recommended in patients presenting such risk factors [12]. The selection of high risk patients will  
22 20 result in a high incidence rate of the primary endpoint, which will result in a study of high clinical  
23 21 relevance and statistical power.

24 22 A wide range of doses of dexamethasone has been tested in surgical or critically ill patients :  
25 23 from low (4-8 mg/day [11,28]), to high doses (1-2 mg/kg [6,29]). The PACMAN trial is designed to  
26 24 investigate the effects of dexamethasone on the risk of major respiratory complications, notably  
27 25 pneumonia, and we thus decided to evaluate the effects of moderate doses as proposed in the latest  
28 26 recommendations and meta-analysis for the treatment with steroids of in patients with pneumonia  
29 27 [30,31]. The timing of administration is also critical to consider. We decided to initiate the study  
30 28 treatment during the post-operative inflammatory response, rather than before the surgery, because  
31 29 glucocorticoids induce the apoptosis of immune cells in absence of inflammation but are stimulate  
32 30 immunity when administrated during an inflammatory response [32,33].

33 31 We selected a composite outcome as the primary criteria. The use of mortality as a primary  
34 32 endpoint is never used in perioperative studies because the risk of death is low and the statistical  
35 33 power would be low. Respiratory complications are particularly frequent and serious after major  
36 34 surgery and we have recently proposed that glucocorticoid prevent the development of  
37 35 inflammation-related immunosuppression [8], and decrease the risk of pneumonia after severe

1 trauma [9,10]. Finally, mortality is not competitive with the primary criteria since the outcome all  
2 cause of death is included in the composite primary outcome.

3 This study has several limits. First, the primary outcome selected (composite of death, sepsis  
4 and pulmonary complications at 14 days) is biased towards the detection of benefit, as steroids are  
5 most likely to reduce pulmonary complications, but may have detrimental effects on other  
6 important outcomes e.g wound infection. This problem will be partially compensated for by the  
7 extensive secondary outcome measures being collected. Second, for the primary statistical analysis  
8 of the primary outcome, we will use a modified intention to treat analysis including patients  
9 fulfilling all the inclusion criteria and who have received at least one injection of the experimental  
10 treatment. This strategy has recently been used in randomized clinical trials evaluating peri-  
11 procedure treatments [17,34], because the time between the randomization, which is realized before  
12 the procedure, and the administration of the study treatment, which is realized during or after the  
13 procedure, expose the study to a high risk of included patients not receiving the allocated treatment  
14 (e.g. cancelled or delayed surgery or perioperative complications). In this setting, we strongly  
15 believe that the mITT is more accurate to the medical field than the ITT. However, the exclusion of  
16 patients in the mITT analysis can theoretically decrease the statistical power of the study. Thus, the  
17 DSMB will have access to the number of patients excluded from the mITT analysis, and if  
18 necessary the DMSB will have the responsibility to propose an increase of the number of patients to  
19 be included to guarantee the study power. Finally, the intention-to-treat analysis will be reported in  
20 the final version of the manuscript.

### 21 ***Trial status***

22 The trial has already achieved many milestones. The trial is sponsored by the French ministry  
23 of health (PHRCN 2016\_0442). Insurance for non-negligent harm has been provided by University  
24 Hospital of Nantes (France). Research ethics committee approval was obtained in September 2019  
25 (Comité de Protection des Personnes Sud Méditerranée V). The French Agency for the safety of  
26 medicines and medical devices authorized the study in September 2017 (#170245RS-21). The study  
27 is registered with the American registry of trials (<https://clinicaltrials.gov/> NCT03218553). The  
28 current emphasis is on opening the recruitment infra-structures, which is ongoing, and in  
29 developing the monitoring infrastructure. The study protocol was submitted to BMJ open before the  
30 first inclusion in the study. On December the 31<sup>st</sup> of 2018, 1050 patients have been included and  
31 randomized in the trial. The expected ending point of the study is February 2019.

32 The principle investigator (KA), the scientific expert (EF), the statistician (FF) and the study  
33 coordinator (AR) will write the first draft of the manuscript. All the co-authors (investigators who

1 had realized not less than 30 inclusions) will append and approve the final manuscript before the  
2 submission. No professional writer will be used.

3 In conclusion, the PACMAN trial is an investigator-initiated randomized controlled trial  
4 powered to test the hypothesis that the short-course of moderate doses of dexamethasone in patients  
5 undergoing major non-cardiac surgery decreases the risk of post-operative complications. The  
6 results of the PACMAN Trial will be relevant to the wide number of clinicians interested in  
7 perioperative medicine.

## 8 9 **ACKNOWLEDGMENT**

10 We thank patients and relatives, patient advisers, physicians, nursing staff and clinical research  
11 associates of the participating centres for their involvement in this important study.

## 12 13 **AUTHORS' CONTRIBUTIONS**

14 KA, EF, FF and AR conceived the study, coordinated its design and drafted the manuscript. AR and  
15 KA wrote the manuscript. EF and FF read and were involved in critical appraisal and revision of the  
16 manuscript. FF provided statistical expertise. All authors approved the final manuscript prior to  
17 submission.

## 18 19 **COMPETING INTERESTS**

20 No competing interests

## 21 22 **SOURCE OF FUNDING**

23 This study is an investigator-initiated trial, funded by a grant from the French Ministry of Health.  
24 Grant Number PHRCN 2016\_0442

## 25 26 **DATA SHARING STATEMENT**

27 The principal investigator will have access to the trial data set. Patient level data and/or full dataset  
28 and/or statistical code will be available on request to the corresponding author. Consent was not  
29 obtained, but the presented data are anonymised and risk of identification is low and the potential  
30 benefits of sharing these data outweigh the potential harms.



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51 **List of abbreviations**

52 33  
53 34 DSMB: Data and Safety Monitoring Board, ICU: Intensive Care Unit, ITT: Intention-to-treat.  
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57 36 **Competing interests**

58 37 The authors declare that they have no competing interests.  
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**Figure 1: Flow chart.**

For peer review only

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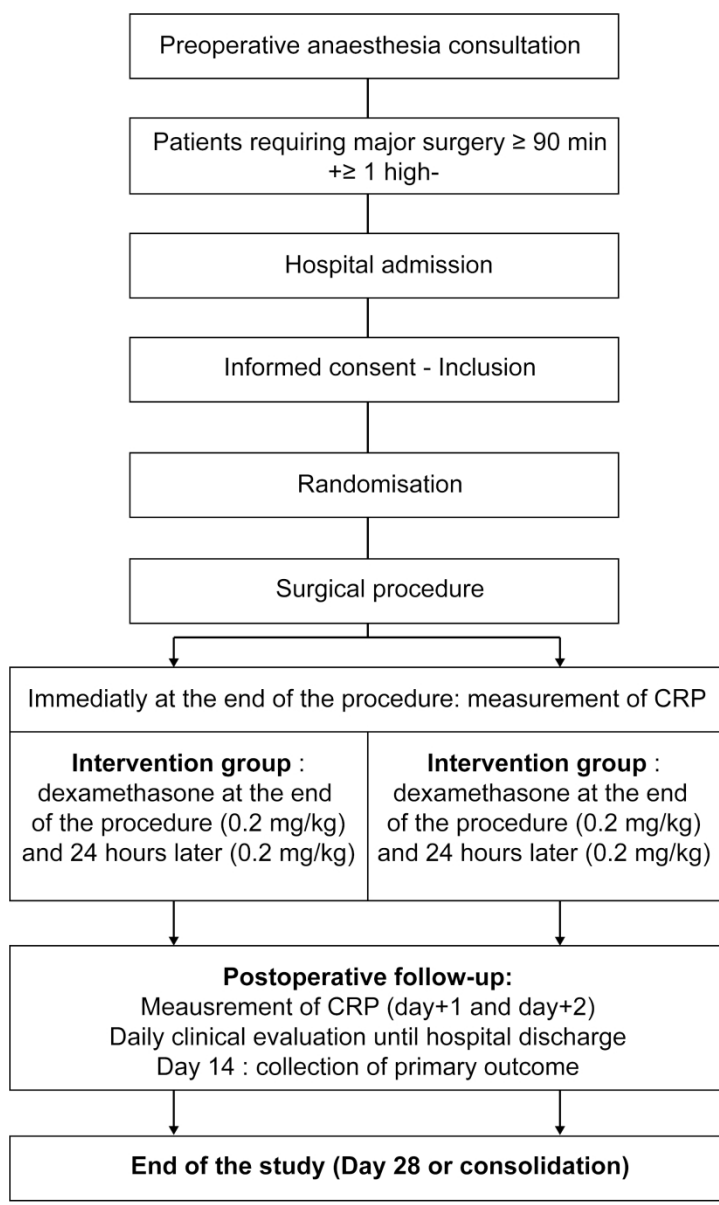


Figure 1

173x289mm (300 x 300 DPI)



Version n° 2  
Date : 16/05/2017

**Attestation of consent**

**The PACMAN trial protocol – Perioperative Administration of  
Corticotherapy on Morbidity and mortality After Non-cardiac major surgery:  
a randomized, multicentre, double blind, superiority study**

**Promotor : CHU Nantes**

**Réf : RC17\_0029 N° EudracT : 2017-000442-21**

I under-sign, Mister, Miss (first name and surname).....  
.....  
.....  
Date of birth: ...../...../.....

**Freely and voluntarily accept to participate to the PACMAN study, coordinated by Prof. Karim Asehounne and organized by CHU Nantes which acts as sponsor of the study.**

**Being said that :**

- A medical doctor has provided clear information and responded to all my questions, has informed me that I am free to remove my consent when ever.
- I confirm that I am not under trusteeship and I am covered by medicare insurance.
- I have received a written letter precisng the study aim, methodology, potential harms and benefice.
- I will have the opportunity to communicate during the study with my medical doctor, and receive informations on my health and outcomes.
- I am aware that I can withdraw my consent to participate when ever, without supporting any responsibility, but that I have to inform the doctor of my decision. The fact of discontinuing my participation to the study will alter neither my relationship with the doctors nor the quality of my cares.
- I accept that the investigators inform my generalist practitioner of my participation to this research:
 

Yes  No
- If I want so, at the end of the study trial, I can be informed of the final results of the study.
- My consent do not limit the responsibilities and the duties of the medical doctor and of the study promotor, and I conserve all my rights guaranteed by the Law.

- I am free to participate to other clinical research providing that the study protocol do not alter the risk of postoperative complications.
- I accept that the information recorded during this study will be electronically stored by the promotor. The right to access to my stored personal data (modified Law of January the 6<sup>th</sup> of 1978, art 39) can be exercise when ever by contacting the investigator. I thus can use my right of rectification and of opposition by informing the investigator who will be responsible to contact the study promotor. My personal data will be anonymized and will remained confidential.
- The information recorded during the study can be provided to other French or foreign searchers, providing they guarantee the same level of exigence for the protection of my personal data.
- I accept that the persons involved in the study have access to my medical files.
- I consent to the use of my medical data in the purpose of communications or publications, provided that they are anonymized.



Version n° 2  
Date : 16/05/2017

**Attestation of consent**

**The PACMAN trial protocol – Perioperative Administration of  
Corticotherapy on Morbidity and mortality After Non-cardiac major surgery:  
a randomized, multicentre, double blind, superiority study**

**Promotor : *CHU Nantes***

**Réf : RC17\_0029 N° EudracT : 2017-000442-21**

Patient signature:

Date :

Name and Surname :

Doctor who guarantees to have fully explain to the patient the aim, the design and the potential harms and benefits of the study research.

Doctor signature :

Date :

Name and Surname :

Signed in 2 copies : the original is to be conserved by the investigator, the copy is provided to the patient.

Doctor to contact in case of emergency : Pr Karim ASEHNOUNE

✉ Département d'Anesthésie et Réanimation, Hôtel Dieu – HME, CHU de Nantes , ☎ Tel : 0240083001 - Fax : 0240087382, Email : karim.asehnoune@chu-nantes.fr



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description	page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<b>1 (line 1)</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<b>3 (line 20) 7 (line 19) 15 (line 23)</b>
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	<b>7 (line 19)</b>
Funding	4	Sources and types of financial, material, and other support	<b>3 (line 22), 16 (line 18)</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<b>7 (line 14)</b>
	5b	Name and contact information for the trial sponsor	<b>15 (line 18)</b>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	<b>11 (line 14)</b>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	<b>From 11 (line 17) to 12 (line 12)</b>
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	<b>5 (lines 25-35)</b>
	6b	Explanation for choice of comparators	<b>6 (line 3)</b>



1				
2	Objectives	7	Specific objectives or hypotheses	<b>6 (line 2)</b>
3				<b>7 (line 3)</b>
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5	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	<b>7</b>
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11	<b>Methods: Participants, interventions, and outcomes</b>			
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13	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	<b>7 (lines 12-14)</b>
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19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	<b>7 (line 24) to 8 (line 11)</b>
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24	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<b>9 (lines 1-17)</b>
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29		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	<b>9 (lines 18-23)</b>
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35		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<b>8 (lines 31-33)</b>
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39		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<b>8 (lines 8-17)</b>
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42	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	<b>9 (line 24) to 10 (line 6)</b>
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51	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	<b>9 (lines 2-7) and 10 (lines 7-12) + Figure 1</b>
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2	Sample size	14	Estimated number of participants needed to achieve	<b>11 (lines 28-32)</b>
3			study objectives and how it was determined, including	
4			clinical and statistical assumptions supporting any	
5			sample size calculations	
6				
7	Recruitment	15	Strategies for achieving adequate participant enrolment	<b>7 (lines 21-23)</b>
8			to reach target sample size	
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### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

14				
15	Sequence	16a	Method of generating the allocation sequence (eg,	<b>8 (lines 26-29)</b>
16	generation		computer-generated random numbers), and list of any	
17			factors for stratification. To reduce predictability of a	
18			random sequence, details of any planned restriction (eg,	
19			blocking) should be provided in a separate document	
20			that is unavailable to those who enrol participants or	
21			assign interventions	
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24	Allocation	16b	Mechanism of implementing the allocation sequence	<b>8 (lines 26-29)</b>
25	concealment		(eg, central telephone; sequentially numbered, opaque,	
26	mechanism		sealed envelopes), describing any steps to conceal the	
27			sequence until interventions are assigned	
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30	Implementation	16c	Who will generate the allocation sequence, who will	<b>8 (line 27)</b>
31			enrol participants, and who will assign participants to	
32			interventions	
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34	Blinding	17a	Who will be blinded after assignment to interventions	<b>3 (line 7), 7 (line</b>
35	(masking)		(eg, trial participants, care providers, outcome	<b>13), 8 (lines 31-</b>
36			assessors, data analysts), and how	<b>33), 9 (lines 1-7)</b>
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39		17b	If blinded, circumstances under which unblinding is	<b>9 (lines 23-24)</b>
40			permissible, and procedure for revealing a participant's	
41			allocated intervention during the trial	
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### Methods: Data collection, management, and analysis

45	Data collection	18a	Plans for assessment and collection of outcome,	<b>10 (lines 15-18)</b>
46	methods		baseline, and other trial data, including any related	
47			processes to promote data quality (eg, duplicate	
48			measurements, training of assessors) and a description	
49			of study instruments (eg, questionnaires, laboratory	
50			tests) along with their reliability and validity, if known.	
51			Reference to where data collection forms can be found,	
52			if not in the protocol	
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56		18b	Plans to promote participant retention and complete	<b>10 (lines 19-25)</b>
57			follow-up, including list of any outcome data to be	
58			collected for participants who discontinue or deviate	
59			from intervention protocols	
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2	Data	19	Plans for data entry, coding, security, and storage,	<b>10 (lines 19-25)</b>
3	management		including any related processes to promote data quality	
4			(eg, double data entry; range checks for data values).	
5			Reference to where details of data management	
6			procedures can be found, if not in the protocol	
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9	Statistical	20a	Statistical methods for analysing primary and secondary	<b>11 (lines 18-29)</b>
10	methods		outcomes. Reference to where other details of the	<b>12 (lines 1-2)</b>
11			statistical analysis plan can be found, if not in the	
12			protocol	
13				
14		20b	Methods for any additional analyses (eg, subgroup and	<b>12 (lines 14-25)</b>
15			adjusted analyses)	
16				
17		20c	Definition of analysis population relating to protocol non-	<b>12 (lines 3-12)</b>
18			adherence (eg, as randomised analysis), and any	
19			statistical methods to handle missing data (eg, multiple	
20			imputation)	
21				
22				
23	<b>Methods: Monitoring</b>			
24				
25	Data monitoring	21a	Composition of data monitoring committee (DMC);	<b>10 (lines 31- to</b>
26			summary of its role and reporting structure; statement of	<b>11 (line 14)</b>
27			whether it is independent from the sponsor and	
28			competing interests; and reference to where further	
29			details about its charter can be found, if not in the	
30			protocol. Alternatively, an explanation of why a DMC is	
31			not needed	
32				
33				
34		21b	Description of any interim analyses and stopping	<b>11 (lines 13-14)</b>
35			guidelines, including who will have access to these	<b>12 (line 22)</b>
36			interim results and make the final decision to terminate	
37			the trial	
38				
39				
40	Harms	22	Plans for collecting, assessing, reporting, and managing	<b>10 (lines 29-31)</b>
41			solicited and spontaneously reported adverse events	
42			and other unintended effects of trial interventions or trial	
43			conduct	
44				
45				
46	Auditing	23	Frequency and procedures for auditing trial conduct, if	<b>10 (line 31) to</b>
47			any, and whether the process will be independent from	<b>11 (line 14)</b>
48			investigators and the sponsor	
49				
50				
51	<b>Ethics and dissemination</b>			
52				
53	Research ethics	24	Plans for seeking research ethics committee/institutional	<b>8 (lines 17-20)</b>
54	approval		review board (REC/IRB) approval	
55				
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2	Protocol	25	Plans for communicating important protocol	<b>12 (lines 25-26)</b>
3	amendments		modifications (eg, changes to eligibility criteria,	
4			outcomes, analyses) to relevant parties (eg,	
5			investigators, REC/IRBs, trial participants, trial registries,	
6			journals, regulators)	
7				
8				
9	Consent or assent	26a	Who will obtain informed consent or assent from	<b>8 (lines 12-23)</b>
10			potential trial participants or authorised surrogates, and	
11			how (see Item 32)	
12				
13		26b	Additional consent provisions for collection and use of	<b>Not applicable</b>
14			participant data and biological specimens in ancillary	
15			studies, if applicable	
16				
17	Confidentiality	27	How personal information about potential and enrolled	<b>8 (lines 12-23)</b>
18			participants will be collected, shared, and maintained in	
19			order to protect confidentiality before, during, and after	
20			the trial	
21				
22				
23	Declaration of	28	Financial and other competing interests for principal	<b>16 (line 20)</b>
24	interests		investigators for the overall trial and each study site	
25				
26	Access to data	29	Statement of who will have access to the final trial	<b>13 (lines 1-4)</b>
27			dataset, and disclosure of contractual agreements that	<b>16 (lines 26-30)</b>
28			limit such access for investigators	
29				
30				
31	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and	<b>Not applicable</b>
32	post-trial care		for compensation to those who suffer harm from trial	
33			participation	
34				
35	Dissemination	31a	Plans for investigators and sponsor to communicate trial	<b>3 (lines 18-20)</b>
36	policy		results to participants, healthcare professionals, the	<b>16 (lines 26-30)</b>
37			public, and other relevant groups (eg, via publication,	
38			reporting in results databases, or other data sharing	
39			arrangements), including any publication restrictions	
40				
41				
42		31b	Authorship eligibility guidelines and any intended use of	<b>15 (line 32) to</b>
43			professional writers	<b>16 (line 2)</b>
44				
45		31c	Plans, if any, for granting public access to the full	<b>Not applicable</b>
46			protocol, participant-level dataset, and statistical code	
47				
48				
49	<b>Appendices</b>			
50				
51	Informed consent	32	Model consent form and other related documentation	<b>Supplemental</b>
52	materials		given to participants and authorised surrogates	<b>File</b>
53				
54	Biological	33	Plans for collection, laboratory evaluation, and storage	<b>Not applicable</b>
55	specimens		of biological specimens for genetic or molecular analysis	
56			in the current trial and for future use in ancillary studies,	
57			if applicable	
58				
59				

1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
2 Explanation & Elaboration for important clarification on the items. Amendments to the  
3 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
4 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"  
5 license.  
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For peer review only