MORESS STUDY

Monitoring resuscitation in severe sepsis and septic shock
Investigators:
Xaime García Nogales
Guillem Gruartmoner de Vera
Caroline Sabatier
Ricard Ferrer Roca
Marcio Borges Sa
Rafael Zaragoza
Gumersindo González Díaz
Pilar Marco
Eduardo Palencia
Pedro Povoa
Cristina Mora
Gisela Gili

Steering Committee
Antoni Artigas Raventós
Claude Martin
Michael Pinsky
Ricard Ferrer
Ignacio Martín-Loeches

Coordination center: Área de Críticos, Hospital de Sabadell
Xaime García Nogales
Guillem Gruartmoner de Vera
Jaume Mesquida Febrer
Cristina Mora
Gisela Gili
Gemma Goma

**Statistical coordinator**
David Suárez

**Data Safety Monitoring Board (DSMB)**
Massimo Antonelli
Francisco Baigorri
David Suárez
Antonio Torres
1. BACKGROUND
2. OBJECTIVES
3. MATERIAL AND METHODS
   a. Study population
   b. Study design
      i. Randomization
      ii. Study protocol
      iii. Data collection and follow-up
   c. End of study criteria
   d. Study protocol algorithm
4. EFFICACY EVALUATION
   a. Primary objective
   b. Secondary objectives
   c. Quality control
5. DATA ANALYSIS
6. ETHICS
   a. Informed consent
   b. Ethical review board
   c. Data safety
   d. Data safety monitoring board
7. FUNDING AND INSURANCE
8. PUBLISHING POLICY
9. REFERENCES
10. WORKING PLAN
11. APPENDICES
The incidence of severe sepsis is increasing, with high mortality rates especially in those patients requiring admission to intensive care units (ICU). In Spain, the estimated accumulated incidence for the population was 25 cases of severe sepsis attended in ICUs per 100,000 inhabitants per year with mortality rates ranging from 33 to 48% (1, 2).

The imbalance between the supply and demand of oxygen in patients with septic shock leads to inadequate tissue perfusion. The early detection and correction of this imbalance is essential to improve the prognosis of these patients.

Fluid loading is one of the first steps in the management of septic patients to improve their hemodynamic status. According to Frank-Starling law, the expected effect of the volume expansion is the increase in end-diastolic right ventricle volume, left ventricle volume, stroke volume and consequently in cardiac output. This increase is also related to ventricular function, therefore a decrease in contractility decreases the slope between end-diastolic volume and systolic volume (3). In all studies that evaluated fluid responsiveness, only 50 % of the patients were fluid responders (4, 5).

Ideally, in the management of a hemodynamically unstable patient we should assess fluid responsiveness before starting volume expansion, in order to avoid excessive fluid that can result in interstitial edema and respiratory insufficiency (6). Static measures of preload like central venous pressure (CVP) or pulmonary arterial occlusion pressure (PAOP) have proved to be poor predictors of fluid responsiveness (7). More recently, dynamic parameters of fluid responsiveness (pulse pressure variation -PPV-, and stroke volume variation -SVV-) have been described on the basis of the variation of stroke volume induced by cyclic changes in mechanical ventilated patients, detecting preload dependence. These parameters have been found to be better predictors than static indicators (8, 9) and they have been successfully used in several resuscitation protocols (10-12).

In a septic population, Rivers et al. (13) showed a greater than 10% reduction in mortality using a protocol based on clinical signs (CVP, mean arterial pressure – MAP- and urine output) and a balance between delivery and consumption of oxygen using central venous oxygen saturation (ScvO2). In this protocol, fluid
loading was guided only by CVP, and vasopressors were started when CVP > 12 mmHg and MAP < 65 mmHg.

The aim of the present study is to compare two hemodynamic resuscitation protocols in septic patients that are commonly used in critical care units in Europe. One protocol uses static parameters (CVP, PAOP) to guide fluid administration, and the other one uses dynamic parameters (PPV, SVV). Both strategies use authorized sanitary monitoring devices (arterial and venous catheters) with the conformance mark in the European Economic area (CE mark).

The principal objective of this study is to determinate whether there is a decrease in mortality in septic patients resuscitated using a dynamic-parameter-based fluid administration protocol.
2. OBJECTIVES

Our hypothesis is that hemodynamic fluid resuscitation guided by dynamic parameters will improve outcome in patients with severe sepsis and septic shock, by limiting the deleterious effects of fluid overload.

To evaluate the efficacy of dynamic parameters versus static measures to guide fluid resuscitation we intend to detect a 10% relative reduction in mortality. In addition, we intend to observe an improvement on the length of resuscitation time, mechanical ventilation and vasopressor support-free days, ICU and hospital length of stay, organ failure and renal function.

Primary outcome: Mortality at 28 days

Secondary outcomes:

Length of resuscitation:
- Vasopressor use and fluid load between 0h to 6h
- Vasopressor use and fluid load between 7h to 72h

Ventilator-free days (from 1 to 28)
Vasopressor-free days (from 1 to 28)
Organ failure-free days (cardiovascular, CNS, renal, hepatic, coagulation abnormalities) (from 1 to 28)
ICU length of stay (days)
Hospital length of stay (days)
Renal function evolution (first 72h)
Fluid Balance (first 72h)
SOFA score evolution (first 72h)
Mortality at 3 months (ICU, hospital)

3. MATERIAL & METHODS

A. STUDY POPULATION

1. Inclusion Criteria (all criteria must be present at the moment of inclusion)
   Age > 18 years
   Clinical evidence of sepsis (microbiology confirmation, radiological or
direct view - pus in biological fluid or surgical direct view-).

≥ 2 SIRS criteria:

- Temperature < 36.0°C or > 38.0°C
- Heart rate > 90 bpm
- Respiratory rate > 20 rpm or PaCO₂ < 32 mmHg or need of mechanical ventilation.
- Leukocytes > 12.0 x10⁹/L or < 4.0 x10⁹/L

Hemodynamic insufficiency defined as (at least one of the following):

- Sustained systemic hypotension (systolic arterial pressure ≤ 90 mmHg or MAP < 65 mmHg) or a decrease in MAP of > 30 mm Hg in a hypertensive patient.
- Need for vasopressors.
- Tachycardia (HR > 110 bpm) or bradycardia (HR < 55 bpm)
- Acute onset of oliguria, defined as a decreased urine output < 0.5 ml/kg/hr for ≥ 2 hours
- Serum lactate > 2 mmol/l
- Peripheral cyanosis, mottled skin, prolonged capillary refill

Mechanical ventilation without any kind of inspiratory effort and Vt 7-10 mL/Kg, P plateau < 30 mmH₂O. Those patients with ARDS under mechanical ventilation will need to tolerate a tidal volume of at least 7 mL/Kg during 30 seconds while the plateau pressure remains < 30 mmH₂O.

Prior hemodynamic monitoring by arterial catheter.
Central venous catheter.

2. Exclusion criteria

Acute myocardial infarction < 7 days.
Pregnancy
Prior request of limited code status or expected life length lower than 3 months.
Sepsis or Shock (hemodynamic insufficiency criteria) > 12h
Aortic valvular disease
Inability to properly measure arterial pressure wave forms

3. Case definition
We will define the first episode of severe sepsis/septic shock requiring mechanical ventilation of a patient as a case. Thus, each patient can be included only once in the study.

B. STUDY DESIGN

- Prospective randomized multicenter study
40-60 international ICUs will participate. All ICUs are closed units with a critical care specialist on hand 24 hours per day, 365 days per year. The General Coordinator Center will be located at the Critical Care Center of the Hospital of Sabadell, Barcelona (Spain).
Each ICU from a geographical area is coordinated by an area coordinator and, at least, by one principal investigator in each center.
Early detection of patients with severe sepsis and septic shock should start in the emergency room, intensive care unit and even pre-hospital assistance. As soon as subjects are identified, the research team will be contacted, and the patients will be randomized within each center to one of the two groups. Inclusion in the study will start with the need for mechanical ventilation. Patients with clinical evidence of sepsis or shock longer than 12 hours of evolution will be excluded.

- General recommendations
In both groups, we strongly recommend controlling the focus of infection and early administration (<3h) of broad-spectrum antibiotics after cultures samples are obtained (17). In case of persistent hemodynamic insufficiency despite high levels of vasopressor support, it is recommended to give high dose corticosteroids (200 mg/24h)(14) and also to evaluate cardiac function by using echocardiography +/- continuous hemodynamic monitoring device. Ensure calibration of arterial pulse contour system each 6-12h.
We recommend the use of crystalloids as the initial choice for fluid replacement in the first steps of the hemodynamic resuscitation. The use of albumin is
suggested when the patient requires high doses of fluids. We do not recommend the use of hydroxyethyl starches.

1. Randomization
When a patient with severe sepsis or septic shock is identified, the local research team will be contacted, and they will proceed to the randomization of the patient to one of the two study groups. This randomization will be performed following a 4 block design (2x2). The 2 study groups are defined as: “standard” and “intervention”.

2. Study protocol (see flow algorithm)
The “standard” group (Early Goal-Directed Therapy) follows a common resuscitation protocol based on Surviving Sepsis Campaign recommendations (14): Fluid loading in patients with hypotension or elevated lactates until normalization of MAP (> 65mmHg) or CVP > 12mmHg. If CVP reaches > 12 mmHg and MAP remains < 65mmHg, noradrenaline (norepinephrine) should be started to reach MAP > 65mmHg. Once MAP is restored, if hypoperfusion signs persist (elevated lactate or urine output < 0.5mL/Kg/h), ScvO2/SvO2 must be measured. In order to reach a ScvO2 ≥70% or SVO2 ≥65%, consider giving blood transfusion if hemoglobin level (Hb) ≤ 7g/dL, and also consider dobutamine (initial dose 2.5 µg/kg/min, increased by 2.5 µg/kg/min every 30 min up to a maximum dose of 30 µg/kg/min, or presence of arrhythmia, or heart rate > 110bpm). At that point, if hypoperfusion signs remain present, consider restart protocol from the beginning.

The “intervention” group (Dynamic Guided Therapy) follows a resuscitation protocol based on dynamic-parameters-guided fluid management.

- In preload-responsive patients defined by the following dynamic parameters:
  a. PPV >12% (PPV: Pulse pressure variation) in patients with an arterial line (central monitorization, Phillips Intellivue, CE-mark;
FloTrac®/Vigileo® - Edwards Lifesciences, Irvine CA; PiCCO ® - PULSION Medical Systems AG, Germany, CE 0124-; LiDCO ® - LiDCO Ltd., Cambridge, UK who are fully adapted to mechanical ventilation* and with sinus rhythm.

PPV = \( \frac{(PP_{\text{max}}-PP_{\text{min}})}{\left(\frac{PP_{\text{max}}+PP_{\text{min}}}{2}\right)} \times 100 \) (during 5 respiratory cycles)

b. SVV > 12% (SVV: stroke volume variation) in patients with an arterial pulse contour system (PiCCO ® - PULSION Medical Systems AG, Germany, CE 0124-; LiDCO ® - LiDCO Ltd., Cambridge, UK) who are fully adapted to mechanical ventilation* and with sinus rhythm (15). Pulse-pressure contour systems must be calibrated each 6-12h.

c. Increase ≥ 5% in CO after an End-expiratory occlusion test (EEOT), as a dynamic parameter for using in patients with atrial fibrillation. Thus, we propose 2 scenarios in which End-Expiratory Occlusion test can be used in the study:

1.- Patients without any other exclusion criteria for the study than atrial fibrillation, who already have an automatic cardiac output measurement system (PiCCO, Swan-Ganz catheter...) at the moment of inclusion in the MORESS study. Once enrolled in the MORESS study if the patient is randomized into the “dynamic” branch, the End-Expiratory Occlusion test will be used instead PPV or SVV.

2.- Patients without any exclusion criteria already included in the MORESS study who develop atrial fibrillation during the hemodynamic resuscitation and already have an automatic cardiac output measurement system in place. In this case, if the patient was randomized to the “dynamic” branch, the End- Expiratory Occlusion test will be used instead PPV or SVV from now on.

End-Expiratory Occlusion test will be performed as follows:

- Patients must be perfectly adapted to mechanical ventilation, without...
any respiratory effort, in any controlled or assisted/controlled ventilatory mode.

- The level of positive end-expiratory pressure under which the end-expiratory occlusion will be made, will be the one set by the medical team in charge of the patient, without modifications for the study measurements.

- An end-expiratory occlusion of 15 seconds will be performed by doing an expiratory pause using the automatic preset of the ventilator to measure the total PEEP.

- Patients will be considered as “responders” to fluid administration when an increase of CO ≥ 5% is observed during the last 5 seconds of the end-expiratory occlusion; and as “non-responders” when the increase in CO is < 5%.

- Those patients in which the end-expiratory occlusion is interrupted by triggering of the ventilator by patient’s inspiratory effort will be excluded from the study due to the impossibility to assess fluid responsiveness.

*A tidal volume (Vt) ≥ 7-10cc/kg in mechanically ventilated (in a controlled mode – control volume or control pressure) and well-adapted patients without any inspiratory effort should be guaranteed.

Fluid loading must be performed with crystalloids (30 mL/Kg) or colloids (5ml/Kg) every 30 minutes until PPV or SVV < 12%; increase in CO after EEOT < 5% , while hypoperfusion signs are present. If hypotension (MAP < 65mmHg) persists despite negative fluid responsiveness parameters (PPV, SVV < 12%; increase in CO after EEOT < 5%), norepinephrine (NE) must be started to reach MAP > 65mmHg. Once MAP is restored, if hypoperfusion signs persist (elevated lactate or
urine output < 0.5mL/Kg/h) with negative fluid responsiveness parameters (VPP, VVS < 12%; increase in CO after EEOT < 5%). ScvO2/SvO2 must be measured. In order to reach a ScvO2 ≥70% or SVO2 ≥65%, consider giving blood transfusion if hemoglobin level (Hb) ≤ 7g/dL, and also consider dobutamine (initial dose 2.5 µg/kg/min, increased by 2.5 µg/kg/min every 30 min up to a maximum dose of 30 µg/kg/min, presence of arrhythmia, or heart rate > 110bpm). At that point, if hypoperfusion signs remain present, consider restart protocol from the beginning.

- In non-preload responsive patients (defined as PPV or SVV < 12%; increase in CO after EEOT < 5%) NE will be used to reach MAP > 65mmHg. Once MAP is restored, if hypoperfusion signs persist, ScvO2/SvO2 must be measured. In order to reach ScvO2 ≥70% or SVO2 ≥65%, consider giving blood transfusion if hemoglobin (Hb) ≤ 7g/dL, and also consider dobutamine (initial dose 2.5 µg/kg/min, increased by 2.5 µg/kg/min every 30 min up to a maximum dose of 30 µg/kg/min, presence of arrhythmia, or heart rate > 110bpm). At that point, if hypoperfusion signs remain present, consider restart protocol from the beginning.

Adhesion to the therapeutic arm control
During the resuscitation time included in the first 72 hours every volume load must be justified in both study arms with the purpose of avoiding overruling between groups. After the first 24 hours, the rationale of volume load will be not recorded.

3. Data collection and Follow up
At the moment of patient inclusion the follow variables will be recorded: age, sex, height and weight, comorbidities as well as the etiology of sepsis. The onset of sepsis (time zero: sepsis diagnosis) and the time of first fluid challenge (resuscitation) will be also recorded. Clinical, physiological and analytical variables (lactate level, SvO2/SvcO2, creatinine level, mean BP, HR, etc) will be recorded at the moment of inclusion as well as the fluid balance and the vasopressor drug dose prior to study inclusion.
During guided resuscitation period we will record at 6h, 12h, 24h and 48h the same clinical physiological and analytical variables recorded at study inclusion as well as the fluid balance in each time interval, vasopressor drugs dose and severity score (daily SOFA during the first 3 days, APACHE II the first 24h). Those variables will be followed until the end of resuscitation or a maximum of 72h. Daily, we will evaluate SOFA score, mechanical ventilation parameters, renal substitution and function, fluid balance and corticosteroid use.

Likewise, we will record the time of blood cultures, and also the time of initiation of broad-spectrum antibiotics, including their adequacy according to antibiogram.

After the first 72h, we will register if the patient has new septic episodes but these episodes will not be included in the study and the resuscitation will be made according to the medical criteria.

Prognosis variables will be also recorded: mechanical ventilation days, vasopressor days, hospital stay and mortality at 28 days and 3 months.

C. END OF STUDY CRITERIA

Once hemodynamic stability is maintained over > 12h the protocol will be stopped. The weaning from vasoactive drugs will be progressive: once the resuscitation criteria have been achieved the noradrenaline (norepinephrine) dose will be reduced (0.02-0.04 mcg/Kg/h every 10 minutes) if MAP remains > 65 mmHg. Dobutamine dose will also be reduced in 25% every hour maintaining resuscitation endpoints on target. In case of catecholamine reinstitution after 6h of stability, the resuscitation will be under medical criteria.

As a general recommendation for both study groups, once the protocol is stopped it is important to implement a conservative fluid management by trying to achieve even/negative fluid balance (or at least avoiding positive fluid balance) (19).
EFFICACY EVALUATION

- Primary objective:

  A. Twenty-eight-day mortality. Survival time will be assessed. Patients will be classified as either “alive at study day 28” or, if dead, “dead at study day 28”. Differences between the two strategies in mortality rates will be evaluated using the assumption of asymptotic normality. Estimates of relative risks and odds ratios and the corresponding 95% interval of confidence intervals will be presented.

- Secondary objectives: The following measures will be used to assess the secondary efficacy endpoints.

  A. Length and dose of resuscitation.
     - Duration of the resuscitation period (from first fluid expansion until correction of hypoperfusion signs or first 72 hours).
     - Volume loading dose and type of fluid.
     - Vasopressor and inotropic dose.
  
  B. Mechanical ventilation-free days. Days free of mechanical ventilation over 28 days.
  
  C. Vasopressor-free days. Days free of vasoactive support over 28 days.
  
  D. Organ failure-free days (cardiovascular, CNS, renal, hepatic, coagulation abnormalities). Days free of any organ failure over 28 days.
  
  E. ICU length of stay. Days of admission in ICU.
  
  F. Hospital length of stay. Days of hospital admission.
  
  G. SOFA score evolution. SOFA score will be performed every day for the first 3 days.
  
  H. Renal function evolution. Creatinine clearance will be calculated every day for the first 3 days (Cockroft-Gault formula).
  
  I. Mortality at 3 months (ICU, hospital).

- Quality control

To ensure patient’s safety and the availability of exact, complete and reliable data, education material will be released to every center taking part in the study. There will be a permanent way to contact the Coordinator Center via email, fax and phone.
All the data will be collected in an electronic database available through the EDUSEPSIS website with restricted access.

5% of global data will be revised to detect potential errors. Most of the monitors used to obtain PPV/SVV have an automatized algorithm to calculate PPV/SVV which ensures the correct value and minimize the possibility of errors. In those cases when PPV/SVV will be obtained manually, 10% of the registers used for the calculation will be revised by the Coordinator Center.

The IP will keep the curve registers, lab determinations, clinical notes and every medical document of the study. Those documents will be available to the Sanitary Agencies and Ethical Committees if required.

5. DATA ANALYSIS

We calculate a sample size of 952 patients necessary to detect a 10 % relative reduction in mortality- estimated at 47% (1, 2)- with a power of 90% and a type I error of 5%. One interim analysis is planned for this study after 400 patients have been included. The analysis will be conducted by an external and independent Data Safety Monitoring Board (see Ethics chapter for details).

<table>
<thead>
<tr>
<th>Control Mortality</th>
<th>Protocol Mortality</th>
<th>Decrease mortality</th>
<th>N 90% power</th>
<th>N 80% power</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>40%</td>
<td>10%</td>
<td>1036</td>
<td>776</td>
</tr>
<tr>
<td></td>
<td>35%</td>
<td>15%</td>
<td>454</td>
<td>340</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>20%</td>
<td>248</td>
<td>186</td>
</tr>
<tr>
<td>40%</td>
<td>35%</td>
<td>5%</td>
<td>3938</td>
<td>2942</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>10%</td>
<td>952</td>
<td>712</td>
</tr>
<tr>
<td></td>
<td>25%</td>
<td>15%</td>
<td>406</td>
<td>304</td>
</tr>
<tr>
<td>30%</td>
<td>25%</td>
<td>5%</td>
<td>3348</td>
<td>2502</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>10%</td>
<td>784</td>
<td>588</td>
</tr>
</tbody>
</table>

Stop for efficacy: CumAlpha1= 0.00305 (O’Brien-Flemming) CI for Z (-2.9626; 2.9626); CumAlpha2= 0.05 (O’Brien-Flemming) CI for Z (-1.6986; 1.6986)

Stop for futility: CumAlpha1= 0.03101 (Pocock) CI for Z (-2.1570; 2.1570); CumAlpha2= 0.05 (Pocock) CI for Z (-2.2009; 2.2009)
6. ETHICS

a) Informed consent
The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have about the study. The informed consent will be used to explain the risks and benefits of the study participation to the patient in simple terms before the patient is entered into the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative including signatures and date on the informed consent document prior to the performance of any protocol procedures.

Each national coordinator will ensure that the consent requirements of their relevant ethics board or committee are met, especially with respect to recruitment of patients who are incapable of consent at enrolment by virtue of their illness.

b) Ethical Review Board
This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. The investigator, head of the medical institution, will promptly submit the protocol to applicable ethical review boards.

This study has been registered in clinicaltrials.gov with the identifier NCT01747057.

c) Data safety
An identification code assigned by the investigator to each patient will be used instead patient’s name to protect patient’s identity when reporting trial-related data.

d) Data Safety Monitoring Board (DSMB)
The main mandate of the DSMB is to review interim trial data to ensure continuing safety of trial subjects as well as the continuing validity and scientific
merit of the trial. DSMB will be responsible of notifying the steering committee if the on-going ethical validity of the trial is threatened by emerging safety concerns, loss of clinical equipoise, or evidence of futility. DSMB is not responsible for the design, approval, conduct, analysis or final publication. However, DSMB will review the design and analysis plans of the trial to ensure that all members of the DSMB are comfortable with the trial’s ethical validity and feasibility from the onset. First meeting will be at 400 patients enrolled (50% of the study sample) for analysis and interim control. Investigators will not receive any information about this interim analysis if there is no indication for stopping due to efficacy or futility.

Following most of the guidelines, DSMB members should have no serious conflicts of interest – academic, financial, or otherwise- with the trial’s outcome and steering committee. According to this, the proposed DSMB members are:

- Massimo Antonielli
- Francisco Baigorri
- David Suárez
- Antoni Torres

7. FUNDINGS AND INSURANCE

At the present time, no financial contribution supports this trial. Pharmaceutical industry only supports logistical aspects but do not participate in any decision. We will apply for different national grants for research. Insurance will not be necessary according to Spanish law “Real Decreto 223/2004” that says no insurance is needed when using sanitary products with the purpose they were approved for and when the IRB considers the study interventions with a risk equal or lower than usual medical practice.

8. PUBLISHING POLICY

Access to electronic register will be restricted to each investigator and only for data from his own center. Steering committee and investigators from the Coordinator Center have access to general data until the first publication. Subsequently, every participating investigator could access to general data by a formal proposal to steering committee. Statistical support will be provided. In every publication, all participating investigators and centers will be referenced.
9. WORKING PLAN

Study design
Approval from different centers (director and investigator, ethics committee)
Preparation of documents (web, spreadsheet program)
Recruitment 6 months
Data analysis
- Intermediate analysis (400 patients, external committee)
- Quality assurance (5% patients)
Publication

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>jan-apr</td>
<td>may-apr</td>
<td>jan-feb</td>
<td>mar-jun</td>
</tr>
<tr>
<td>Study design</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approval Ethics committee</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitment</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
REFERENCES