Intensive Care Med (2011) 37:1384–1385
DOI 10.1007/s00134-011-2272-7

V. Marco Ranieri
B. Taylor Thompson
Simon Finfer
Philip S. Barie
Jean-François Dhainaut
Ivor S. Douglas
Bengt Gårdlund
John C. Marshall
Andrew Rhodes
The PROWESS-SHOCK Academic Steering Committee

Unblinding plan of PROWESS-SHOCK trial

Received: 23 April 2011
Accepted: 17 May 2011
Published online: 21 June 2011

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-011-2272-7) contains supplementary material, which is available to authorized users.

Dear Editor,
On November 15, 2010 the independent Data Monitoring Committee completed the second protocol-specified interim analysis and recommended that the PROWESS-SHOCK trial continue to completion. We estimate that the study remains on track for enrollment of the last patient during early summer 2011. As outlined in our previous publications in *Intensive Care Medicine*, the Academic Steering Committee (ASC) seeks to conduct the trial with maximum transparency [1, 2]. Accordingly, we now wish to inform readers of our plans for study completion and unblinding.

The PROWESS-SHOCK trial is being conducted at the request of the European Medicines Agency (EMEA) with an agreed timeline for the Sponsor (Eli Lilly) to submit the results of the primary outcome, all-cause mortality at 28 days. Important secondary endpoints include 90- and 180-day mortality. As a result of the requirements of the EMEA, the database must be locked and analyzed once the primary outcome data are available, with the valuable longer-term outcomes at 90 and 180 days locked and analyzed when they become available. Prior to data lock, the Contract Research Organization (Parexel) will check the data for consistency with input on clinical queries from the Sponsor and the ASC. Clean data will be then provided to the Academic Research Organization (Duke Clinical Research Institute) that will independently program all analysis datasets. Furthermore, if the study is clearly positive (or negative) based on the primary outcome, a long delay in knowing and releasing this information could raise ethical concerns. Accordingly, we have developed a three-stage plan for database lock (for 28-, 90-, and 180-day locks) and an unblinding plan that appears as an online supplement to this letter. This plan integrates and updates the section of the Statistical Analysis Plan (SAP) [2] that deals with the unblinding plan outlined for the planned interim analyses. Both the ASC and the Sponsor agree that this final plan does not change the principal features of either the SAP or the protocol, and thus does not qualify as an amendment as defined by the protocol [1].

The new plan reiterates that no member of the Lilly clinical team or the ASC will be unblinded to the clinical data before all patients have completed follow-up for the primary endpoint (mortality at 28 days post-randomization) and the data have been locked. Once the 28-day data have been locked, we have outlined in detail our procedures to ensure that individuals who are unblinded to 28-day patient level data will have no further active role in the collection or programming of outstanding 90- and 180-day clinical data. The ASC strongly prefers to include the 90-day outcomes in the primary manuscript to describe trial results more completely. Accordingly, we have made these clarifications to the SAP to ensure the integrity of the 90- and 180-day outcomes.

The members of the ASC again thank all our study subjects and their families, as well as our co-investigators and research coordinators, for their participation and hard work on this important study.

Respectfully yours,

The PROWESS-SHOCK Academic Steering Committee

References

1. Finfer S, Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Gårdlund B, Marshall JC, Rhodes A (2008) Design, conduct, analysis and reporting of a multi-national placebo-controlled trial of activated protein C for persistent septic shock. Intensive Care Med 34:1935–1947
2. Thompson BT, Ranieri VM, Finfer S, Barie PS, Dhainaut JF, Douglas IS, Gårdlund B, Marshall JC, Rhodes A, PROWESS SHOCK Steering Committee (2010) Statistical analysis plan of PROWESS SHOCK study. Intensive Care Med 36:1972–1973

V. M. Ranieri (✉)
Ospedale S. Giovanni Battista-Molinette, Università di Torino, Torino, Italy
e-mail: marco.ranieri@unito.it

B. T. Thompson
Pulmonary and Critical Care Unit, Bullfinch Building, Room 148, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

S. Finfer
The George Institute for International Health, University of Sydney, Sydney, Australia

P. S. Barie
Department of Surgery, P713A, Weill Cornell Medical College, 525 East 68 St, New York, NY 10065, USA

J.-F. Dhainaut
Cochin Port Royal Hospital-Paris Descartes University, Paris, France

I. S. Douglas
Denver Health and University of Colorado, Denver, USA

B. Gårdlund
Department of Infectious Diseases, Karolinska University Hospital, 14186 Stockholm, Sweden

J. C. Marshall
Departments of Surgery and Critical Care Medicine, St Michael's Hospital, 4th Floor Bond Wing, Rm. 4-007, 30 Bond Street, Toronto, ON M5B 1W8, Canada

A. Rhodes
Consultant in Intensive Care Medicine and Anaesthesia, St George's Hospital, London SW17 0QT, UK