### Anesthesiology

Continual Reassessment Method for Dose-finding Studies: The type and distribution of prior for power model.

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28 November 2013

To:
Editor-In-Chief
James C. Eisenach, M.D.
Editor-in-Chief, Anesthesiology
Department of Anesthesiology
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I am submitting the enclosed material for possible publication in Anesthesiology. It has not been submitted for publication nor has it been published in whole or in part elsewhere. I have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to Anesthesiology. I acknowledge that I have read the Instructions for Authors and agree with its contents. I acknowledge that if the enclosed manuscript is part of a larger whole or if the primary analysis has been previously published, this must be explicitly stated in the manuscript and the previous publication cited.

I wish to bring to kind attention that I communicated on 2nd October 2013 through email with statistical expert of the study i.e. Sarah Zohar, MD requesting him to forward the R algorithm that was used for analysis. I did not any response till date. I wanted clarity on the issues that are raised in my letter that I am submitting for consideration for publication in Anesthesiology.

Conflicts of interest, sources of financial support, corporate involvement, patent holdings, etc. Copyright transfer and the signatures of all authors will be requested prior to publication of accepted manuscripts.

Signature : Srinivas Mantha
Date 28 November 2013

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*Cover Letter*
Conflicts of Interest

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   No

(2) Does any author or participant have any financial interest in the subject matter, materials or equipment discussed or in competing materials?
   No

(3) Has the laboratory in which the research was performed been funded by, or has any participant in the planning, conduct, or reporting of the research been funded by or have financial interests in any source with a real or potential interest in the subject matter, materials, equipment or devices discussed or in any competing product or subject?
   No

(4) Has the laboratory in which the work was performed or any of the authors or participants been funded by any Foundation or other non-governmental source that has received funding from any organization with a real or potential interest in the subject matter, materials, equipment or devices discussed, or in any competing product or subject?
   No

If you answer yes to any of the above items, please provide details, including the name(s) of the supported authors as well as the corresponding names of the persons or organizations involved.
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2 October 2013
to sarah.zohar
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2 oct 2013
From:
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Dear Dr. Zohar:
I read with interest your recent article

Can you please forward me the R function used specifically for the study.

Thanks
Srinivas Mantha, MD
To The Editor

I read with interest the recent article by Kant et al. 1, in which the authors used continual reassessment method (CRM) to determine dose-finding studies in regional anesthesia. Specifically, the methodology with Bayesian paradigm was used to estimate ED95 dose for 0.5% bupivacaine for ultrasound-guided supraclavicular block. The idea is novel and may be applied for relevant studies in our speciality in the future. Although, CRM was originally designed for dose-finding phase I trials in cancer drug research several versions and modifications of CRM with different models have evolved over the past two decades. Kant et al. 1 employed a modified version using a Bayesian approach with one parameter power model $p_{\theta}^\theta$

In any Bayesian approach, the type and distribution of prior is of paramount importance, and they are not clear from the methods described in the study. In the present context, the parameter of interest is $\theta$. Two types of distributions i.e. gamma and lognormal are applicable as negative values for $\theta$ are not compatible with the power model. The exact R algorithm was neither described nor referred to a web source for readers to get an idea about the required information about distribution of the prior. By the statement in methods “…where $\theta$ is the model parameter to be estimated, considering as a random variable with exponential prior ….” Kant et al appeared to use lognormal prior. 3 However, when Kant et al data were examined with a recently (September 2013) published R package “bcrm”, 2, the results obtained by the authors could be reproduced when gamma prior for $\theta$ with shape=1 and scale =1 were used for defining prior distribution of $\theta$, and not with the recommended lognormal prior (mean=0, SD=2). 3 Hence the output and the entire sequence dose allocation in cohorts would be different.
The package is freely available on Comprehensive R Archive Network (CRAN) [http://cran.r-project.org/](http://cran.r-project.org/) and can be accessed through Task Views → Clinical Trials → bcrm.

The documentation for the package is available at [http://cran.r-project.org/web/packages/bcrm/bcrm.pdf](http://cran.r-project.org/web/packages/bcrm/bcrm.pdf)

The bcrm function in R is invoked by typing `bcrm()` with arguments presented in the parenthesis. As with other R functions, the associated code for the function can be viewed by typing `bcrm` without parenthesis.

One more area of concern in Kant et al study is the nomenclature used when describing the scheme of CRM in Figure 1. Although the current study is related to determining ED$_{95}$ dose in *post-marketing* phase, the nomenclature appears to be that related to dose-finding studies of phase 1. For example, the statements in the figure used the phrase “posterior toxicity probability”. The nomenclature in this situation should have replaced the word “toxicity” with “failure”. As described in methods, the study proceeds to compute an updated probability of failure at each dose level and the failure probability closest to the 0.05 target is chosen as the current ED$_{95}$, and given to the next cohort.

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References

the ED95 Dose for 0.5% Bupivacaine for Ultrasound-guided Supraclavicular Block.

