**Model-based Dose Escalation Designs in R with crmPack**

**Responses to Reviewers**

Reviewer comments are copied in italic font below, and responses are in normal font.

**Reviewer 1:**

*This paper describes the crmPack package for Model-based Dose Escalation. It is well-written, it is relevant, and it is novel. I was not previously aware of it, but I have begun using it after receiving the draft.*

Thank you for your positive feedback! We are pleased that you have started using crmPack.

*I have only a few, minor corrections:*

*- Please rewrite the two sentences in the abstract beginning with "By providing a simple..." They are wordy and confusing. I'm having trouble parsing them.*

We have rewritten the two sentences as follows:   
“The R-package crmPack provides a simple and unified object-oriented framework for model-based dose escalation designs. This enables the standard use of such designs, while being able to flexibly adapt and extend them. The framework comprises classes and methods for the data structure including the dose grid, statistical models including prior specification, rules for maximum increments, next best dose, and adaptive stopping and cohort sizes.”

*- Please rewrite the first sentence in the introduction. It is also long and confusing.*

We reworded the beginning of the introduction as follows:   
“Phase I trials that are testing new investigational agents in humans for the first time escalate from low to high doses in a sequential fashion. This dose escalation design is necessary in order to reduce the risk of too high and therefore too toxic doses for the probands. These can either be…”

*- Page 8. The description in "Adaptive stopping of the trial" is confusing. The trial stops as soon as myStopping1 is true or either myStopping2 or myStopping3 is reached. The code is clearer than the description.*

We would like to apologize for the confusing description. Please note that the code specifies that the trial stops as soon as “myStopping1” is true or both “myStopping2” and “myStopping3” are true. In order to clarify this, we reworded the description as follows:   
“…, or if we have sufficient precision for the MTD estimate. We can specify the latter condition as follows: The probability that the next dose is in the target toxicity range is above 50%, and at least 9 patients were already dosed within +/- 20% range of .”

**Reviewer 2:**

*This paper introduces a new R-package, crmPack, for dose-finding clinical trials. It allows some*

*flexibility for the planning of the clinical study and it can be easily extend to new designs thanks to*

*the S4 classes and methods.*

*The structure of the article is particularly clear and organized. Each section is well written and well*

*developed, including a diversity of interesting figures. The R package Implements model-based and*

*algorithm-based designs, ranging from ‘3+3’ to modified CRM based on dose limiting toxicity*

*endpoints to dual-endpoint designs taking into account a biomarker/efficacy outcome.*

Thank you for your review and this positive feedback!

*Major comments:*

* *It seems that the proposed CRM design is a modified version of the CRM. However this is not clearly written and it causes confusion, since placebo groups cannot be used in the classic version of the CRM (for example as implemented in the dfcrm package). The package name is also misleading.*The R-package crmPack is not related to a specific design, in the sense that it already contains multiple dose-toxicity models, further allowing to easily introduce new ones (e.g. in Section 3.3 we showed how to implement the original version of CRM by O'Quigley et al., 1990). Similarly the possibility to include placebo groups in the design is just an extension which does not prevent the user from considering a design without placebo groups. To make this clearer we emphasized this in the abstract as follows:  
  “In addition to multiple modified classic continual reassessment method (CRM) and escalation with overdose control (EWOC) designs with possibly advanced prior specifications (e.g. minimal informative and mixture priors), crmPack currently…”  
  Moreover, in the introduction section we explain now:  
  “While the package's name pays tribute to the original CRM as the first model-based dose escalation design, the package's functionality differs from the above existing implementations in three fundamental ways.”
* *The new R-package is proposing the implementation of existing methods (3+3 design, CRM, etc), similar to the already existing softwares (e.g. crm in Stata, dfcrm and bcrm in R, etc). The crmPack has no big novel statistical designs (except of the dual-endpoint designs and the placebo group for healthy studies) as we would expect to see in a new R-package for dose escalation designs. For example, all the mentioned commercial packages (ESCALATE in East, df in ADDPLAN and FACTS) can offer extensions for the 3+3 design and/or implement various versions of the CRM. Similarly, the Stata package crm and the R packages dfcrm and bcrm can implement CRM models and offer a wide range of different dose escalation designs. Why would the user need to learn/use this new R-package? What is the advantage in using this package and not the other ones? Why this version cannot be an extension of dfcrm package?*The obvious limitation with using commercial *closed-source* software is the impossibility of quickly self-implementing new features (without heavily relying on timelines and willingness of the proprietary company) when specific needs may arise on a given project. In our experience this is a common challenge.   
  We believe that the main advantage of crmPack over existing R implementations is its flexible framework based on the S4 classes and methods system, which easily allows the user to extend the current options, tailoring the package to user’s specific needs. For example in Section 3.3 we showed how to define a new dose-toxicity model, which would then automatically benefit from all the *methods* which are already available for an object of the “Model” class (e.g. would be straightforward to calculate the operating characteristics of the new model, use it with or without placebo or introduce it as the safety component of a dual-endpoint design).   
  While “dfcrm” uses the older S3 classes and methods system, it is not built in a modular way. For example, the main function “crm” has a parameter “model” which allows the user to choose either the “empiric” or the one-parameter “logistic” model. No other model options are foreseen. Hence, in order to extend “dfcrm” with a two-parameter logistic model, the user would need to rewrite the “crm” function of “dfcrm” accordingly. However, the user would also need to rewrite the associated functions “cohere” for checking coherence of the design, “getprior” for calibrating the prior DLT rates, “crmsense” to evaluate the model sensitivity, and the helper functions “print.mtd” and “print.dxcrm”.  
  We added the following sentence to the summary section:   
  “Therefore, crmPack allows the user to easily extend the package by keeping modifications local and limited to what needs to be changed, which in our experience has been a key success factor for the wider use of model-based dose escalation designs.”   
  We hope that others may also benefit from this framework in a similar way now.
* *There is no novelty in the structure or on the flexibility of the package, except the class structure, which is still similar to the other packages, in order to intrigue the user to use this new package instead of using the already existing packages.*Please see the above answer.
* *Since the crmPack is using a modified CRM and the article is already mentioning some existing solutions, it could also include other packages that are using modified CRM dose finding designs. For example the R-package ordcrm using likelihood-Based Continual Reassessment Method (CRM) dose finding designs has not been mentioned. Another Rpackage, dfpk, implements bayesian dose finding designs (including a modified model of CRM design) using pharmacokinetics for phase I clinical trials. Other existing packages should be mentioned, besides the classical ones (dfcrm, bcrm, etc.), in order to provide the reader with a better overview of what already exists and what is missing in the programming domain of these designs.*

Thank you for this suggestion, we included the following part in the introduction accordingly:  
“Several R-packages with extensions are available. The bcrm package (Sweeting, Mander, and Sabin 2013) implements a variety of one and two parameter models, and facilitates different ways to specify prior distributions, escalation and stopping rules. The ordcrm package (Dressler and Huang 2016) implements ordinal proportional odds and continuation ratio models for CRMs. The dfpk package (Toumazi, Ursino, and Zohar 2017) uses pharmacokinetic data in the dose escalation.”

* *Looking at the different examples, only one of the available models is used (i.e. LogisticLogNormal), but the article suggests that the package includes many different models without giving details about each model neither where to search for more information on this matter. It might be better to be clearer on where to find more documentation (i.e. in the R documentation on CRAN). Also it will be more understandable if the article could include a figure with the model class structures including the GeneralModel & the ModelPseudo classes.*Thank you for your suggestions. We now refer to the R documentation in Section 4:   
  “The package does, however, already include a wide range of model-based and algorithmic dose escalation procedures, which are described in the package’s documentation available through crmPackHelp() and provide end-users easy access to these approaches without the need for further coding.”  
    
  We believe it would still be sub-optimal to create a figure or list of all the available model classes (inheriting from the “GeneralModel” or “ModelPseudo” classes), given that it would be difficult to provide a short meaningful description for each and every model (the user is instead referred to the package’s manual).
* *Figure 1 (page 3) is not so clear. It’s a little confusing and it does not give the first clear idea of the package’s framework. It might be better to split it in two figures.*We considered splitting the figure into two figures, but decided to keep it as is. We reworded the figure’s caption as follows in order to better explain the framework from it:  
  “Schematic of the framework. Separate design features are implemented as classes (shown as gray boxes) and bundled together in the overarching Design object. They can be processed with various methods (blue text) to run the dose escalation trial and produce results (blue boxes). For example, the Data and Model objects can be processed by the mcmc method in order to obtain posterior samples of the model parameters, and given the sample size and the dose for the next cohort, the updated Data from the next cohort closes the dose escalation loop. On the higher level, designs can be investigated with the examine and simulate methods to obtain hypothetical trial courses and operating characteristics, respectively. Note that individual model classes and methods are not shown here for clarity, please refer to the package documentation for details, e.g. by calling crmPackHelp().”