Help document for Remifentanil study

1. Introduction

This document gives an explanation of the software for the Remifentanil dose-escalation study, along with a step-by-step guide to its use. As the Bayesian dose-escalation procedure progresses, an interim analysis will be conducted within this software after each new patient is treated and their primary endpoint observed: accumulated data from the trial will be combined with the prior pseudo-data to derive the current posterior distributions of the dose-response model parameters. Recruitment into the trial will stop once the maximum sample size has been reached or sufficient accuracy has been attained for estimating the target dose. If recruitment is to continue, the Bayesian procedure will make a dose recommendation for the next patient.

2. Using the software

A step-by-step guide follows:

1. Running the app will load the Remifentanil study page (Figure 1):

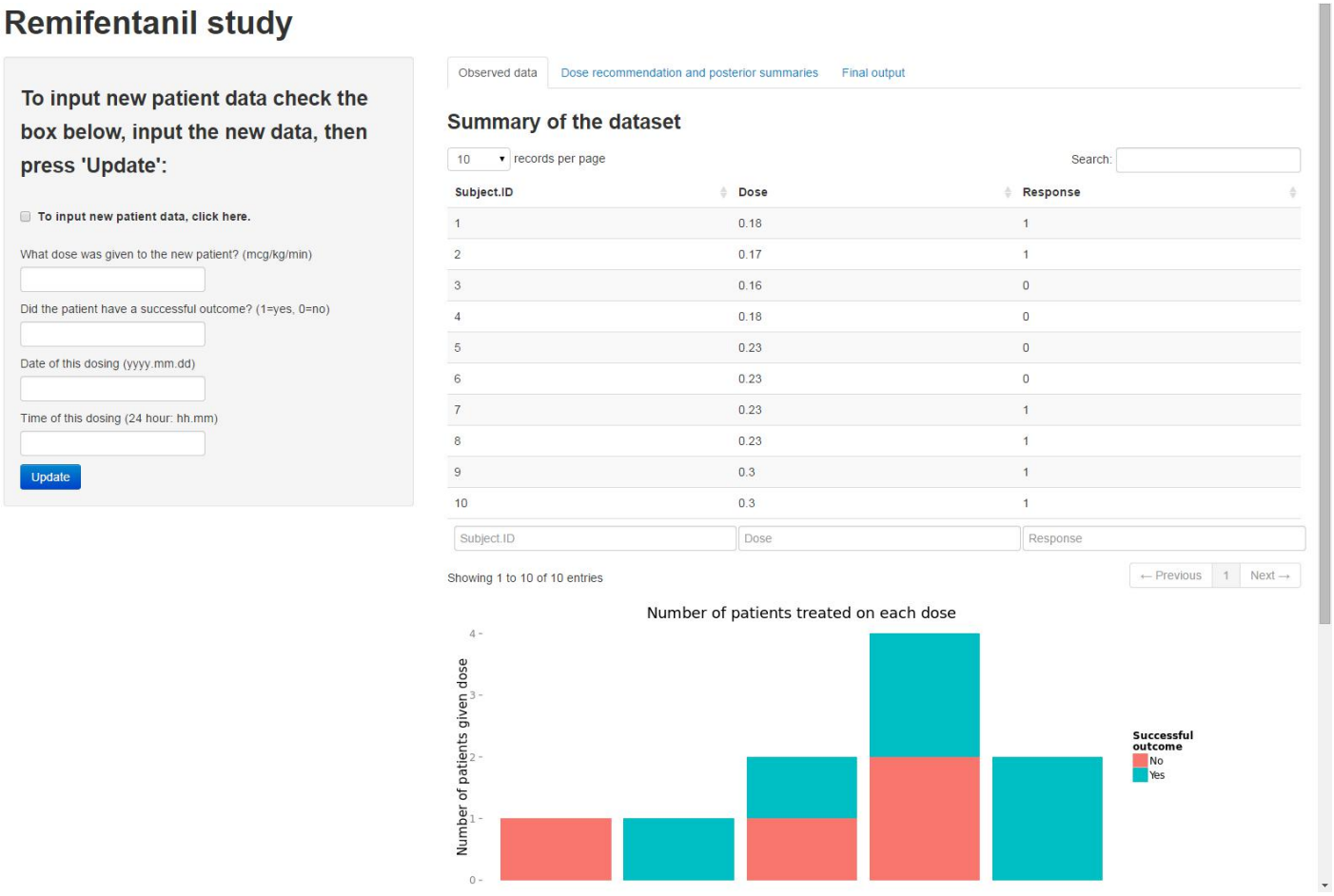

Figure 1: The Remifentanil study page at start-up.

The right hand panel has three tabs (Figure 1). The first tab, “Observed data”, (Figure 2) is displayed at start-up and displays:

- An interactive table of the current data.
- A bar chart showing how many of each dose has been given so far, and how many of the doses have had a successful outcome.
- A plot showing the dose given to each patient so far, also highlighting whether each patient had a successful outcome.

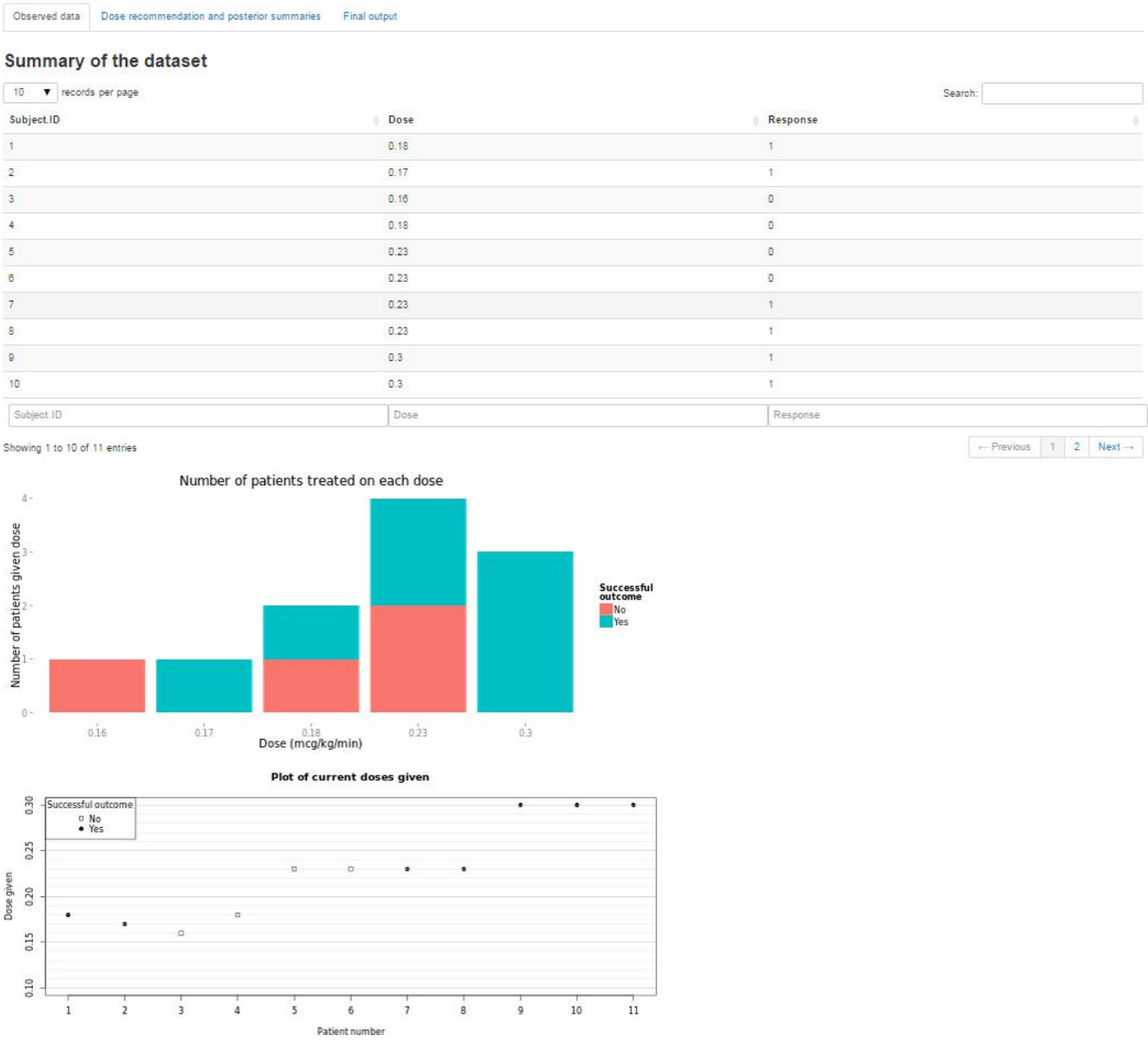

Figure 2: Right hand panel showing the “Observed data” tab.

The second tab, “Dose recommendation and posterior summaries”, (Figure 3) displays:

- The recommended next dose (mcg/kg/min), which will be between the values of 0.1 and 0.3, in increments of 0.01 mcg/kg/min.
- The posterior modal estimate of the ED80 for remifentanil, which is the current most likely value of the ED80. Here the ED80 is defined as the dose at which the probability of an apnoea of 30 seconds duration during the observation window is 0.8.
- Credibility intervals which summarise our uncertainty about the true value of the ED80. For example, the 50% credibility interval is the interval that contains the true ED80 with probability 0.5, given prior opinion and data observed so far. The 95% credibility interval is interpreted similarly.
- A graph of the dose-response relationship, displaying the probability of a successful outcome for a given dose and the current recommended dose (dashed line), along with 50% and 95% credibility intervals.

Figure 3: Right hand panel showing the “Dose recommendation and posterior summaries” tab.

The third tab, “Final output”, presents the final analysis at the end of the trial and will be empty until that point.

The left hand panel of Figure 1 displays a check box to be ticked if data from a new patient is to be entered, along with the text entry boxes for data entry and an 'Update' button which updates the current dataset with the new patient data.

2. If the dataset is up to date and the software is being used just to check the recommended dose for the next patient, everything required will be displayed in the tabs on the right hand side now, without having to press any buttons or input any data.

3. If data from a new patient is available for entry, tick the check box which says "To input new data, click here" (Figure 4). **Nothing should happen at this point**.

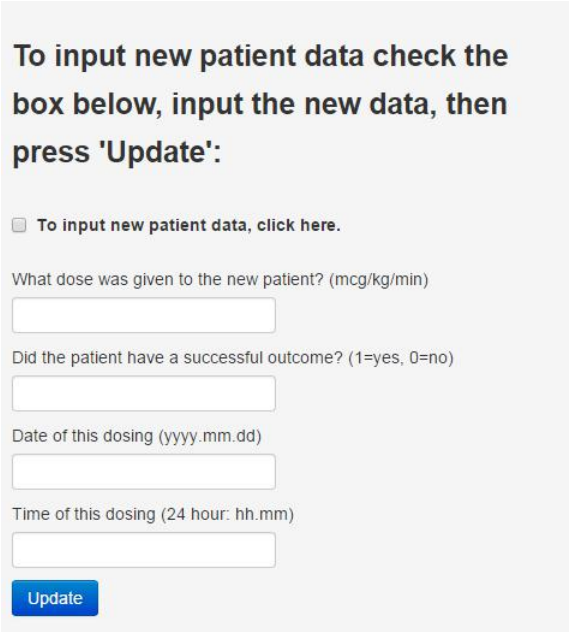

Figure 4: Left hand panel, showing the ticked "To input new data, click here" check box.

4. Fill in all the text entry boxes for the last patient to have been treated in the trial (if their data does not already appear in the displayed summary). An example is shown in Figure 5.
   - **What dose was given to the new patient? (mcg/kg/min):** Input the dose given to this patient which should be between 0.1 and 0.3 mcg/kg/min.
   - **Did the patient experience a successful outcome according to the criteria defined in the study protocol ? (1=yes, 0=no):** Input 1 if the subject experienced a successful outcome, 0 if the subject did not.
   - **Date of this dosing (yyyy.mm.dd):** Input the date of the current dose given, for example 2015.06.02 for the 2nd of June, 2015.
   - **Time of this dosing (24 hour: hh.mm):** Input the time of the current dose given, for example 09.25 for 9:25am.

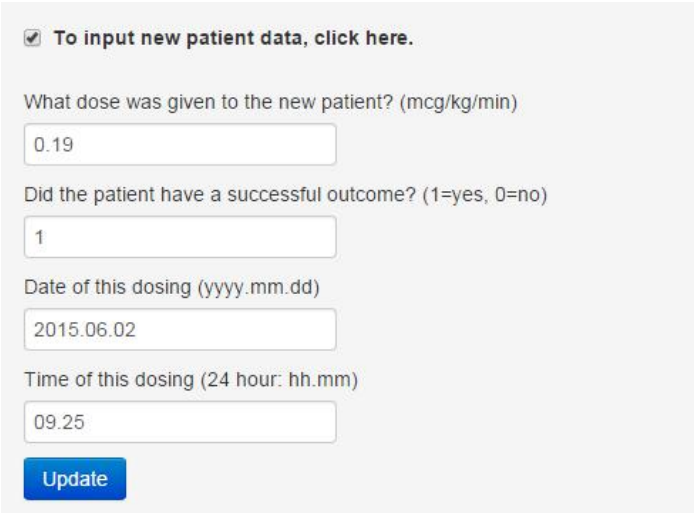

Figure 5: Left hand panel, showing an example of the text entry boxes filled in.

5. Press the 'Update' button below the text entry boxes in the left hand panel. This will update the page with the data you have just inputted. The tabs in the right hand panel will be updated, with the "Dose recommendation and posterior summaries" tab displaying the current posterior estimate of the dose-response relationship for remifentanil and the recommended dose for the next patient who enters the trial.

6. Once you have finished looking at the output, the software may be closed. Upon opening the app again the up-to-date dataset will be displayed and the previous steps may be repeated to either simply check the recommended dose for the next patient or to input new patient data.
   If new patient data is available before closing the app, steps **7** and **8** may be repeated to update with the new patient data, though at least one of the text entry boxes must change for the new input to be updated when the "Update" button is pressed. For example, if two patients following each other both have the same dose given and both have the same response, the date or time must differ between them for the new data to be recognised.

With each update, a recommended dose for the next subject will be given. Once a certain level of accuracy has been reached, as defined by the ratio of the upper and lower limits of the 95% credibility interval for the ED80 falling below 1.3, or the full 60 patients have been recruited the trial will stop and give additional output from a frequentist analysis of the primary outcome data, discarding the "pseudo-data" characterising prior distributions of the model parameters.

On the "Final output" tab, maximum likelihood estimates of the slope and intercept of the dose-response logistic regression model, as well as the ED80, will be presented alongside standard errors and 95% confidence intervals. Posterior distributions of the ED80 and parameters of the dose-response logistic regression model will be summarised by their posterior modal estimates, standard deviations and 95% credibility intervals. Additionally, a graph of the dose-response relationship for the frequentist analysis will be presented on the "Dose recommendation and posterior summaries" tab, below the Bayesian dose-response graph.