Case study for a continually adapting design

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EFSPI/BBS Meeting on Adaptive Designs in Drug Development

Outline

- Background
- Study design
- Logistical considerations
- Conclusion

Background

Study purpose

- A Phase II study in the treatment of acute migraine during the mild phase
  - Determine the minimum efficacious dose
  - Gain an understanding of the dose response
- To investigate the utility and feasibility of a novel design
  - Understand the logistics of setting up an alternative study design
    - Not to be constrained by standard internal practices and systems
    - Seek out and implement solutions
  - Experience of an alternative study design

Designs considered

- Traditional dose response study
  - Randomising subjects to doses in a given ratio

- “Up and Down” design
  - A design used by Olesen et al in Demark
  - Sequential procedure to identify the lowest dose that is superior to placebo
  - Patients dosed in groups of 6
    - 4 subjects randomised to active and 2 to placebo
  - Dosing decisions
    - Decrease dose if at least 3 out of 4 active subjects respond
    - Increase dose if less than 3 out of 4 active subjects respond
    - At the highest or lowest dose rule modified to prevent dosing out of the range
  - Up and down process terminated when a dose had been tested in at least 5 groups, with at least 4 groups having 3 out of 4 active subjects respond

Designs considered

- D-optimal design
  - Aims to learn about the whole dose-response curve.
- Continual Reassessment Model (CRM)
  - Targets a certain EDx
  - As a consequence gets information about dose response

Study Design

Study Design

- Single dose
- Parallel group
- Male and female migraineurs
- Primary endpoint of migraine pain at two hours
- Maximum number of subjects to be recruited – 126
  - Based on feasibility
- Treatment allocation performed centrally using the continual reassessment model
- Target minimum efficacious dose
  - Response rate of 50%
- Final dose response curve estimated using a four-parameter logistic regression model
- Trial conducted single blind with both the subject and investigator blinded and GSK unblinded

Continual Reassessment Model (CRM)

- Uses subject responses for migraine pain at 2 hours
- Assumes the response rate is related to dose according to a logistic regression model
- Uses the response and prior distribution to compute a posterior distribution for the slope regression parameter
- Posterior mean used to estimate response at each dose level

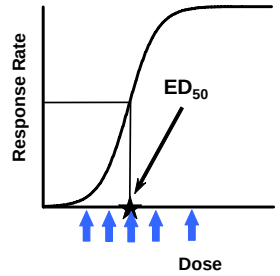
Adaptive design rules

- Allocation Rule
  - Determined by the CRM
  - Forced randomisation
    - 25% to placebo
    - 25% to highest dose
    - 50% to ED50
- Sampling Rule
  - After each subject has provided their 2 hour response
- Stopping Rule
  - Efficacy and futility
- Decision Rule
  - The model was updated to determine the ED50

Adaptive Design Process

Patient is randomised
in blinded fashion to:
placebo (25%),
high dose (25%)
or “optimal” dose (50%)
[5, 15, 30, 60, 120, 180]mg

Logistic Regression Model



1 New Patient

2 Randomisation

3 Data

4 Update the model

5 Stopping Rule

Continue

Stop

Go

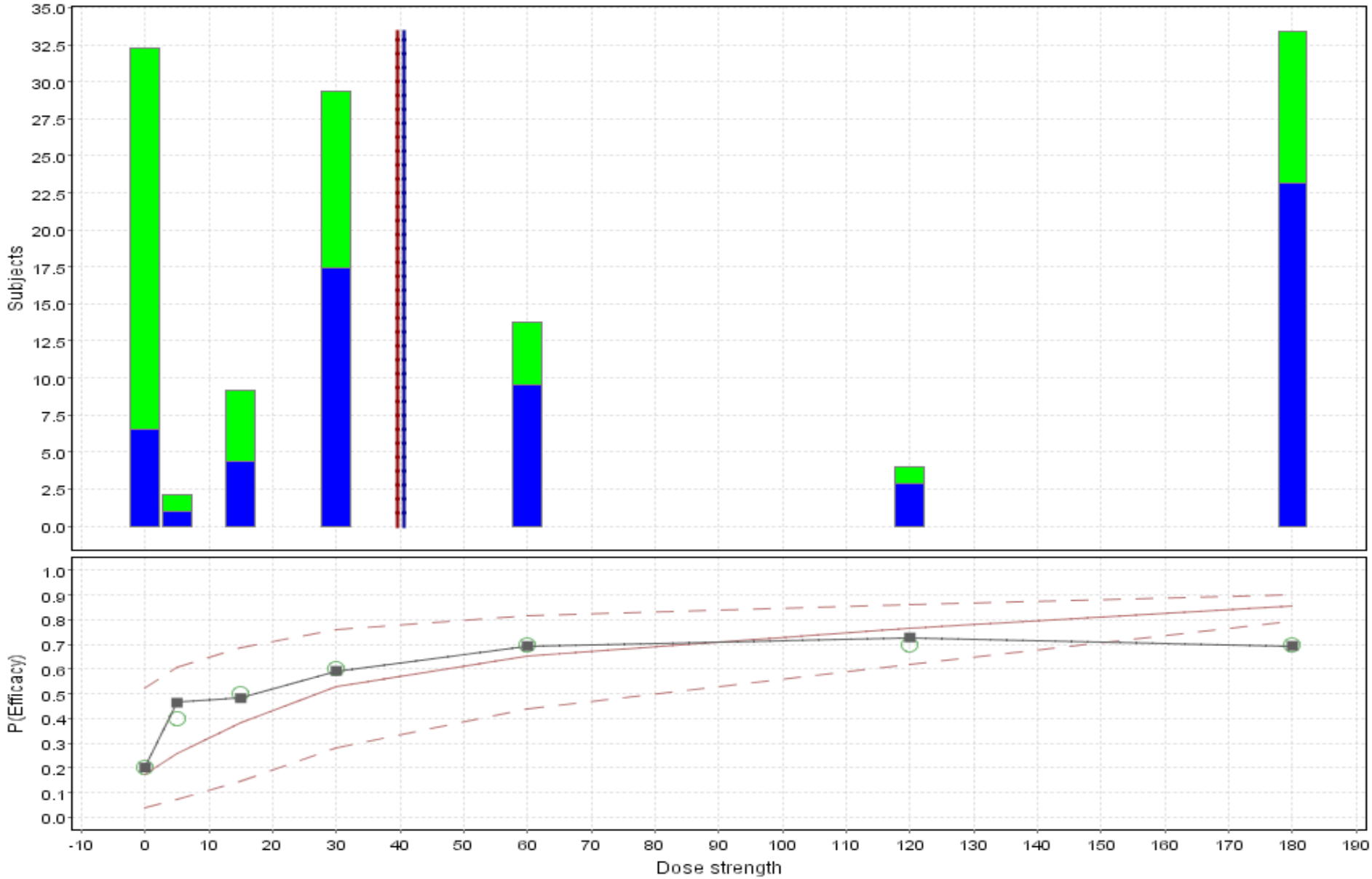
STOP for Futility

STOP for Efficacy

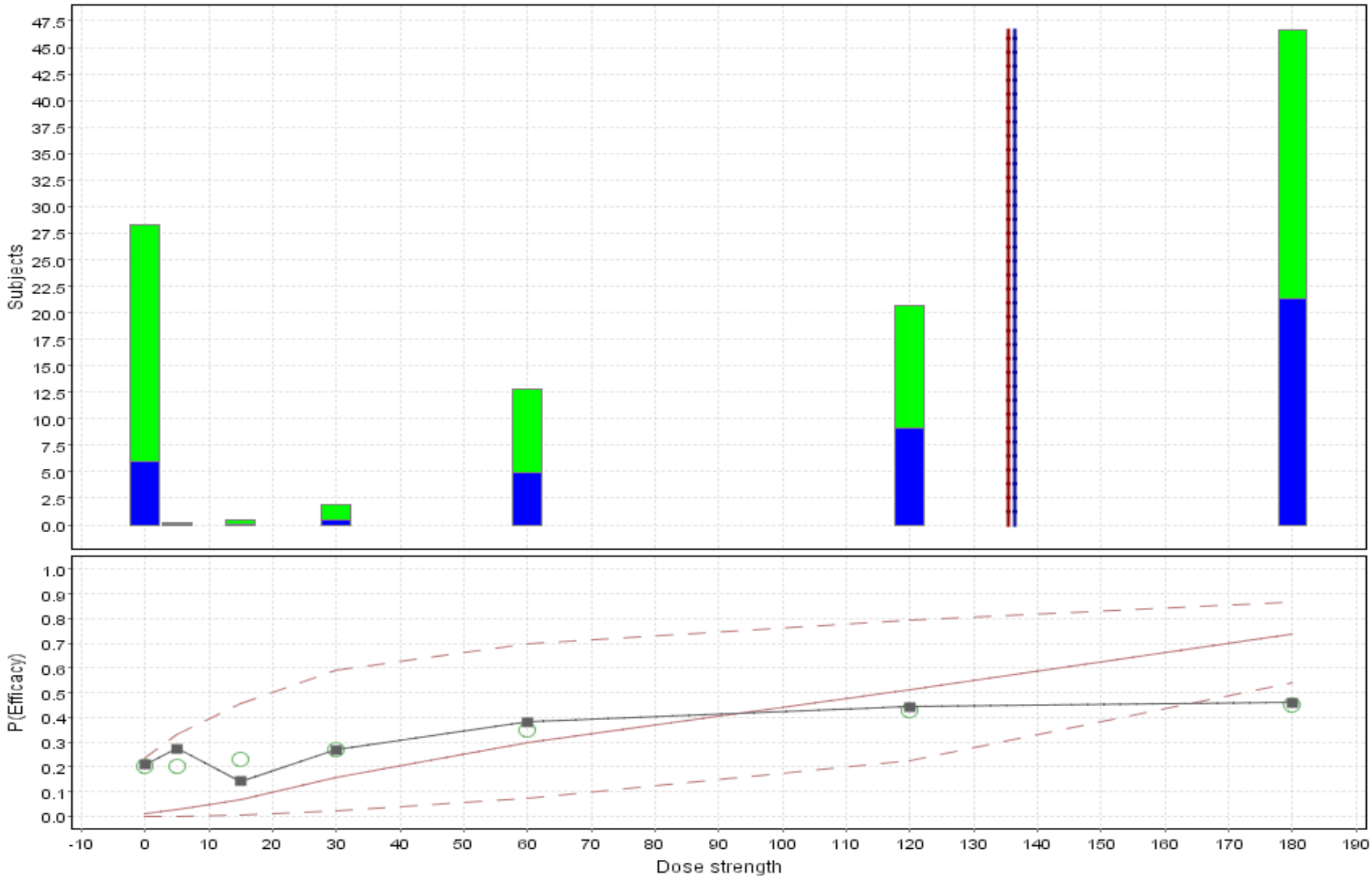
6 Allocation Rule

Continual Reassessment Method
chooses the “optimal” dose
that will optimise learning about the ED50

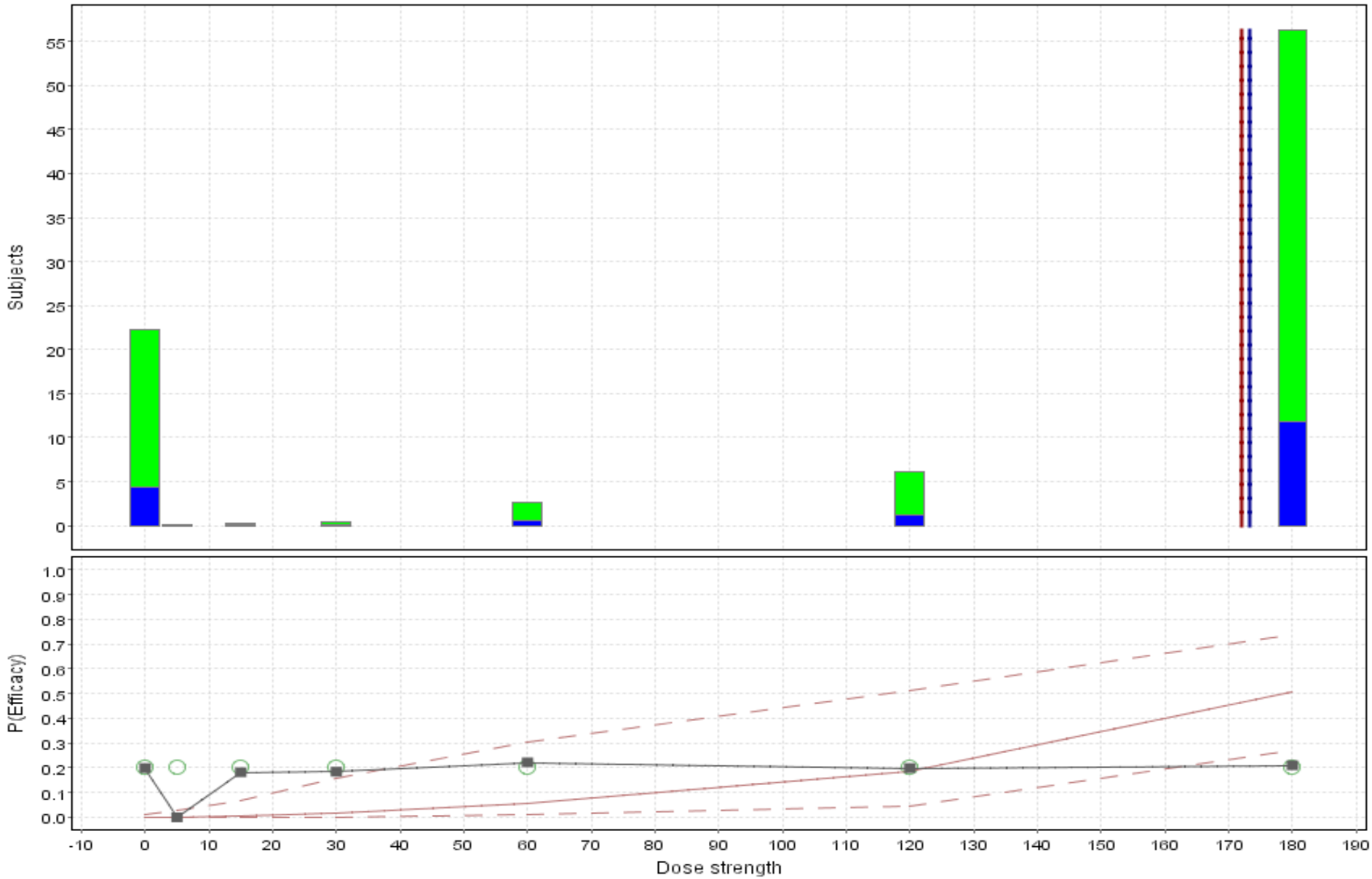
Simulations – Early Effect



Simulations – Small Effect



Simulations – Flat Effect



Logistical considerations

Challenges

- Continually adapting design
  - Collect data used by the statistical model
  - Updating the model
  - Updating the randomisation
- Expectations on the subject
  - Self randomisation
  - Self dosing
  - Reporting migraine pain at 2 hours

Continually adapting design

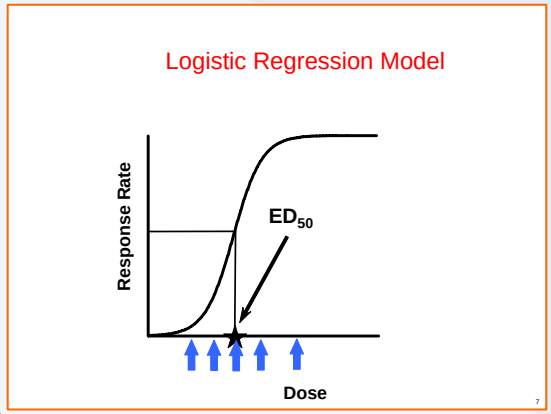
- In-house systems could not provide functionality we required
  - An external supplier was brought on board to provide suitable systems

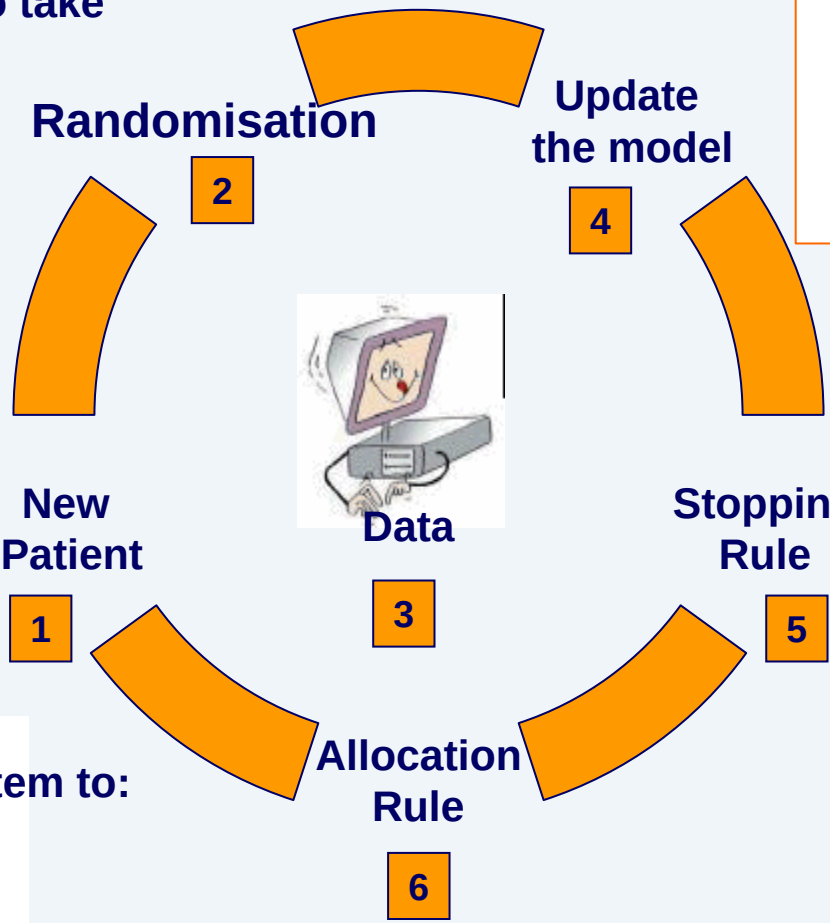
Continually adapting design

- Functions provided by Tessella
  - Fax based system for site activities
  - IVRS based system for subjects
  - Randomisation
  - Running of the statistical model
  - System to run simulations of the trial
    - Used to check sample size
  - Web interface for the study team
    - Information about subject progression (screening, enrolment, randomisation)
    - Details of response
      - Observers were unable to influence the study
    - Statistical model information

Adaptive Design Process in Practice

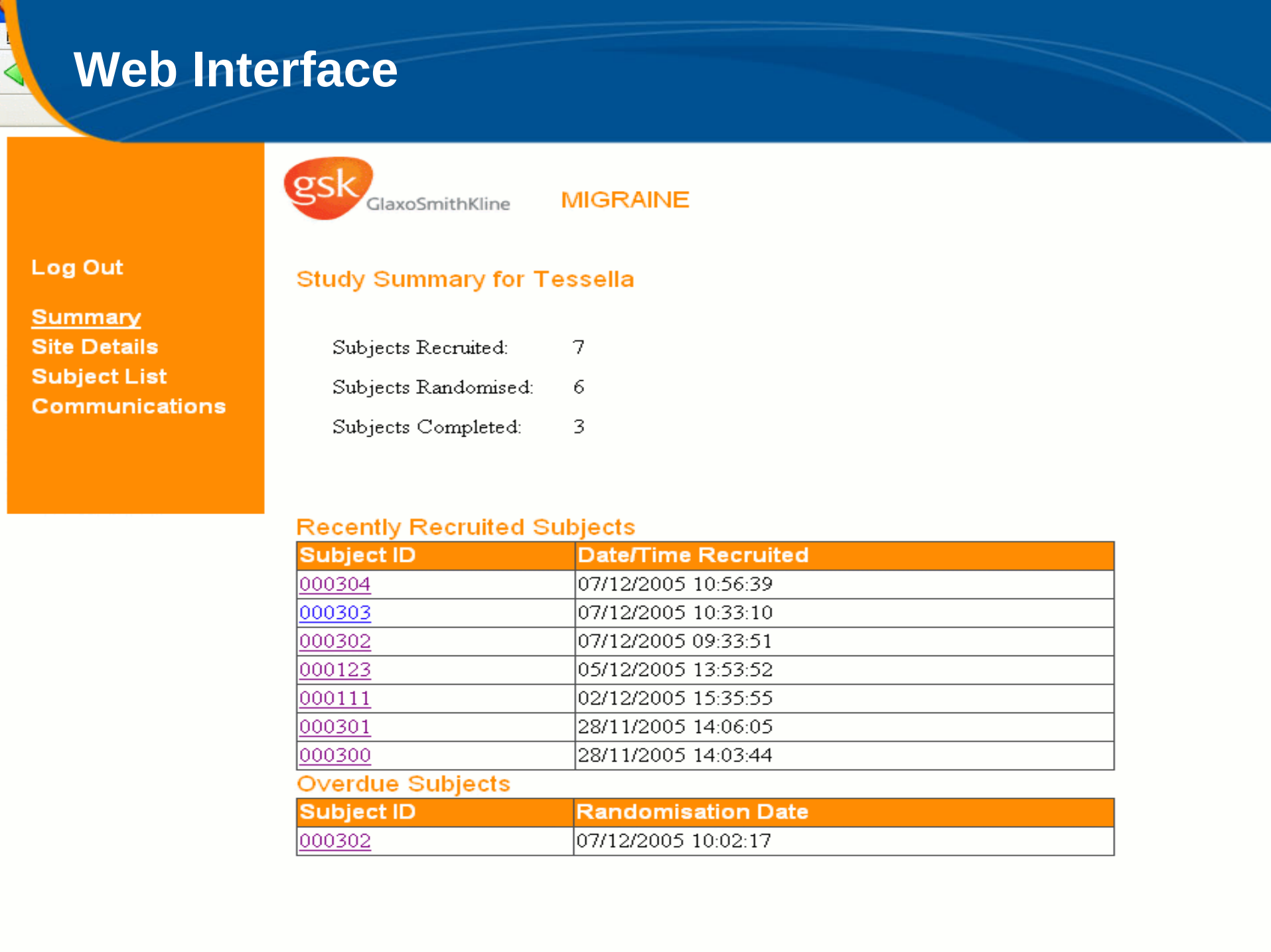
Patient will call to:
- **Find out which dose to take**
- **To report response**



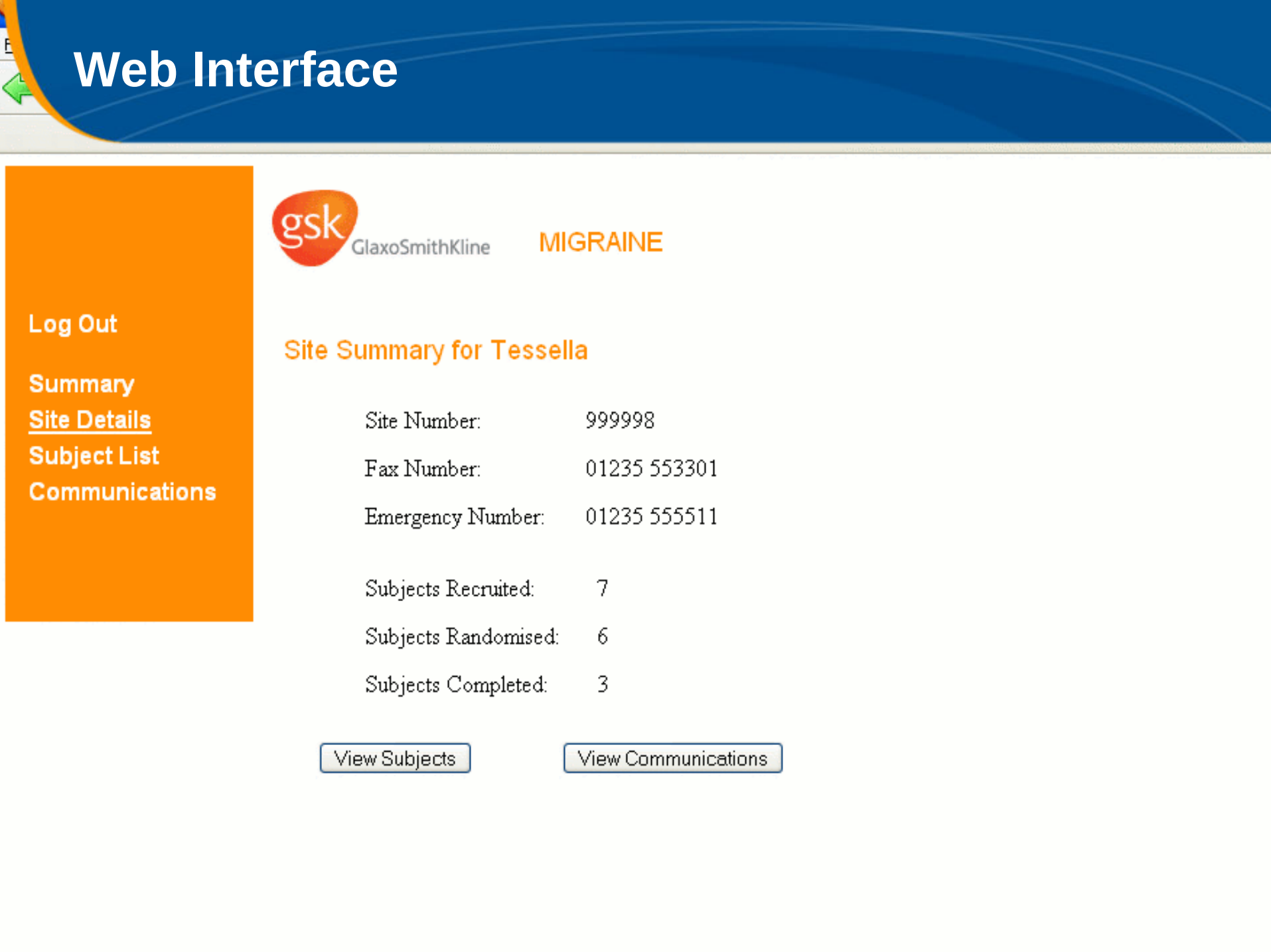


Site will fax IVRS system to:
- **register patient**
- **Confirm eligibility**

Web Interface



Web Interface



Web Interface

Log Out

Summary
Site Details
Subject List
Communications

GlaxoSmithKline MIGRAINE

List of Participating Subjects

Filter by: State: Any

Subject ID	State
000111	Completed
000123	Completed
000300	Completed
000301	Withdrawn
000302	Randomised
000303	Randomised
000304	Randomised

Web Interface

Web Interface

GlaxoSmithKline MIGRAINE

Log Out

Summary
Site Details
Subject List
Communications

List of Communications

Filter by: Subject: Type: Any

Subject ID	Type	Date/Time	State at Start	State at End	OK?	
000304	FAX	07/12/2005 12:12:25	Randomised		T	View Details
000304	FAX	07/12/2005 12:05:03	Randomised		T	View Details
000304	FAX	07/12/2005 11:26:55	Randomised		T	View Details
000304	FAX	07/12/2005 11:20:39	Randomised		T	View Details
000304	FAX	07/12/2005 11:19:30	Randomised		T	View Details
000304	FAX	07/12/2005 11:04:18	Randomised	Randomised	T	View Details
000304	IVRS	07/12/2005 11:03:46	Passed screening	Randomised	T	View Details
000304	FAX	07/12/2005 11:00:24	Enrolled	Passed screening	T	View Details
000304	SMS	07/12/2005 10:56:42	Enrolled	Enrolled	T	View Details
000304	FAX	07/12/2005 10:56:41	Enrolled		T	View Details
000304	FAX	07/12/2005 10:56:40			F	View Details
000304	FAX	07/12/2005 10:56:39		Enrolled	T	View Details
000303	IVRS	07/12/2005 10:38:06	Passed screening	Randomised	T	View Details
000303	FAX	07/12/2005 10:33:22	Passed screening		T	View Details
000303	SMS	07/12/2005 10:33:22	Passed screening	Passed screening	T	View Details
000303	FAX	07/12/2005 10:33:20	Passed screening	Passed screening	F	View Details
000303	FAX	07/12/2005 10:33:18			F	View Details
000303	SMS	07/12/2005 10:33:11	Passed screening	Passed screening	T	View Details
000303	FAX	07/12/2005 10:33:10		Enrolled	T	View Details
000303	FAX	07/12/2005 10:33:10	Enrolled	Passed screening	T	View Details
000303	FAX	07/12/2005 10:33:10	Passed screening		T	View Details
	FAX	07/12/2005 10:26:46			F	View Details
000302	SMS	07/12/2005 10:24:36	Randomised	Randomised	T	View Details
000302	FAX	07/12/2005 10:24:35	Randomised		T	View Details
000302	FAX	07/12/2005 10:09:38	Randomised	Randomised	T	View Details

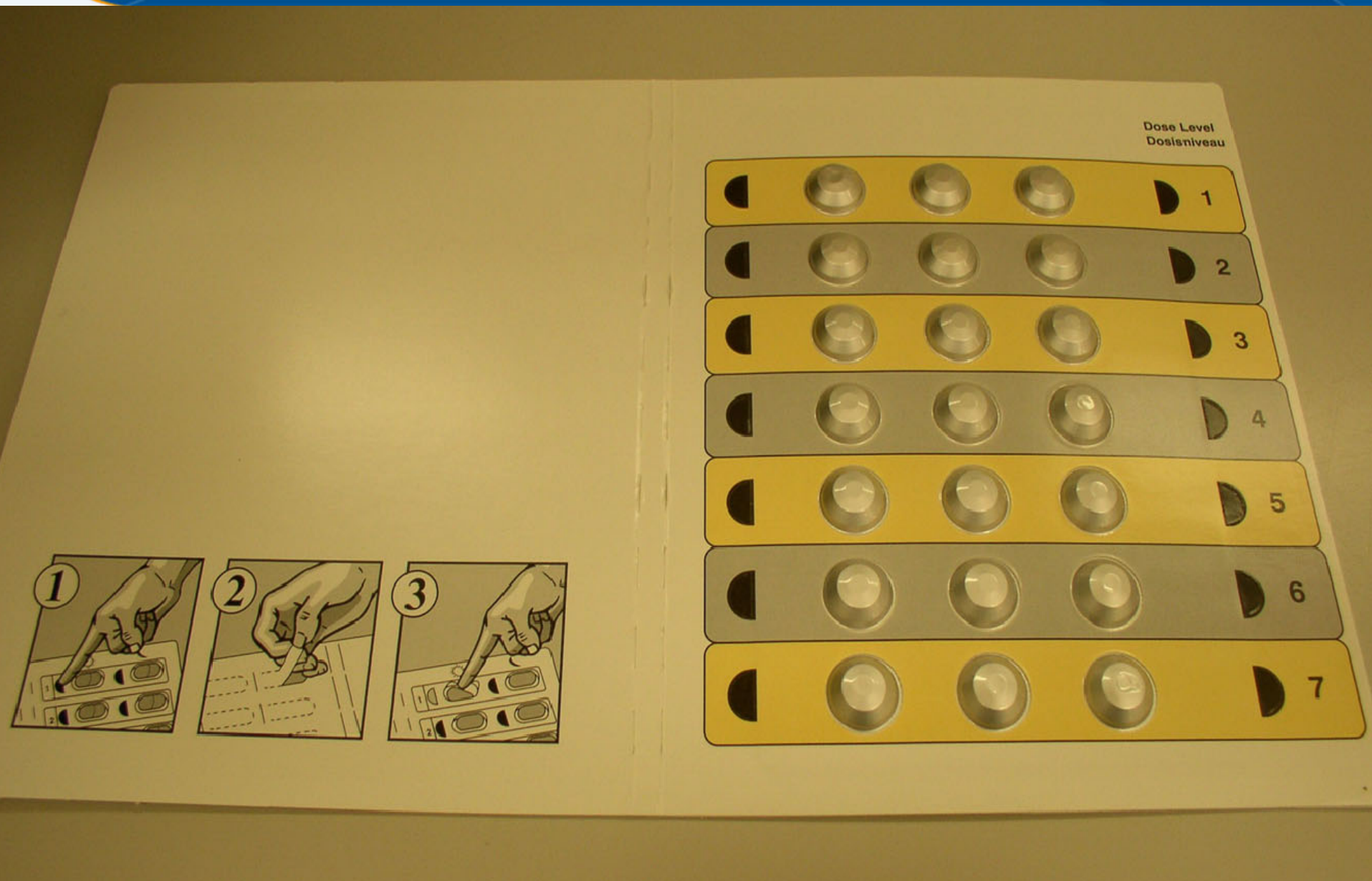
Expectations on the Subject

- Issues
  - Subject randomising themselves
  - Subject requires all seven doses to be available to them
  - Seven doses
    - 4 possible tablet strengths
    - Doses made up of three tablets

- Subjects randomising themselves
  - Subjects were asked a number of questions by the IVRS system before they were able to randomise and dose
  - Doses were checked at the unit to ensure the correct dose was taken

Study Medication – Traditional Supply

Study Medication – Solution



Study Medication - Solution

- Three randomly ordered packs were developed to prevent investigator unblinding.
  - As the study evolves investigators may be able to identify a dose that is appearing repeatedly
  - Used three sequences randomly selected from a Williams Square design
  - Each subject was randomised twice.
    - Firstly to a packet of study medication
    - Secondly to a dose

Conclusion

Conclusions

- The objective to conduct a novel trial was successfully achieved
  - A non-traditional design was executed
  - Where in house systems didn't meet requirements of the studies alternative systems/approaches were sought
  - Subjects successfully did all that was asked of them
    - Randomising and dosing
- The web interface was very useful
  - Readily accessible
  - Provided a useful reference for clinical operations
  - Very exciting to watch the study progress

Acknowledgements

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References

- Olesen J, Diener H-C, Husstedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko LM. (2004). Calcitonin Gene-Related Peptide Receptor Antagonist BIBN 4096 BS for the Acute Treatment of Migraine
- www.tessella.com