

# LISA: Leukaemia Intervention Scheduling and Advice

Collaboration between Cancer Research UK's:

- Information Systems Team
- Advanced Computation Laboratory
- Children's Cancer Group – RLH

Aim:

- Provide system to support shared care of paediatric leukaemia

# ALL Treatment 1

- 95% of children with ALL are enrolled into MRC clinical trial (compares 2 steroids, 2 thiopurines) and treatment follows the trial protocol
- Collaborative care in 'Hub and Spoke Model' – *some care is given at a Shared Care Unit (e.g. district hospital) and some at regional treatment centre (e.g. RLH) – obvious problem of “where are the patient notes?”*
- Coordination of care by Clinical nurse specialists based at RLH who liaise with staff at DGHs
- All communication by pen/paper and fax/phone

# ALL Treatment 2

3 stages of protocol:

- Induction of clinical remission
- Consolidation of remission
- Continuing therapy (maintenance)

Maintenance is thought to be most critical determinant of therapeutic outcome:

- Split into 12 week cycles
- 24 months for girls and 36 months for boys

Maintenance treatment consists of:

- Regular administration of 2 oral chemotherapy agents: methotrexate and thiopurine
- Occasional intravenous vincristine
- Oral steroids 5 days a month
- Intrathecal chemotherapy once every 3 months

## **APPENDIX B.**

### **Thiopurine and methotrexate dose alterations**

Only thiopurine and MTX will be interrupted for myelosuppression; vincristine and steroid should be given on schedule. The omitted doses of thiopurine and MTX will not be made up. The oral doses of thiopurine and MTX should be adjusted to maintain ANC between 750/ $\mu$ L and 1500/ $\mu$ L and platelets  $\geq$  75,000/ $\mu$ L.

#### **(a) Escalation of thiopurine and methotrexate for ANC $>1.5 \times 10^9/l$ during consolidation in regimen A, interim maintenance in regimens A and B, and continuing maintenance in regimens A,B and C:**

The oral doses of thiopurine and methotrexate should be adjusted to maintain the ANC between 0.75 and  $1.5 \times 10^9/l$  and the platelet count  $> 75 \times 10^9/l$ . If:

- (1) ANC is  $> 1.5 \times 10^9/l$  and
- (2) platelets  $> 75 \times 10^9/l$  on Day 1 of any maintenance course, and
- (1) ANC was  $> 1.5 \times 10^9/l$  and
- (2) platelets were  $> 75 \times 10^9/l$  on Days 1, 29 and 57 of the preceding course, the dose of thiopurine should be escalated by 25% (from 75mg/m<sup>2</sup>/day).

If the subsequent monthly ANC is:

- 1) ANC  $> 0.75$  and  $< 1.5 \times 10^9/l$  (and platelets  $> 75 \times 10^9/l$ ), keep thiopurine at the 125% dose.
- 2) ANC  $< 0.75$  and  $> 0.5 \times 10^9/l$ , or platelets  $< 75 \times 10^9/l$ , thiopurine and methotrexate should be reduced to 50% of original (i.e. of 100%) dose until the ANC recovers to  $\geq 0.75$ . Thiopurine and methotrexate should then be increased to 75% of the original dose and then to full (i.e. 100%) dose one week later, provided the ANC remains  $\geq 0.75 \times 10^9/l$ .
- 3) ANC  $> 1.5 \times 10^9/l$  (and platelets  $> 75 \times 10^9/l$ ), keep thiopurine at 125% dose and increase methotrexate by 25% to 25 mg/m<sup>2</sup>/dose.
- 4) Continue to increase the thiopurine dose at Day 1 of each maintenance course as outlined above if ANC  $> 1.5 \times 10^9/l$  persists. Continue to increase the methotrexate dose one month later if ANC  $> 1.5 \times 10^9/l$  as outlined above. There are no maximum doses for thiopurine and methotrexate.

#### **(b) Reductions of thiopurine and methotrexate during regimen A, interim maintenance in regimens A and B and continuing maintenance in regimens A, B and C:**

- 1) If the neutrophil count falls to between  $0.5 \times 10^9/l$  and  $0.75 \times 10^9/l$ , halve the dose of thiopurine.
- 2) When the ANC recovers to  $\geq 0.75$ , thiopurine should then be increased to 75% of the original dose and then to full dose one week later, provided the ANC remains  $\geq 0.75 \times 10^9/l$ .
- 3) If the neutrophil count falls below  $0.5 \times 10^9/l$ , **STOP** thiopurine and methotrexate.
- 4) **RESTART** when the count is over  $1.0 \times 10^9/l$ . Restart at 100% of protocol dose or, if less, the previously tolerated dose.
- 5) The same dose modifications apply to falling platelet counts. If the count is less than 75 but more than  $50 \times 10^9/l$  HALVE dose as 2 above; if less than  $50 \times 10^9/l$ , STOP thiopurine and methotrexate.

**RESTART** as above when the count is greater than  $100 \times 10^9/l$ .

- 6) If counts seesaw wildly when restarting after cytopenia, starting at 50% of protocol dose and titrating upwards is permissible, so as to avoid frequent interruptions to thiopurine exposure. This manoeuvre is not often necessary. (Protocol note added May 1998).
- 7) Thrombocytopenia may be more marked for patients on 6-thioguanine. If it proves impossible to maintain the neutrophil count in the range outlined above without **unacceptable** thrombocytopenia, it may be necessary to change the patient to 6MP

**NOTE: Tolerance of 150% or more of the target protocol thiopurine dose for prolonged periods may be indicative of partial or non-compliance, and is potentially dangerous if the patient suddenly starts to comply fully. Metabolite assays in such circumstances can be helpful to exclude non-compliance and can be arranged with Professor Lilleyman or Dr. Lennard (contact addresses on p.3). Rare individuals (1 in 300) taking thiopurine who are congenitally lacking intracellular TPMT will show profound myelosuppression at standard dose. These patients will be identified prospectively at the time of diagnosis, and advice on dosing will be given by the trial co-ordinators.**

# Project aims

## Problems

- Poor protocol conformance and thus low trial validity and poor patient outcome
- Unreliable patient record-keeping due to shared care and lack of validation of pen and paper – *important because dose decisions depend on previous blood results and doses prescribed*
- Where are the patient notes? Duplication and reliance on coordinating nurses.
- Protocol is likely to change
- Protocol is ambiguous and difficult to read

## Solutions

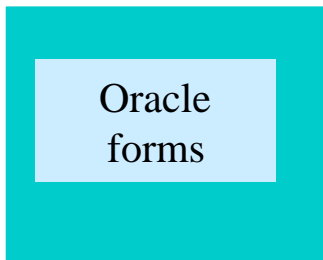
- Providing support for dose decisions during maintenance via the internet
- Unambiguous and easily editable protocol model component in Proforma
- Replacing the current pen/paper method of recording blood result/dose decision with a centralised database and data entry via validatable forms

# The System

Web browser (anywhere)



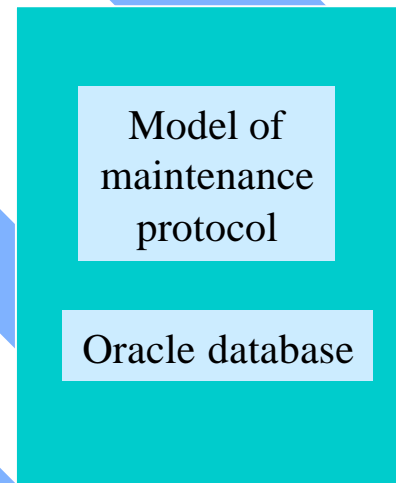
- Limited view of database: just maintenance
- Used from anywhere with web access
- Explore the use of PDAs



Trial Manager (RLH)

- Read/write view of whole database
- Only accessible by trial/data manager at RLH

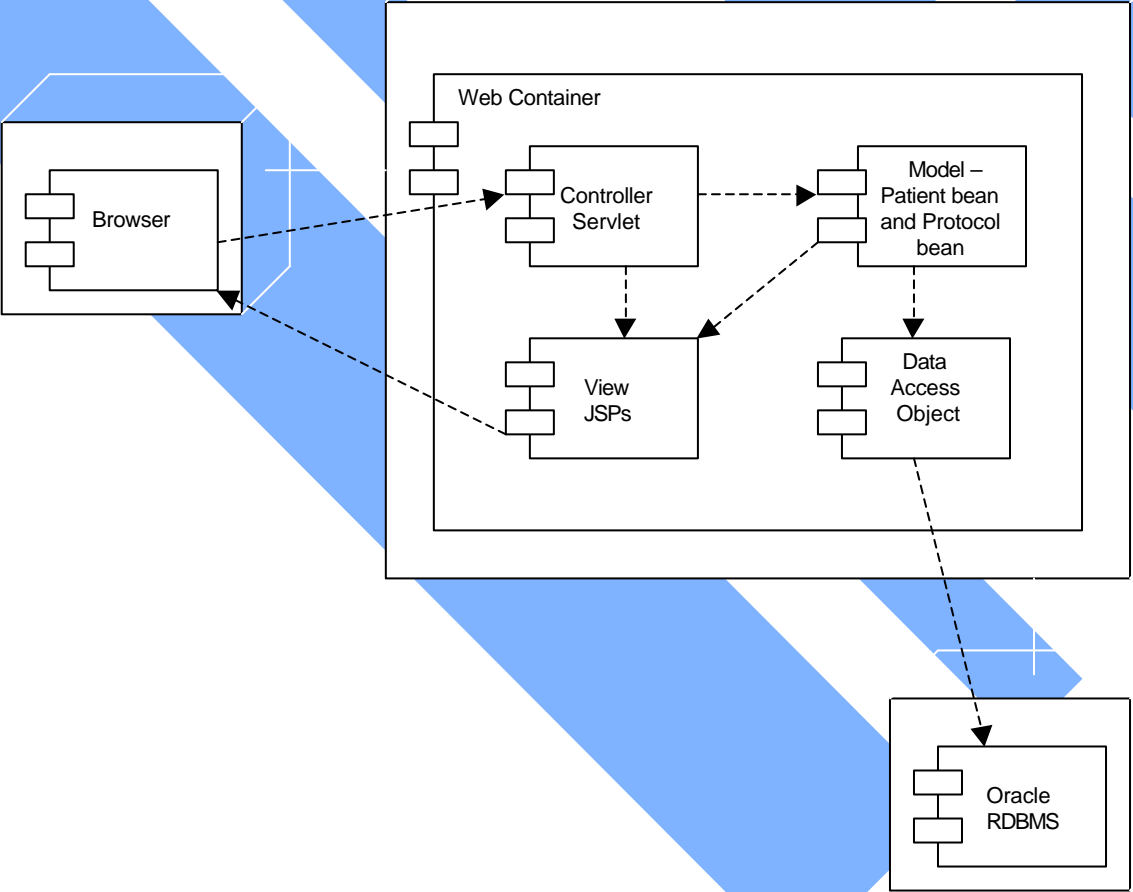
CRUK central server (LIF)



- Model written in a language developed at ACL
- This can be altered by someone with limited technical knowledge without any impact on the rest of the system

- Data for each patient for the whole of treatment i.e. induction to end of maintenance
- Which drugs given when, blood results, toxicity and other measurements etc.

# UML deployment diagram: JSP Model 2 (Model-View-Controller)



# LISA web application

- Accessible via a web browser
- It displays a view of the basic patient details and blood results taken/dose decisions made during maintenance
- Allows entry of a current blood result
- Provides advice about what doses of oral chemotherapy (thiopurine and methotrexate) should be administered based on:
  - Latest blood result
  - Current 'state' i.e. the thiopurine and methotrexate doses
  - How long has chemotherapy been tolerated for (ANC  $\geq$  1.5 Plts  $\geq$ 75)?
  - How long has the patient been at the current state?
- Allows the user to enter a dose decision
- Blood and dose are then written to the central database
- Has a log in system via a username and password:
  - If someone wants access then they ring the trial manager and give him/her their name and hospital. Specify read or write access privilege.
  - The trial manager will then ring them back with a username and password
- DEMO

# Further work

- Test the system
- Go live in September with a persuadable subset of hospitals
- EJBs to enable a patient's protocol model to persist
- Generic solution to database access from proforma engine
- Extend system to provide more detailed support for scheduling and coordination of intervention
  - Enable users to query whether tasks are overdue or have been cancelled
  - Enable users to query whether or not a task's intended rescheduling is within bounds defined by the protocol