LISA: A Clinical Information and Decision Support System for Collaborative Care in Childhood Acute Lymphoblastic Leukaemia

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ABSTRACT
The treatment of a child with Acute Lymphoblastic Leukaemia (ALL) requires the collaboration of multiple providers across different organisations. We describe the implementation of a clinical information system for supporting collaborative care in the management of children with ALL. The system integrates the provision of patient data and clinical information with protocol-based, patient-specific decision support. The approach illustrated here should find applicability in the management of other diseases requiring collaborative care across institutions.

INTRODUCTION
The treatment of patients with cancer can last months or years. Providing a consistently high standard of care throughout that period requires close liaison between different providers. In the UK, cancer care is typically organised according to a ‘Hub and Spoke Model’, in which a regional Treatment Center collaborates with a network of local ‘shared care’ Units. Treatment Centers are typically large tertiary referral hospitals with expertise in the management of specific cancers and complex procedures. More routine components of an individual patient's treatment plan are delivered by a Cancer Unit - typically a district hospital more easily accessible to the patient. Similar models operate in other countries.

Acute Lymphoblastic Leukaemia (ALL) is the commonest paediatric malignancy, with approximately 320 cases registered annually in the UK. ALL accounts for 25% of the total number of UK cancer registrations for children and is the commonest cause of cancer death in childhood. Treatment of the disease can be viewed as comprising three phases – the Induction of clinical remission, the Consolidation of this remission, and subsequent Continuing Therapy. Various treatment protocols are in use internationally, but all incorporate a lengthy period of Continuing Therapy (often referred to as maintenance therapy). ALL is unique amongst paediatric cancers in requiring such a long period of ongoing treatment and all evidence suggests that this period is the single most critical determinant of therapeutic outcome.

Currently in the UK, over 95% of children diagnosed with ALL are enrolled into the Medical Research Council UKALL 97/01 trial, and hence treatment follows the protocol defined by that trial. In this protocol, Continuing Therapy lasts between 24 months (girls) and 36 months (boys). The mainstay of treatment during this period is the regular administration of two oral chemotherapy agents, 6 mercaptopurine (given daily) and methotrexate (given weekly). There is great individual variation in response to these drugs, and dosages have to be continually adjusted to avoid inducing episodes of severe marrow suppression which would necessitate interruption of treatment to allow marrow recovery. These dosage adjustments are based on weekly Full Blood Counts (FBCs) which reflect the degree of recent marrow suppression. The UKALL 97/01 protocol includes rules describing how doses should be modified in response to these FBC results. These rules are moderately complex and their application requires knowledge not only of a child’s most recent blood count but also of blood counts and chemotherapy dosages during the preceding twelve weeks.

Continuing Therapy is typically delivered collaboratively by Treatment Centers and associated Paediatric Oncology Shared Care Units (POSCUs). If dosage modifications are to be made in accordance with the treatment protocol, sharing of clinical information between Treatment Centers and POSCUs is essential and must happen in a timely fashion. Trial statisticians also require accurate information about FBCs and dosages during continuation therapy, and compliance with the treatment protocol is essential if meaningful inferences are to be made about its efficacy.

Shared care in the treatment of ALL
The LISA (Leukaemia Intervention Scheduling and Advice) system has been developed as part of a collaboration between Cancer Research UK’s Information Systems (Development) team, Children’s Cancer Group (CCG) and Advanced Computation Laboratory (ACL). The CCG is based at the Royal
London Hospital (RLH), UK, which is one of 22 Paediatric Oncology Treatment Centres in the UK accredited by the United Kingdom Children's Cancer Study Group (UKCCSG). An individual child with ALL is managed by the RLH in collaboration with one of a network of 60 POSCUs in south-east England.

The first 40 weeks of any child's treatment is relatively intense and is delivered primarily at the RLH itself. However, Continuing Therapy is less intense and requires fewer specialist interventions. Most treatment during this phase is delivered at a POSCU nearer the child's home. In addition to the oral treatment described above, children receive monthly doses of intravenous Vincristine and monthly 5-day courses of oral steroids. Care is coordinated by Clinical Nurse Specialists based at the RLH who liaise with staff at POSCUs. Children typically only attend the RLH once every three months, for intrathecal chemotherapy (i.e. chemotherapy injected into the spinal fluid, intended to reduce the likelihood of recurrence of the disease within the central nervous system).

A child's FBC and dosage history during Continuing Therapy is currently recorded on paper, with copies held both at the RLH and at the appropriate POSCU. The Clinical Nurse Specialists at the RLH provide advice, if needed, to staff at POSCUs on the appropriate scheduling of interventions and adjustments to doses of oral chemotherapy agents. Access to accurate FBC and dosage information at RLH and POSCUs is essential. At present, information is shared between sites using fax and telephone communication. A full time data manager at the RLH collates information for forwarding to the UKALL 97/01 trial co-ordinators.

Current data quality and protocol compliance

We undertook a retrospective audit of oral chemotherapy dosage decisions made during Continuing Therapy. The aims of this audit were to establish completeness of information recording at the RLH, and the extent to which prescribing during Continuing Therapy is consistent with the guidelines laid down in the UKALL 97/01 treatment protocol.

Two of the authors (JB and CB) reviewed the records of 19 children who had received Continuing Therapy at the RLH and associated POSCUs since 1999. Both reviewers were familiar with the UKALL 97/01 treatment protocol. The duration of therapy reviewed for each child varied between 12 and 96 weeks (corresponding to one to eight 12-week cycles of Continuing Therapy). A total of 984 weeks of therapy were reviewed.

For each week of therapy, we recorded whether FBC data was recorded in the paper records held at the RLH, and whether the dose of oral chemotherapy, if recorded, was consistent with the guidelines described in the treatment protocol. Ascertaining whether or not a recorded dosage decision was consistent with the treatment protocol was not always possible. In part this was due to minor ambiguities in that protocol. More often, there was insufficient information recorded about previous doses and FBC tests to make an unequivocal judgement as to what doses would have been appropriate in a given week.

We therefore classified dosage decisions as 'possibly consistent with the protocol (Y/N)' and 'possibly inconsistent with the protocol (Y/N)'. Some dosage decisions fell into both categories when reviewed.

This audit showed that FBC data was not recorded for 298 (30.3%) of the 984 weeks of treatment reviewed. Dosage information was not recorded in 317 (32.2%) of the weeks reviewed. Of the 667 weeks in which a dosage decision was clearly recorded, there was insufficient information about previous doses or FBC results to judge unequivocally whether the dose decision was consistent with the trial protocol in 181 weeks (27.1%). Of the 486 weeks in which such a judgement was possible, we felt the decision recorded was inconsistent with the defined protocol in 36 cases (7.4%). Most of these inconsistencies represented only minor deviations from the protocol or differences in its interpretation. Nevertheless, these figures illustrate the difficulties faced by clinicians and trial managers alike in ensuring protocols are adhered to and clinical data is recorded.

THE LISA SYSTEM

Aims

The LISA project was initiated to provide an information infrastructure to address the data quality and protocol compliance issues described above. We have initially focussed on piloting the system within one Paediatric Oncology Treatment Center (the RLH) and its associated POSCUs, but our intention has been to develop a system capable of ultimately being deployed in all Treatment Centers and POSCUs throughout the UK. Our first priority has been to develop a robust database for storing comprehensive data on interventions, scheduling, dosages and side-effects during treatment. As well as facilitating data management for the UKALL 97/01 trial, this has provided an infrastructure, both technical and administrative, which can support the development and deployment of novel decision-support tools for point-of-care use by clinicians.
The key software components of the LISA system are (figure 1):

- An ORACLE database capable of representing comprehensive clinical information on each stage of treatment for individual children.
- A set of forms to allow data managers at Treatment Centers to view and modify information in that database.
- A web-based user interface to allow clinicians at Treatment Centers and POSCU's to view and enter clinical information during Continuing Therapy.
- A formal model of the trial protocol and an associated inference engine, used to provide decision support on dosing and scheduling during Continuing Therapy.

The Clinical Information Database

As in most clinical trials operating in the UK, data management within the UKALL 97/01 trial is currently paper-based, a time consuming and potentially error-prone process. One of our motivations has been to develop a scalable electronic infrastructure to facilitate data gathering within the current trial and its successors. Given the emerging evidence of the key role of Continuing Therapy in effecting long-term cure, we have been particularly keen to gather detailed information on the treatment administered to individual children during this period as well as the results of haematological and other investigations.

The foundation of the LISA system is an ORACLE database. This stores comprehensive clinical information on each child enrolled into the trial. The treatment protocol is divided into seven phases: Induction, Consolidation, Interim Maintenance 1, Delayed Intensification 1, Interim Maintenance 2, Delayed Intensification 2 and Continuing Therapy. The database stores information for each of these phases, and supports the enrolment and randomisation of new patients. Risk stratification is carried out automatically at enrolment, with children allocated to one of three treatment arms according to risk factors at presentation. Doses and administration dates of all drugs in phases prior to Continuing Therapy are automatically calculated, and can be recalculated in response to changes in a child's weight or delays to treatment. Results of biochemistry and haematology investigations and bone marrow examination can be stored, as can information about drug toxicity and side effects during treatment.

Access to the database is via ORACLE forms which are intended for use by data managers and seniors clinicians at treatment Centers. The trial protocol requires that multiple case report forms be submitted to the trial co-ordinators during treatment. These can be automatically generated by the system and submitted electronically.

The Clinical User Interface

The ORACLE forms described above provide access to comprehensive data on each child. However, these forms have not been designed to satisfy the information requirements of typical clinicians. Such users require a concise summary in which the data relevant to everyday clinical decisions is given prominence. We have implemented a separate Clinical User Interface to meet these requirements.

After user-identification and selection of the patient of interest, the user is presented with a single screen displaying the key information needed to support clinicians' decision-making during
Continuing Therapy (figure 2). This includes demographic information, what point of treatment has been reached, current doses of oral chemotherapy agents and a table of historical dose and FBC data.

This table has been designed to reflect the 'look and feel' of the old, paper-based history sheets, with separate rows for each week of Continuing Therapy. FBC data, dosage information and any free text annotation are displayed for each week. Clicking on any row interrogates the decision-support engine, which returns a list of tasks usually due that week.

We wished to provide an interface that was as simple as possible would be reliably accessible from POSCUs with widely differing IT systems. We adopted a pure HTML interface to ensure maximum availability and minimise local maintenance requirements. HTML pages are dynamically generated by server-side Java Server Pages (JSPs). Clinical logic is separated from display logic using the JSP Model 2 Model-View-Controller architecture to enhance extensibility and facilitate maintenance. The Database Access Object pattern is used to separate domain objects and clinical logic from the ORACLE RDBMS persistence mechanism.

### The Decision Support Module

LISA’s decision support module was built using the PROforma decision support technology developed at Cancer Research UK. The PROforma language is a knowledge modelling system designed to allow the creation of formal, machine-readable models of clinical protocols and guidelines. The language uses a task-based approach, which emphasises the relationships between the clinical procedures described, and the constraints which govern their scheduling and applicability to different patients in different circumstances. For this project, we created a PROforma model of Continuing Therapy which included all eight of the drugs used. We also modelled the rules associated with the decision needed to adjust the dose of oral chemotherapy drugs in response to weekly FBC tests.

Decision support is invoked via the clinical user interface in a number of circumstances. First and most simply, clicking on any row of the clinical information table initiates the PROforma engine, which returns a list of clinical tasks which would usually be indicated that week. Secondly, if a user

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**Figure 2:** The Clinical User Interface to the LISA system. This is intended for point-of-care use by clinicians at Treatment Centers and POSCUs. Selecting a row in the Blood and Dose History table triggers the PROforma decision-support engine, as does entering new haematology or dosage data.
enters new FBC data, the decision support system is
invoked to provide guidance as to whether doses of
oral chemotherapy will need to be adjusted and if so,
how. Should a user wish to enter a new dosage
decision based on FBC data already recorded in the
database, the decision support system is similarly
invoked. PROforma uses an argumentation-based
approach to reasoning\(^6\) which enables a
recommended course of action to be presented to the
user together with patient-specific arguments for and
against this proposal.

The UKALL 97/01 treatment protocol is, like all
such protocols, subject to modification by trial co-
ordinators as new evidence emerges. Such changes
are likely to require modifications to the PROforma
model of treatment. That model is entirely separate
from other software components and accessed
through an inference engine with defined operational
semantics. This approach has enabled us to
incorporate changes to the treatment protocol that
have been made during the lifetime of the project
without needing to re-engineer other components of
the LISA system. The PROforma toolset includes
Computer Assisted Software Engineering (CASE)
tools to facilitate such authoring and editing
PROforma models via a graphical user interface.

DISCUSSION
The potential for computerised decision-support
systems to improve physician compliance within
clinical trials, as well as supporting safety and
efficiency, is well-recognised\(^6\). However, there has
been little progress in realising this potential – largely
due to the difficulties of translating promising
experimental systems into routine practice in
complex clinical environments. In this project, we
have been able to exploit an infrastructure developed
to support electronic data gathering to additionally
support the deployment of a decision-support system
across a large number of institutions.

The decision-support tools developed have been
targeted at recognised clinical needs - specifically
dosage adjustments and scheduling of interventions
during collaboratively delivered Continuing Therapy.
We look forward to feedback from users and
suggestions of other areas in which they feel
decision-support would be valuable. A number of
clinicians have expressed a desire to see the system
extended to provide more detailed support for
scheduling and co-ordination of interventions during
Continuing Therapy. At present, the decision-
support component informs users what tasks would
normally be due in a given week, but this information
is not patient-specific. We are exploring ways of
extending the PROforma language and inference
engine to enable users to query, for example, whether
tasks are overdue or have been cancelled, or whether
a task's intended rescheduling is within the bounds
defined by the protocol.

Other Paediatric Oncology Treatment Centers
have expressed an interest in adopting the system.
We anticipate using a number of components of the
LISA system in a similar system to be deployed
nationally to support the MRC UKALL 2002 R3 trial
of therapy for children with relapsed ALL.

The development of the LISA system has
followed an iterative design strategy, with successive
prototypes being demonstrated to potential users at
the RLH and its associated POSCUs as well as other
treatment Centers. Feedback from these clinicians
has guided revisions of the software. A formal
evaluation study of the LISA system is now planned,
aimed at exploring clinicians perceptions of the web
interface's usability and utility.

CONCLUSIONS
We have demonstrated the feasibility of deploying a
web-based clinical information and decision support
system for use in a 'Hub and Spoke' system of
collaborative cancer care. The LISA project also
demonstrates how a formal, task-based model of a
treatment protocol can be used as the knowledge
bases for a decision-support system which can be
readily centrally updated - potentially by clinical staff
with minimal technical expertise - as treatment
protocols evolve.

The approach illustrated here may be beneficial
in the management of other diseases, not only in the
field of cancer care, but for any disease for which
treatment is prolonged and requires co-ordinated
input from providers in geographically disparate
institutions.

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