

Prevention, detection and amelioration of adverse events in protocol-based decision support

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1 Introduction

The prevention, detection and amelioration of adverse events feature prominently in oncology protocols, the detailed plans for conducting clinical trials of therapies for the treatment of cancer. This paper summarises a safety review of such protocols prior to implementing OaSiS, a decision support system (DSS) in oncology [11]. OaSiS, shortly to undergo preliminary field evaluation in an oncology clinic, has been strongly influenced by the ONCOCIN [19], OPAL [17] and EON [16] family of computer systems developed at Stanford University in the last fourteen years. Like EON, OaSiS is a shell to be used with any oncology protocol provided it can be suitably represented. It does not support or critique the design of new protocols as do OPAL and DaT [21]. Even so, the safety review is still relevant to design tools like OPAL and DaT.

OaSiS is being developed at the Imperial Cancer Research Fund (ICRF) in RED, a multi-partnered project funded under the UK Safety Critical Systems Programme. A safety critical system is one where operator error or system malfunction gives rise to serious injury, death, environmental damage or financial disaster, with possible legal liability. The safety related interests of RED partners include the assessment of safety critical software (Lloyd's Register of Shipping) and the legal liability arising from safety critical systems (Masons Solicitors). Logical reasoning about safety issues is an important focus (ICRF and Queen Mary and Westfield College, University of London), as is the production of a generic decision support system generator for safety critical systems (Integral Solutions Ltd). A more detailed account of the safety review can be found in [12] and [10] contains a more general discussion of safety and soundness in relation to expert systems.

2 Oncology trials, protocols, decision support and safety

Because of variation in tumour behaviour, treatments and their administration, oncologists do not know the optimal treatment for many cancers. Instead, they enter

patients in clinical trials comparing the efficacy and safety of combinations of surgery, hormone therapy, radiotherapy and chemotherapy. Trials are governed by protocols detailing therapy plans; oncology clinics may employ as many as 40 protocols, each of the order of 30 - 50 pages in length [13]. With the increased role of chemotherapy in managing cancer, more doctors are becoming involved and so there is the potential for inconsistency in patient management (as highlighted recently in a UK national newspaper [1, 2]). Indeed, the existing administration of the majority of cancer therapy in the outpatient setting is undergoing a growing trend to home-based care [9]. With the volume of patient data collected for analysis (see fig 1) and the complexity of many protocols (see fig 2), the existing computer support will inevitably grow. However, the potential benefits of more consistent application of protocols and more complete collection of clinical data could be significantly diminished by inadequate attention to the hazards associated with chemotherapy.

Adverse events arise primarily because chemotherapy causes bone marrow suppression and damage to the gastrointestinal mucosa. A low white cell count makes patients susceptible to life-threatening infections and low platelet counts may result in life-threatening bleeding. Mucositis is unpleasant, causes severe weight loss and dehydration, and provides a route for infection. There is usually a narrow "therapeutic window" between giving sufficient drug for optimal anti-tumour effect and life-threatening toxicity. There are also other unusual side-effects relating to the total dose of chemotherapy e.g. bleomycin and lung fibrosis, adriamycin and weakening of the heart muscle. Inappropriate choice of routes of administration also causes difficulties. For example, there have been fatal "accidents" where an incorrect dosage of methotrexate or other drug was given by the intrathecal route. Incidents involving incorrect drug administration have also attracted attention in the UK press in recent months [3].

Our safety analysis is restricted to the use of computers to support the application of cancer protocols and ignores the equally important safety issues arising from the use of computers to control equipment delivering treatment, such as in radiotherapy [20], and from risks to health workers in the handling and disposal of chemotherapeutic

drugs [5].

3 Some generic safety rules

Following the analysis of many written protocols and discussion with clinical and pharmacy staff, we have formulated a number of rules for use in the safety components of "trial management" systems such as ONCOCIN and OaSiS and protocol and trial design tools such as OPAL and DaT. For lack of space, we illustrate just four rules in detail - two concerning adverse event prevention and two for policing clinicians' amendments of the protocol recommendation. They are stated in a generic format that suggests they could be reused in other application domains.

3.1 Avoiding adverse events with prophylactic treatments and warnings

Avoidance of hazards is common in many oncology protocols. The following informal representation provides a suitable generic framework - strings in italics represent variables:

(P) *Action₁* should be performed to counteract *Action₂* in *Plan* if
Action₂ is necessary part of *Plan* and
Action₂ produces *Effect* and
Effect is potentially hazardous and
Action₁ helps avoid *Effect* and
Action₁ is compatible with *Plan*

Specific examples of P are:

- P1 Prehydration helps avoid dehydration due to vomiting induced by chemotherapy.
- P2 Folinic acid rescue helps ameliorate methotrexate-induced bone marrow suppression.
- P3 Prophylactic antibiotics helps avoid infection due to bone marrow suppression.

In a trial design system, rule (P), along with a suitable pharmacological knowledge base, could be used to generate clauses such as P1-P3 for inclusion in the associated protocol, both in its paper and computerised formats. The latter could then be used as part of a trial management decision support system to generate suitable warnings and guidance on correct clinical procedures. The time-savings resulting from such semi-automated generation of paper protocols must also be balanced against its potentially patronising nature, especially when used by a highly trained clinician.

The incorrect performance of actions is a major contributor to the onset of adverse events. Once again we give the informal generic rule first:

(W) warning: *Effect of Action in Plan* is hazardous if
Action is necessary part of *Plan* and
incorrect execution of *Action* produces *Effect* and
Effect is potentially hazardous

In drug administration, hazards can arise from careless handling and from inappropriate routes or rates of injection:

- W1 Extravasation [escape to other vessels] must be avoided during the administration of adriamycin.
- W2 Bleomycin is not vesicant [blistering] but direct contact with the skin should be avoided.
- W3 Slow infusion of piroxantrone is required because of the risk of major motor seizures [9].
- W4 Severe retinal toxicity, blindness and seizures can occur when carmustine is injected by intracarotid artery [9].

Even if some of these effects might not directly threaten life, they can cause sufficient local damage to disallow other cancer treatment, or indirectly diminish its efficacy. Other examples where the hazard is not immediate occur during the preparation of treatments:

- 1 a suspension of medroxyprogesterone acetate MUST BE SHAKEN WELL before administration [9];
- 2 GM-CSF MUST NOT BE SHAKEN [9].

A related generic rule covers the sequencing of actions in order to avoid hazards. For example, the drug taxol is always given before the drug cisplatin because the reverse order can produce severe neutropenia [18] which is potentially hazardous. Since this particular example involves two chemotherapeutic drugs, it is likely to be relevant only when designing a protocol.

3.2 Avoiding augmented toxic effects and diminished efficacy

The protocol-based treatment suggestions computed by OaSiS provide the basis for a negotiated treatment plan whereby the clinician is able to modify recommendations of the DSS. Of course, such modifications need to be vetted and, if found unsuitable, replaced by safer alternatives. It is important to identify actions that might exacerbate predictable hazards - for example, the potential damage to kidney function from chemotherapy. Informally, we have

(AE) *Action₁* should not be performed during *Action₂* in *Plan* if
Action₂ is necessary part of *Plan* and
Action₂ produces *Effect* and
Effect is potentially hazardous and
Action₁ aggravates or makes *Effect* more likely and
Action₁ has alternative without *Effect*

with the following examples:

AE1 Nephrotoxic antibiotics such as gentamycin should be avoided during and immediately after giving cisplatin.

AE2 Cytarabine is incompatible with fluorouracil [9].

AE2 is another example of a safety constraint that is more useful during protocol design than during application.

Some actions, unfortunately, can reduce the desirable effects of essential treatment even though their original motivation is to make a positive contribution to therapy. In oncology, any diminishing of the efficacy of treatment can certainly give rise to hazardous situations:

(RE) *Action*₁ should not be performed during *Action*₂ in *Plan* if *Action*₂ is necessary part of *Plan* and *Action*₁ reduces efficacy of *Action*₂ and *Action*₁ is unnecessary part of *Plan* or has an alternative

In the three examples of (RE) below, the last one is likely to be useful only during protocol design.

RE1 Aspirin reduces the efficacy of Interferon-a2a. Indomethacin does not have this effect.

RE2 Presence of food significantly reduces oral absorption of didanosine. Take oral doses on an empty stomach [9].

RE3 Bleomycin can lose potency when combined with mitomycin [9].

3.3 Rules concerned with best practice and acceptable arguments for reacting to hazards

In our safety review of protocols, we have come across examples of reasoning which require a slightly different approach from those we have already cited. For example, when designing a clinical trial and an associated protocol it is assumed that every effort is made to employ the most effective and least harmful treatments in keeping with principles of beneficence and nonmaleficence [9]. Computer systems supporting trial design should include (as DaT [21] already does) relevant knowledge about acknowledged successes and failures of previous cancer trials. Examples that might be used for this purpose are

E1 Ifosfamide is believed to be more efficacious when given daily for 5 days as compared with a single dose [9].

E2 Tumour necrosis factor is not a useful antitumour agent when administered by IV or IM routes [4].

E3 Tumour necrosis factor is very active against malignant melanoma when given by isolated limb infusion [14].

Finally, there are occasions where protocols describe unacceptable arguments on which to base treatment modification even when, presumably, a potential adverse event has been detected. For example, it is unclear yet how best to handle the following:

Arg1 Doses of etoposide should not be reduced for elevated serum bilirubin concentrations [9].

Arg2 No dose modification of r-metHuG-G-CSF based on blood counts will be made [15].

4 Formalisation and implementation of the generic safety rules

We are employing a logic-based approach to the representation and application of these generic safety rules in OaSiS. Initially, we have employed an extended Horn Clause representation. For instance, rules (AE) and (RE) are applied as logic-based integrity constraints validating updates to the "database" of treatment decisions negotiated between the user and the DSS. This is a reasonable starting point, but it does not capture the temporal ordering of actions, related adverse events and pre-emptive or corrective actions undertaken to ameliorate the hazard. Moreover, it does not capture the notions of obligation, permission and authorisation that arise frequently in protocols. In view of this, we are experimenting with a modal logic, \mathcal{L}_{safe} [7, 8], with predicate symbols divided into properties and actions and modal atomic formulae expressed in the form:

[RECO]a	Action a can be recommended
[SAFE]a	Action a is safe
[AUTH]a	Action a is authorised
[PREF](a,b)	Action a is preferred to action b
[OBLG]f	Action or property f is obligatory
[t1,t2]f	Action f is taken or property f is true during the interval t1 to t2

A patient's condition can change frequently and treatment needs to be modified accordingly. We require a formalism that copes with such dynamic behaviour. Modal logic has the advantage that its possible world semantics reflects the dynamic nature of the world. Classical logic lacks a proper semantics for updates. We have viewed updates to a theory through actions. Semantically, an action changes a world to another world. The accessibility relation connects the present and permissible worlds. Therefore, each of a set of permissible worlds can be obtained by performing an action on the present world.

Note that the presence of deontic and preference modal operators makes our formalism strictly beyond first-order. This means that, in general, sentences including these operators cannot be translated to an equivalent first-order (and therefore Horn clause) representation. In contrast, if sentences contain only temporal, safety, recommendation and authorisation modal operators then we have a transformation procedure that eliminates the modal operators by shifting their relevant information to the term level so that inferences can be carried out in first-order logic. The advantage of representing these concepts through modal operators is to have a simple, but useful, uniform formalism.

Conclusion

Drug therapy in oncology is a critical balance between beneficial effects and serious side-effects. Because of the increased role of chemotherapy in cancer management, more doctors will be involved in its supervision. However, patient deaths and morbidity from treatment could produce a significant reduction in potential benefits. Thus new approaches to optimise safety are essential. Computerised decision support in oncology is inevitable, so safety analysis is an important activity to undertake before such systems become routinely available. Our approach is to follow a natural progression from informal analysis and representation, through formalisation, to implementation.

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References

- [1] 'Doctors' fail to refer cancer patients to specialist centres. *The Guardian*, December 1st 1993.
- [2] Breast cancer care inquiry call. *The Guardian*, January 14th 1994.
- [3] 'You'll die' doctor tells patient after mistake. *The Sunday Times*, 21st November 1993.
- [4] Alexander RB, Rosenberg SA: Tumour necrosis factor: Clinical applications. In: De Vita VT, Hellman S, Rosenberg SA (eds): *Biological Therapy of Cancer*. Philadelphia, J.B.Lippincott Co (1991) 378-392.
- [5] American Society of Hospital Pharmacists: Technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 47 (1990) 1033-1049.
- [6] BO03: A randomised trial of two chemotherapy regimens in the treatment of operable osteosarcoma. MRC CTO, 1 Brooklands Ave, Cambridge CB2 2BB.
- [7] Das SK and Fox J. A logic for reasoning about safety in decision support systems, 2nd European Conference on Symbolic and Quantitative Approaches to Reasoning and Uncertainty, Granada, Spain. Springer-Verlag Lectures Notes in Mathematics No 747 (1993) 79-84.
- [8] Das SK and Hammond P. An interval-based modal temporal logic. In: *Research and Development in Expert Systems X* (eds. M A Bramer and A L Macintosh) BHR Group Ltd and BCS SGES (1993) 131-141.
- [9] Fischer DS, Knobf MT and Durivage HJ. *The cancer chemotherapy handbook*. 4th Edition. (1993) Mosby, St Louis.
- [10] Fox J. On the soundness and safety of expert systems. *Artif Intell Med* 5 (1993) 1-21.
- [11] Hammond P. OaSiS: a decision-support system for the protocol-based treatment of cancer. International Conference on the Practical Application of PROLOG, London, April 1994.
- [12] Hammond P, Harris AL, Das SK and Wyatt JC. Safety and Decision Support in Oncology. *Meth. Inf. Medicine* (1994), in press.
- [13] Lane CD, Walton JD, Shortliffe EH. Graphical access to expert systems:II. Design of an interface for physicians, *Meth. Inf. Med.* 25 (1986) 143-150.
- [14] Lienard D, Ewalenko P, Delmotte J, et al. High-dose recombinant tumour necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma. *J Clin Oncol* 10 (1992) 52-60.
- [15] Mead GM and Kaye SB. A MRC/EORTC collaborative randomised trial of BEP/EP vs BOP/VIP-B with or without G-CSF in the management of poor prognosis metastatic and extragonadal teratoma. MRC CTO, 1 Brooklands Ave, Cambridge CB2 2BB.
- [16] Musen MA, Tu SW and Shahar Y. A problem-solving model for protocol-based care: from e-ONCOCIN to EON. *Proceedings of MEDINFO'92*, Geneva, Switzerland.
- [17] Musen MA, Combs DM, Walton JD, Shortliffe EH and Fagan LM. OPAL: Toward the computer-aided design of oncology advice systems. *Proceedings of Computer Applications in Medical Care*. Washington (1986) 43-52.
- [18] Rowinsky EK, Gilbert MR, McGuire WP, et al: Sequences of taxol and cisplatin: A phase 1 trial and pharmacologic study. *J Clin Oncol* 9 (1991) 1692-1703.
- [19] Shortliffe EH, Scott AC, Bischoff MB, Campbell AB, Van Melle W, Jacobs CD. ONCOCIN: An expert system for oncology protocol management. *Proc. IJCAI 1* (1981) 876-881.
- [20] THERAC Software bugs, a matter of life and liability, *Datamation*, May 15th 1987.
- [21] Wyatt JC, Altman DG, Pantin CFA, Heathfield HA et al. Design-a-Trial, a knowledge-based aid for writers of clinical trial protocols. In *proc. Medical Informatics Europe'93*, Jerusalem (1993) 68-73.

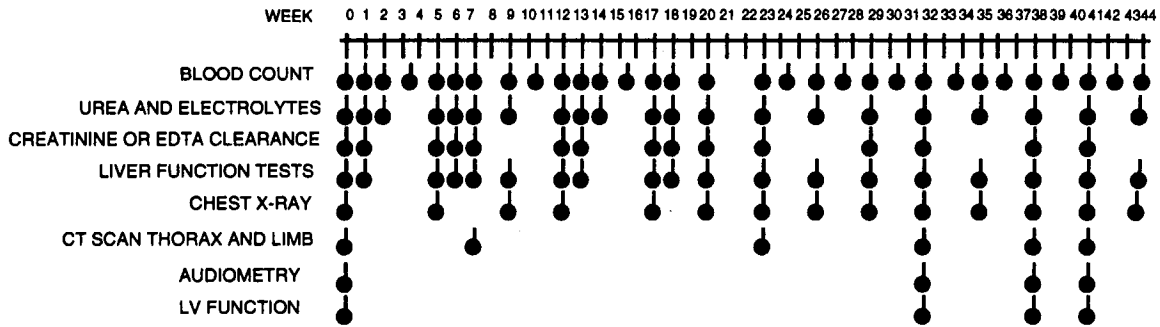


Figure 1: Data collection over 44 weeks as part of a bone cancer trial[6]

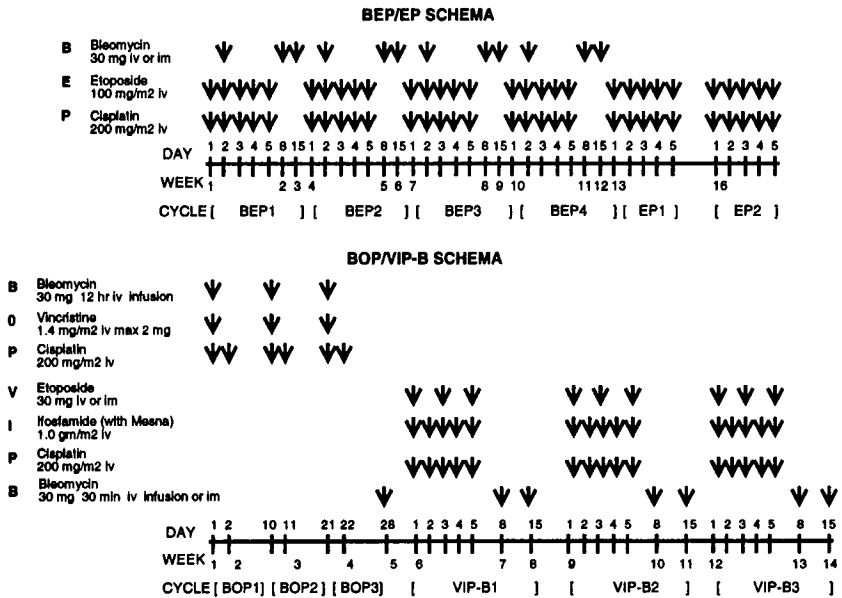


Figure 2: Part of a complex chemotherapy plan for treating testicular cancer[15]