DEVELOPMENT OF AN ELECTRONIC TREATMENT DECISION AID FOR PARKINSON'S DISEASE USING MULTI-CRITERIA DECISION ANALYSIS

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Abstract

Clinicians constantly weigh the relative importance of multiple attributes when they make decisions about how to treat patients. The literature shows that this is generally done in a relatively informal manner using intuition rather than evidence-based medicine. Decision analysis methods and computer decision support systems (CDSS) have been developed to help implement evidence-based medicine and to aid clinicians in their decision making. Multi-criteria decision analysis (MCDA) is a methodology used to break complex problems into manageable pieces, allow data and judgement to bear on them and then reassemble them to present an overall picture of the problem. The aim of the study was to use MCDA to develop a model to aid practitioners to choose the most effective drug treatments for Parkinson's disease (PD). A CDSS was developed from this model.

Two surveys were sent to 304 neurologists, 88 geriatricians as well as Parkinson's disease nurse specialists across the UK to determine the criteria for the model. The seven steps of developing a MCDA model were carried out. A value tree was created from the criteria established from the surveys. The drugs were scored for their performance against the criteria using data from clinical trials and the weights were determined by the clinician for each individual patient. Software was developed using Excel and Visual Basic for Applications (VBA) to implement the functions of the model. A sensitivity analysis was carried out to determine whether the model was suitable for use with individual PD patients and whether the software was quick and easy to use.

A total of 68 criteria were generated from the surveys, which was reduced to 11.This showed that clinicians were perhaps using personal experience more than evidence-based medicine. Scoring the data on the drugs showed that some drugs performed either better or worse than expected. The weights were phrased so that users could use swing-weighting to weight the criteria for their importance to each patient. The combined scores and weights were calculated by Excel and the result returned on the screen to the user by VBA. An expert panel carried out the sensitivity analysis and showed that there were some issues with the scores developed, such as potential bias from the trials data and that not all the expected criteria were included in the model, for example bradykinesia and tremor were not included. However, the expert panel felt that the software was quick and easy to use and overall the principle of the model was approved, subject to some modifications.

Therefore, a model was successfully developed for Parkinson's disease using MCDA and a CDSS developed to implement the model's functions. The model needs further refinement but has the potential to be successfully used in a clinical setting. MCDA could additionally be used to develop models for other diseases.

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Glossary of Abbreviations

ADL: Activities of daily living

ADR: Adverse drug reactions

AHP: Analytical hierarchy process

ANN: Artificial neural networks

BNF: British National Formulary

CDSS: Computer decision support system

COMT: Catechol-o-methyl transferase

CR: Controlled release

EBM: Evidence-based medicine

EPSS: Electronic Prescribing Support System

GP: General Practitioner

HRQoL: Health-related quality of life

IT: Information technology

MADRS: Montgomery-Asberg Depression Rating Scale

MAOB: Monoamine oxidase type B

MAUT: Multi-attribute utility theory

MCDA: Multi-criteria decision analysis

MMSE: Mini-mental state examination

NHS: National Health Service

NICE: National Institute for Clinical Excellence

NSF: National Service Framework

OD: Omni die (once daily)

PC: Personal computer

PD: Parkinson's disease

PDA: Personal digital assistant

PDNS: Parkinson's disease nurse specialists

PRN: Pro re nata (when required)

QDS: Quarter die sumendus (to be taken four times daily)

SOB: Shortness of breath

TDS: Ter die sumendus (to be taken three times daily)

UK: United Kingdom

UML: Unified modelling language

UPDRS: Unified Parkinson's disease rating scale

VBA: Visual Basic for Applications

V&V: Verification and validation

Glossary of Terms

Adverse drug reaction: An unwanted or negative consequence associated with the taking of a medicine

Computer decision support system: A computer implementation of a model used to help clinical practitioners make medical decisions

Criterion: The interest or point of view from which the alternatives are compared in a multi-criteria decision analysis problem

Decision aid: An aid used in medical decision-making to help practitioners make decisions, which may or may not be computer-based

Evidence-based medicine: The process of reviewing, appraising and using research findings to ensure optimum care is provided to patients

Multi-criteria decision analysis: A decision analysis methodology which breaks complex problems down into smaller, more manageable pieces, allows data and judgement to bear on them then reassembles them to provide an overall picture of a decision problem

Options: The alternatives available to be evaluated in a multi-criteria decision analysis problem

Parkinson's disease: A neurodegenerative disease characterised by tremor, rigidity and bradykinesia

Scoring: The process of assessing the performance of each option in a multi-criteria decision analysis problem against all the other options

Swing-weighting: A method used in multi-criteria decision analysis to rate the importance of each criterion to the decision problem. Each criterion is judged by the swing in preference on a scale of 0 to 100 against the swing on another preference scale

Unified Modelling Language: A language which describes the functionalities of a software system

Unified Parkinson's Disease Rating Scale: A rating scale which measures the functionality of different aspects of disease progress in a Parkinson's disease patient

Visual Basic for Applications: A Microsoft application used with other Microsoft software, such as Excel, which enables the user to develop an interface to carry out their own designated tasks

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CHAPTER 1

General Introduction

"Decide promptly, but never give any reasons. Your decisions may be right, but your reasons are sure to be wrong."

Lord Mansfield

BACKGROUND

The field of medical decision-making is a complex affair. The decisions clinicians make are an extremely important factor in the control of cost and quality in medical care. Medical decisions implement theory into practice and are part of the process that determines the promotion of particular prevention programmes, the diagnoses that are made and the treatments that are chosen (Eddy, 1986). Doctors need to meet the needs of patients by drawing on the 5000 years' worth of knowledge acquired by medicine (Smith, 1996).

Medical decisions, as with decisions in other fields, are often particularly complex. They may involve multiple factors, relationships and outcomes, with uncertainty involved in every aspect of the decision-making process (Eddy, 1996). Physicians are trained to make endless decisions on a daily basis regarding patients' diagnoses and treatments and have to consider huge quantities of often changing, incomplete and confusing information. They must do all this whilst under time pressure and having to consider what is often ambiguous information from the literature (Blumenthal, 2004).

There are many factors clinicians need to consider when choosing drug treatments for a patient. They need to consider all the outcomes that a patient may consider important for each possible treatment, to understand the value the patient places on each outcome and also to choose the treatment that is most appropriate for maximising the patient's health. As well as all this, there may be uncertainty about the effects a treatment can have on outcomes, how the treatment may be affected by the patient's individual characteristics and any interactions with other diseases the patient may have. Besides this, there used to be no formal languages that were available to clinicians for discovering or weighing patients' preferences (Eddy, 1986). However, tools and scales have been developed for such a purpose, such as the Visual

Analogue Scale, which measures how the patient ranks health outcomes according to their preferences (Torrance et al., 2001), the time-trade-off where the respondent gives their values of a lifetime in a perfectly healthy state compared to a period in a particular health state and the standard gamble where the patient chooses between the option of living all their life in a particular health condition against a gamble of either living in perfect health or facing certain death (Tijhuis et al., 2000).

Eddy (1986) suggests that medical practice would be virtually paralysed if physicians were to physically consider every possibility necessary when choosing a drug treatment for patients. For example, they would need to estimate the effect of the treatment on all the important clinical outcomes, to assess the patient's preference for different outcomes and weight the patient's preferences to choose the treatment with the most desirable effect. Instead of this, decisions are normally based on one or two of the most important outcomes. The decision problem then needs to optimise the outcomes selected, whilst trusting that any effects the procedure has on other outcomes is relatively unimportant. In dynamic work settings, it is often the decision-maker's aim to reach a satisfactory solution in order to gain control of a problem, rather than attempting to devise a perfect or optimal response. A continuous cycle of monitoring is involved in order to assess the situation, take appropriate actions and re-evaluate the results (Flin et al., 2007).

DIFFICULTIES IN MEDICAL DECISION-MAKING

Clinical decisions can be problematic for a number of reasons. Tavakoli et al. (2000) identified five main reasons why medical decisions are so problematic.

1. Complex information being integrated from a variety of sources
2. Information being imperfect or incomplete
3. The presence of uncertainty
4. The complex interaction between clinicians and patients
5. The imperative account for both costs and effectiveness of strategies.

These will each now be detailed in turn.

Complex Information

Clinical decisions may mean choosing between broad approaches, such as surgical or pharmacological, or choosing the specific details of therapy, such as which drug, the dose or duration of treatment. The range of choices may be bewildering, with the clinicians having to make choices between alternative therapies and to revise and review treatment with regard to the patient's status. The pathways between the actions and the outcomes may not be clear. Therefore, the problem may be unstructured but also the clinician may possess only an incomplete picture. Even if all the information is present, the clinician may lack the ability to integrate such complex information (Tavakoli et al., 2000).

Imperfect Or Incomplete Information

The rapid changes that take place in the knowledge base and the volume of information available often limit the individual's capacity to maintain and develop their skills. Decisions may therefore often be made with incomplete or imperfect knowledge. Clinicians may be unsure of factors such as the full impact of interventions, the likelihood of specific outcomes or the value patients place on those outcomes. Perfect information is frequently unattainable and the evidence that is available may not be appropriate for the decision problem being considered. Randomised clinical trials, for example, are very specific and do not necessarily cover all potentialities (Tavakoli et al., 2000).

Uncertainty

A good decision can often be affected by chance, turning it into a poor outcome. The clinician's and patient's attitudes to risk can also have a bearing on what constitutes a good decision (Tavakoli et al., 2000).

Clinician / Patient Interaction

Patient involvement in decision-making has increased sharply in recent years. Patients are better informed and want more information on treatment options and the benefits and risks of treatments, which can place greater demands on clinicians when they are considering treatment options (Tavakoli et al., 2000). However, it can also help having the patient to be involved in the decision-making process as they are able to inform the clinician of their values and preferences (Kaplan and Frosch, 2005).

Costs And Effectiveness Of Strategies

Despite the emphasis on effectiveness, the reality may be that decisions have to reflect a scarcity of resources. Therefore, decision-making has to consider both the costs of decisions and the values of the outcomes from those decisions (Tavakoli et al., 2000).

Decisions Under Uncertainty

Medical decision-making can be characterised by the need to make decisions despite having incomplete knowledge of the patient's true condition or the therapeutic effect of a given management strategy (Kuipers et al., 1988). The critical decision a clinician must make between diagnostic and therapeutic alternatives is a paradigm example of decision-making under uncertainty (Hall, 2002). The spectrum of decision-making in medicine runs from simple to complex and relates to the level of uncertainty. A variety of tasks need to be carried out which have varying degrees of certainty (Croskerry, 2005). Rather than being certain most health outcomes from medical decisions are probabilistic (Lurie and Sox, 1999, Ratliff et al., 1999).

Many of the medical decisions made by clinicians can be classed as being made by intuition. This is a form of cognitive 'short-circuiting', where the decision may be made even though the reason for the decision cannot be fully described (Hall, 2002). Any decisions made are therefore made under uncertainty. Uncertainty may be classed as technical, personal or conceptual.

Technical uncertainty

Where there is insufficient information to predict prognosis or the effect of an intervention this could be classed as 'technical' uncertainty. There may not be adequate research on the best way to use new technologies. Uncertainty could also come from the rapid growth of medical knowledge, with the practitioner being unsure whether or not they are really up-to-date with all the current information (Hall, 2002).

Personal uncertainty

'Personal' uncertainty may arise from the doctor-patient relationship where the patient's wishes may not be known and it may be difficult for the practitioner to establish what their wishes are. A practitioner may also be uncertain because of their own emotional attachment to a patient, leading to a fear that their decision-making may be impaired. Uncertainty may also arise from the practitioner's lack of knowledge of their patients (Hall, 2002).

Conceptual uncertainty

'Conceptual' sources of uncertainty may stem from an inability to assess different patients' needs competing for limited resources or the application of general criteria such as guidelines to individual patients. Another source may come from uncertainty about applying past experiences to current patients, as well as uncertainty about the future (Hall, 2002).

Decision-making Strategies

Decision-making in medicine can be broadly categorised into four groups of decision-making strategies. These are 'intuitive', 'rule-based', 'option comparison' and 'creative' decision-making.

Intuitive decision-making

'Intuitive' decision-making is where a problem can be recognised and a solution recalled from a rule that has been memorised or from a personal or observed technique that had been used before in a similar situation. The course of action chosen is likely to be an automatic process where little conscious deliberation has been involved (Flin et al., 2007). This strategy is

most likely to be used by experienced practitioners as less experienced practitioners would by definition have less experience to draw on.

Rule-based decision-making

With this strategy procedures for a particular situation need to be looked up or remembered. This could mean referring to an evidence base or implementation of guidelines from a body such as the National Institute for Clinical Excellence (NICE). More mental effort is involved than intuition. This form of decision-making is often used by novice practitioners who learn particular procedures for certain situations. The process can become automatic with time and the rule retrieved from memory with little effort. It can however lead to skill decay if practitioners find themselves in an unfamiliar situation where no rule exists (Flin et al., 2007).

Option comparison decision-making

'Option comparison' is often referred to as 'analytical' or 'rational choice' decision-making. A number of possible courses of action are recalled and compared simultaneously to determine which is most fitting to a particular situation. A number of mathematical and statistical techniques can be used to help select the optimal choice. However considerable time and concentration is required to conduct a thorough analytical comparison (Flin et al., 2007).

Creative decision-making

This particular strategy is rarely used in high time pressure environments as a novel course of action must be devised for each new situation. However, it may be used in surgery, for example, for an intraoperative endoscopy to look for an occult bleeding source for a gastrointestinal bleed (Flin et al., 2007).

Bias In Decision-making

Heuristics are often used as part of intuitive decision-making. Heuristics are rules or guidelines that are used to make complex tasks simpler to streamline decision-making (Nierenberg et al., 2008, Hall, 2002). Heuristics are often regarded as being a source of error or bias (Hall, 2002). Individuals may be helped by heuristics in addressing complicated scenarios, but they can also

lead them to make systematic errors in their interpretation of the probability of events. Personal events may help practitioners to formulate heuristics which can simplify and bias future decisions they make regarding complex case presentations. Personal clinical experience or the experience of other colleagues can unduly influence the prescribing choices they make by presenting them with easily recalled examples of events (Nierenberg et al., 2008).

DECISION-MAKING MODELS

Several different models of medical decision-making exist: namely the 'paternalistic', 'informed' and 'shared' models. These will each be outlined in turn.

Paternalistic Model

This is the model which was the dominant approach to decision-making in medicine for many decades (Charles et al., 1997, Charles et al., 1999a, Charles et al., 1999b). In this form of decision-making the patient adopts a passive role to the professional's authority and agrees to their choice of treatment. There is an assumption that the doctor will make the best treatment decision and does not need to elicit personal information from, or involve the patient in, the decision-making process. The flow of information is one way from the physician to the patient (Charles et al., 1999a). The physician's role in this model is as a guardian of the patient's best interest (Charles et al., 1997). The physician weighs the benefits and risks of treatment options by himself or in conjunction with other physicians. In implementing a treatment choice the physician is the decision maker, although their decision is not totally autonomous as the patient's consent must be obtained (Charles et al., 1999a). There is no sharing at any stage of the decision-making process though, so a doctor-patient partnership does not exist by definition (Charles et al., 1999b). It could be argued, states Charles et al. (1999b) that the doctor and patient enter a form of partnership based on agreement about how the process will be undertaken, but an explicit

discussion of alternative models of decision-making would be needed for this and the doctor may already have adopted a paternalistic approach from the outset of the process. In certain situations though, this may be the best approach for physicians to adopt, such as in emergency situations where no other model is feasible (Charles et al., 1997).

Informed Model

With the 'informed' model there is a partnership between the doctor and patient with a division of labour. The doctor communicates information to the patient on the relevant treatment options and their benefits and risks. This is the doctor's main contribution to the decision-making process, with the patient deliberating the evidence and making the decision. The doctor has no involvement in these two phases or investment in the treatment decision the patient makes (Charles et al., 1999b, Gafni et al., 1998). The 'informed' decision-making model is based on the assumption that the patient is empowered by the information they receive to become a more autonomous decision maker (Charles et al., 1997).

Shared Model

The 'shared' model of decision-making is different, in that the doctor and patient share all stages of the decision-making process together (Frosch and Kaplan, 1999, Elwyn et al., 1999b, Charles et al., 1997, Charles et al., 1999a). There is therefore a two-way exchange of information, with both the doctor and the patient sharing their treatment preferences and both agreeing on the decision that will be implemented (Charles et al., 1999b). The patient must provide the physician with information about their values, preferences and beliefs, ensuring that both patient and doctor can evaluate the treatment options in light of the patient's specific situation and needs (Charles et al., 1999a, Kaplan and Frosch, 2005). Doctors may face a challenge with this approach in needing to create an environment in which patients feel comfortable about expressing their treatment preferences (Charles et al., 1999b).

Charles et al. (1997) identified several key characteristics of shared decision-making. These they consider to be the minimum necessary criteria for classifying the physician-patient decision-making process as shared decision-making.

- Two participants – shared decision-making always involves two participants; the patient and the clinician. Very often more than two participants may be involved, particularly if the patient chooses a family member or carer to be present. There may also be more than one clinician involved in the process.
- Both parties participate in the process – patient preferences for participation in decision-making may not match their actual participation however. Patients may express a preference for participation in decision-making but not actually translate this into actual information seeking behaviour. There may be a number of reasons why patients do not use the information they seek:
    - Firstly, a patient's preference not to participate may reflect personality characteristics;
    - Secondly, their preference not to participate may reflect a response specific to a certain situation;
    - Thirdly, patients may express a preference for a passive role in decision-making because previous experience has taught them that more active roles are not well received by clinicians;
    - Finally, taking a passive role may reflect a cohort effect, for example with elderly patients.
- Sharing information is a pre-requisite to shared decision-making – the physician must as a minimum give patients treatment alternatives and their potential consequences so that the patient can obtain informed consent. Otherwise, it could be possible that the patient has nothing to evaluate. Both patients and clinicians bring information and values.
- Both parties agree on a decision – shared decision-making can refer to an outcome as well as the type of decision-making process. If decision-making is shared clinician and patient may agree on one outcome or may make no decision or may disagree about the preferred

treatment. If the decision is truly shared both parties should agree that a particular treatment should be implemented, regardless or whether they both think this is the best treatment for that patient. This distinguishes shared decision-making from other types of decision-making processes.

Barriers to shared decision-making

Shared decision-making has been emphasised as the model of medical decision-making to be practised, yet despite this shared decision-making has not always been happening in practice, as was shown by one study of GPs in the UK (Stevenson et al., 2000) and their communication with patients showed that the first two of Charles et al.'s (1997) key characteristics of shared decision-making (patient participation and doctors sharing information) were not observed. Where information was shared patients' beliefs were often not taken seriously, therefore there was little consensus about the preferred treatments. GPs in Stevenson et al.'s (2000) study cited lack of time and other organisational pressures as reasons for not engaging in shared decision-making, alongside a belief that patients may lack the will or ability to participate in decision-making. Further studies of GPs' attitudes to shared decision-making (Weston, 2001, Elwyn et al., 2001b, Stevenson, 2003, Elwyn et al., 1999a, McKinstry, 2000) showed that doctors supported the idea of shared decision-making, although patients vary in the extent to which they wish to participate in shared decision-making and time constraints act as a barrier to shared decision-making being carried out. It has also been shown (Kaplan et al., 1995) that male patients were less likely to participate if they saw a male physician and that female patients participated more in shared decision-making regardless of the clinician's gender. For shared decision-making to be more widely accepted more time is needed for the consultation process and patients need to be more comfortable with the uncertainty and chance of less than perfect outcomes that medical decision-making offer (Holmes-Rovner et al., 2000).

EVIDENCE-BASED MEDICINE

What Is Evidence-Based Medicine?

Evidence-based medicine (EBM) is an increasingly common approach to medical decision-making. It broadly encompasses a process of turning clinical problems into questions and locating, appraising and using research findings as the basis on which clinical decisions are made (Belsey and Snell, 2001, Rosenberg and Donald, 1995). EBM, say Sackett et al. (1996) is the conscientious, explicit and judicious use of current best evidence to make decisions about individual patients' care. EBM is important in helping to resolve some of the problems with uncertainty in medical decision-making (Kaplan and Frosch, 2005) and also attempts to eliminate bias as much as possible (Borry et al., 2006). Obtaining good quality evidence, such as from randomised trials, is essential in order to provide good quality healthcare (Barratt, 2008, Haynes, 2002). The randomised controlled trial generally provides the best means of determining the effect of therapy, therefore a randomised controlled trial or a meta-analysis of such trials should inform all medical decisions made (Devereaux and Yusuf, 2003). EBM integrates individual clinical expertise with the best external clinical evidence available from systematic research (Sackett et al., 1996), a necessary process when information on a specific field is lacking in the literature or is of poor quality (Lacaine, 2005). Clinicians also need to incorporate the opinions and values of the patients and their carers, as well as personal experience, judgement and skills (Akobeng, 2005).

EBM uses formal rules to allow clinicians to interpret and accept or refute results from clinical research (Lacaine, 2005, Kaplan and Frosch, 2005). Critical appraisal is used to determine the validity and applicability of the evidence found, which is then used to inform clinical decisions. Evidence-based medicine can be both taught to and practised by clinicians at all levels and can help to close the gulf between good clinical research and clinical practice. It can also help to promote self-directed learning and teamwork, producing faster and better doctors (Rosenberg and Donald, 1995). Good doctors tend to use both clinical expertise and the best available evidence,

with neither proving to be enough on their own (Sackett et al., 1996). EBM emphasises that for clinical expertise to be used for optimal decision-making clinicians need to also understand rules of evidence to be able to interpret and apply literature on causation, prognosis, diagnostic tests and medical interventions (Chou, 2005). Reviewing the available evidence may help decision-making when there are several therapeutic options available, which allows clinical acumen and autonomy to still play a central role in the care of patients (Kruer and Steiner, 2008).

The basis of evidence-based medicine is not a new idea, as practitioners identify questions raised by caring for their patients and often consult the literature available. However, an explicit evidence-based framework provides two distinctions. Firstly, it makes consulting and evaluating the literature a routine and fairly simple procedure. Secondly, the process can be made workable for clinical teams as well as for individuals (Rosenberg and Donald, 1995).

EBM is a term for five linked ideas (Sackett and Rosenberg, 1995a).

- Clinical and other healthcare decisions should be based on the best available patient and population-based evidence, not just laboratory-based evidence.
- The decision problem determines the nature and source of evidence that is searched for.
- In order to identify the best evidence epidemiological and biostatistical ways of thinking need to be integrated with those from pathophysiology and personal experience.
- The conclusions of the evidence search and critical appraisal of the evidence are only worthwhile if they are translated into actions which affect patients
- Clinicians' performance should be continuously evaluated in the application of these ideas.

The practice of EBM is therefore a process of life-long, self-directed learning.

The Process of Evidence-Based Medicine

There are four steps involved in the process of using evidence-based medicine (Rosenberg and Donald, 1995, Guyatt et al., 2000):

- Formulation of a clinical question from a patient's problem
- Searching of the literature for relevant articles
- Critical appraisal of the evidence for its validity and usefulness
- Implementation of useful findings in clinical practice.

Setting the question

The question that is formed regarding a patient's problem can be related to diagnosis, prognosis, treatment, iatrogenic harm, quality of care or health economics. The question should be as specific as possible and should include the type of patient, the clinical intervention and the relevant clinical outcome (Rosenberg and Donald, 1995).

Finding the evidence

Once the question has been set the best available evidence needs to be searched for next. Clinicians need to develop effective searching skills and have access to bibliographic databases, examples including the Cochrane Database of Systematic Reviews, the ACP Journal Club and search engines such as PubMed (Rosenberg and Donald, 1995).

Appraising the evidence

The evidence needs to be critically appraised for its validity and clinical usefulness. This step is crucial for the clinician to be able to decide whether an article can be relied on for its guidance. Clinicians need to be able to ask key questions about the validity of the evidence and its relevance to particular patients (Rosenberg and Donald, 1995). Good quality studies from higher levels of the evidence hierarchy should have more impact on clinical decisions than poorer quality or lower level evidence (Chou, 2005).

Acting on the evidence

Once clinicians have identified valid and relevant evidence they can either implement it directly in patients' care or develop team protocols or hospital guidelines. Evidence can also be used to change continuing medical education programmes or audit. According to Rosenberg and Donald (1995) implementation of evidence is best carried out through group discussions on ward rounds or other clinical team meetings.

Clear data presentation

Published evidence needs to be presented quickly and clearly. A one page user-friendly summary, similar to an abstract on a published paper can be used by clinicians to present evidence to their teams (Rosenberg and Donald, 1995).

Advantages of Evidence-Based Medicine

Evidence-based medicine provides a number of advantages for clinicians. Firstly, it integrates medical education with clinical practice. Rosenberg and Donald (1995) state that doctors who begin learning evidence-based medicine become adept at generating their own questions and then following the questions through with literature searches. Evidence-based medicine can also be learnt by people from varied backgrounds and at any stage of their career. Additionally, evidence-based medicine has the potential for improving continuity and uniformity of care due to common approaches developed by its practitioners. It can provide a structure for effective team work and communication through team-generated guidelines. Evidence-based medicine can also help providers of healthcare make better use of limited resources by enabling them to evaluate the clinical effectiveness of various treatments and services.

A number of advantages also exist at individual and group level for practitioners and also for patients (Rosenberg and Donald, 1995):

Individuals:

- Clinicians can upgrade their knowledge base on a routine basis

- Clinicians' can improve their understanding of research methods and become more critical in their use of data
- Confidence is improved in management decisions
- Computer literacy and data searching techniques are improved
- Reading habits are improved

Clinical teams:

- Gives a team a framework for group problem solving and teaching
- Junior staff can contribute usefully to teams

Patients:

- Resources are used more effectively
- There is better communication with patients about the rationale behind decisions.

Disadvantages of Evidence-Based Medicine

Despite the advantages of evidence-based medicine there are also a number of disadvantages. Firstly, the time it takes to both learn and practise it. For example, it takes time to set a proper research question, to find and appraise the evidence and act on the evidence. For teams to benefit from evidence-based medicine all members needs to be present when both the question is set and for the evidence to be acted on. There is also a cost involved in establishing an infrastructure for practising evidence-based medicine, such as purchasing the necessary hardware and software as well as subscriptions to databases. However, these costs may be small compared to the cost of many medial interventions and the costs may be recovered by reducing ineffective practice. Evidence-based medicine may also expose gaps in the evidence which can be frustrating for practitioners, particularly if they are not very experienced. The identification of such gaps can help to generate local and national research projects however (Rosenberg and Donald, 1995). Clinicians are assumed to be proficient in the methodology and statistics needed to validate the evidence, needing to be capable of analysing the methods used to achieve published results, something which Lacaine (2005) says many clinicians, particularly surgeons, are not 'experts' in. Many of the databases used for searching for literature, such as Medline, are not always terribly well

indexed or comprehensive. Additionally, senior clinicians may see evidence-based medicine as a threat if a junior member of a team has as much authority on a subject as a senior member through literature searches and this can alter the team dynamic (Rosenberg and Donald, 1995). EBM however, can never replace clinical expertise and it is the clinician's expertise which decides whether the evidence can be applied to an individual patient (Sackett et al., 1996). EBM provides clinicians with guides to help them decide how applicable evidence from randomised controlled trials is to individual patients and to quantify the risks and benefits for individual patients when treatment decisions are made (Bassler et al., 2008a). EBM can be considered to be patient-oriented and recognises individual patients' needs (Bassler et al., 2008b).

Barriers to Evidence-based Medicine

EBM constitutes a considerable challenge to clinicians, with many clinicians needing to develop skills that they would not have acquired during medical school. This could lead some clinicians to reject EBM due to their lack of the specific skills needed, leading them to consider it as impractical or inappropriate (Ghali et al., 1999, Guyatt et al., 2000). Clinicians may also feel that they are too busy to have time to search for and critically appraise the relevant published evidence (Guyatt et al., 2000, Ghali et al., 1999). Clinicians often find when they are searching for information that the existing knowledge is not accessible to them in real time and may not even map to the issue they are concerned with (Clancy and Cronin, 2005). A study of clinicians' attitudes towards EBM found that clinicians' lack of knowledge and familiarity with the skills needed was the main barrier against them using EBM, although they were not necessarily sceptical about the concept (McAlister et al., 1999). There still remains, however, a huge problem with implementing EBM and its implementation is therefore only achieved in a fairly patchy manner in practice (Barratt, 2008).

Three strategies have been suggested for removing barriers to EBM (Sackett and Rosenberg, 1995b, Sackett and Rosenberg, 1995a). The first of these is learning evidence-based medicine so that clinicians become life-long, self-

directed learners of EBM. Secondly, clinicians need to seek and apply evidence-based medical summaries created by other clinicians. Lastly, clinicians must accept the evidence-based practice protocols that have been developed by their colleagues. Sackett and Rosenberg (1995a and 1995b) consider that these three strategies would be effective in helping overcome some of the barriers imposed on clinicians by lack of information and the context within which medicine is practiced. In order to improve uptake of evidence into practice those working in evidence translation need to be more acquainted with clinician behaviour and the clinician's view of compelling evidence. Being more aware of clinicians behaviour could lead to a clearer map of the barriers to, and incentives for, evidence uptake (Scott, 2007).

Teaching Evidence-based Medicine

A commentary (Dobbie et al., 2000) suggested that there was little good evidence that teaching programs of EBM changed learners' practice behaviour or improved patient treatments and outcomes. However, other studies (Ghali et al., 2000, Schilling et al., 2006, Dorsch et al., 2004) have shown that introducing EBM into medical students' teaching programs improved students' literature searching and critical appraisal skills and their knowledge and awareness of EBM. Ghali et al (2000) state that educational interventions targeting each of the skills necessary to use EBM must be taught to undergraduate medical students if they are to become effective evidence-based practitioners. Dorsch et al.'s (2004) study showed that introducing EBM to third year medical students gave them an opportunity to practice the skills and reinforced that current best evidence should be used to make decisions about individual patient care, even if they did not have all the necessary skills to do so at that stage. Schilling et al. (2006) used e-learning technologies to teach EBM to undergraduate medical students and found that it increased the likelihood of them identifying the best available evidence for patient management. They further found that students who had completed their on-line curriculum showed superior performance over control students in areas such as literature searching. Contrary to these studies, an evaluation of EBM teaching to undergraduates in Thailand (Wanvarie et al., 2006) showed that students were able to complete the EBM steps, but the results for their

final multiple choice question examination were less satisfactory than was hoped. Handheld computers (PDAs) have also been developed to help students use EBM (Lam et al., 2004, Johnston et al., 2004). One was developed for medical students to use to facilitate the adoption of EBM at the point of care (Johnston et al., 2004) which the students found useful, although its utilisation was low overall. Lam et al. (2004) found that there were barriers to implementing the learning of EBM in an undergraduate setting though, such as a limit to its usefulness because students felt that their use of the PDA would be criticised by their teachers and the PDAs were therefore considered to not be as useful as they could have been.

Reviews and appraisals of teaching of EBM skills (Taylor et al., 2000, Parkes et al., 2001, Coomarasamy and Khan, 2004, Straus et al., 2005, Yew and Reid, 2008, Smith et al., 2000, Dinkevich et al., 2006, Moharari et al., 2008, Norman and Shannon, 1998, Shuval et al., 2007a) showed mixed results. Both Taylor et al.'s (2000) review and Straus et al.'s (2005) study showed an improvement in clinicians' EBM skills, Taylor et al. (2000) showing that an improvement in assessed outcomes of 68% was demonstrated after critical appraisal skills training, although they state the results should be viewed with caution due to the poor quality of the studies reviewed. Straus et al. (2005) showed that a multifaceted EBM intervention improved evidence-based practice patterns among clinicians and residents in a district general hospital. However, Shuval et al.'s (2007a) study showed no statistically significant impact on doctors' performance in test ordering or on their patients' use of drug treatments after an EBM educational intervention. Three studies of teaching EBM skills to residents (Smith et al., 2000, Dinkevich et al., 2006, Moharari et al., 2008) showed improvements in EBM skills, although contrary to this other studies (Norman and Shannon, 1998, Yew and Reid, 2008) showed either only small changes in knowledge of critical appraisal after changes in EBM education or that residents did not practise the EBM skills they had learnt. An interactive, longitudinal EBM course was shown to improve the main skills needed for practising EBM; literature retrieval and critical appraisal skills (Nicholson et al., 2007). A two week EBM rotation for residents was shown to increase their skills and confidence, with residents

and faculty staff feeling that the teaching improved the quality of patient care (Thom et al., 2004). Parkes et al.'s (2001) review showed there are large gaps in the evidence as to whether the teaching of critical appraisal could have a positive impact on decision-making or patient outcomes. One study showed the need to enhance physicians' skills and perceptions of EBM and to also improve the ease with which evidence-based resources can be used at the point of care (Shuval et al., 2007b). Evidence-based information retrieval could be simplified by tailoring the system to the clinic, such as through integration with a CDSS (Shuval et al., 2007b). Coomarasamy and Khan (2004) suggest that the teaching of EBM should be moved from the classroom to clinical practice in order to achieve improvements in patient outcomes.

Application of Evidence-based Medicine

Various studies (McAlister et al., 1999, Fairhurst and Huby, 1998, Douketis and Lloyd, 2008, Forbes et al., 2008, Rigg et al., 1999, Lockwood et al., 2004) have looked at the impact of EBM on clinicians' practice. Fairhurst and Huby (1998) looked at GPs' use of EBM for prescription of statin drugs and found that GPs were aware of evidence for statins in secondary prevention of coronary heart disease but not so clear about the evidence for primary prevention, but they lacked technical skills for appraising the evidence from clinical trials. A study in Canada developed new practice algorithms based on EBM to prevent surgical site infections (Forbes et al., 2008) and found that evidence-based care pathways could be feasibly implemented in their day to day patient care, although they suggest a larger, multi-centre study would need to be carried out in the future. Also in the field of surgery, a programme of 'fast-track' surgery (Kehlet and Wilmore, 2008), that is accelerated recovery and decreased convalescence, has been shown to enhance postoperative recovery. This 'fast-track' surgery is based on evidence-based care and both enhanced postoperative recovery and reduced morbidity. Lockwood et al. (2004) assessed the impact of routine EBM meetings on routine clinical practice over a period of seven years and found that treatment guidelines became more closely based on published evidence and led to improvements in patient care.

DECISION ANALYSIS

Decision analysis is a process which is undertaken prior to the decision being made, using the available evidence to create a model. The subsequent decision is informed by the model, although not necessarily predicted from it (Waller and Evans, 2003). Decision analysis techniques formalise the question of whether an intervention should be adopted or rejected. It identifies the set of consequences of concern for the decision maker that could result from each of the available options and determines the associated probabilities. An expected net impact can be obtained for each option from the aggregation of the probability-weighted consequences (Claxton et al., 2005). Decision analysis can help overcome decision-making complexity by structuring the problem clearly and providing a formal analysis of the implications of different treatment outcomes (Tavakoli et al., 2000).

One of the strengths of decision analysis is that it offers an explicit and systematic approach to decision-making based on rationality, rather than intuition (Elwyn et al., 2001a). Many factors can be presented and incorporated in decision analysis, with the decision being based on a fuller range of information than it would be in an unstructured approach. Another strength is that it is not just based on probabilities, but also on the value placed on various outcomes. Thus, it represents a method for synthesising both facts and human values, which, put together, determine the best course of action (Lilford et al., 1998).

Healthcare is a clear example of an area where human ability to integrate the range of relevant variables is outstripped. With clinical decision analysis, choices and potential outcomes need to be defined and ideally contextualised for individual patients. This may make the decision-making process more rigorous and tailored to the individual (Elwyn et al., 2001a). Decisions made by healthcare professionals based on intuition do not lessen the problem that the basis for the decisions cannot be made with certainty. Clinicians need to be able to relate the results of a trial to particular patients. Although this is usually done intuitively, formal decision analysis provides a framework for

developing decision-making algorithms. Making complex decisions intuitively can result in oversimplification of the problem as it is difficult to consider several components of the decision simultaneously. However, using decision analysis provides transparency through the decision-making process as well as providing an audit trail, both of which lead to an improvement in the quality of decision-making.

Decision analysis can help clinicians choose between different treatment options in the following ways. Firstly, a decision tree is used to present the options graphically, with all the possible outcomes being displayed for all the treatments and 'nodes' signifying which paths can be influenced by decisions and which cannot (Yentis, 2006, Tavakoli et al., 2000). The aim of the decision analysis is to reduce the decision process into the relevant individual decision points (Lilford et al., 1998). The clinician then assists the patient in assigning a 'utility' to each outcome, this is often a figure between zero (the worst possible outcome) and one (the best possible outcome) these then allow meaningful comparison to be made between the alternative outcomes (Yentis, 2006, Lilford et al., 1998).The utilities are then multiplied by the probability of each outcome, with the sum of the values indicating which treatment is the best option for that particular patient (Yentis, 2006). Sensitivity analysis is used to determine how robust the choices that have been made by the decision analysis are. The utilities can be varied to see how a decision might change, determining the sensitivity of the analysis (Lilford et al., 1998).

Decision analyses can be carried out for groups of patients with similar clinical features and personal utilities. Decision analysis can therefore provide a means for clinicians to move from finding evidence to implementing it (Lilford et al., 1998). Decision analysis can help the ethical principle of veracity be achieved as the analysis is explicit about the uncertainties in clinical practice and also uncovers the complexity of decision-making (Elwyn et al., 2001a). The robustness of a decision analysis model can be tested by carrying out the sensitivity analyses which will show the model and its decisions are credible if the decisions suggested by the model are stable when underlying

assumptions are varied. Stakeholders can openly interrogate or challenge the problem definition and identify parts of the model or assumptions which they may disagree with. These can then be tested with further sensitivity analysis. Such a process leads to clearer conceptualisations, better models and better decision-making (Tavakoli et al., 2000).

The problems of using probabilities and values, which cannot be measured with any certainty, are not lessened if clinicians approach decisions intuitively. Decision analysis is needed to make uncertainties explicit. Complex decisions cannot be made intuitively because it is not possible to incorporate and consider the various components of the decision simultaneously and clinicians need help in thinking about such complex situations (Lilford et al., 1998, Elstein, 2004). Decision analysis is an aid to solving complex problems in a systematic way within a background of imperfect information and uncertainty. It is not, however, designed to replace the judgement of the decision maker (Tavakoli et al., 2000).

Decision Aids

Both evidence-based medicine and decision analysis are involved with improving the quality of medical decisions and both emphasise a quantitative approach to providing guidance to clinical decision makers (Elstein, 2004). Decision aids have been developed as a way of creating a mechanism for empowering patients and applying research evidence to clinical practice. Decision aids can therefore help to align medical practice with the best available evidence (Holmes-Rovner et al., 2007). They can also assist in improving the amount of informing and decision sharing with patients. Many clinicians believe they practice EBM, although the rules of evidence have rarely been formally applied (Kaplan and Frosch, 2005). Practitioners may therefore be exercising their own opinions of what treatments do or do not work (Davidson et al., 2003). Decision aids may be used to help patient involvement in decision-making in order to facilitate shared decision-making (Kaplan and Frosch, 2005) as well as incorporating evidence-based medicine. Decision aids are not designed to replace the consultation between physician

and patient but to provide information about clinical options and their likely outcomes (Barry, 2002, O'Connor et al., 1999).

A decision aid was developed for vascular surgeons (Timmermans et al., 2001), which showed that surgeons agreed with the model's choices in 81% of cases. Timmermans et al. (2001) suggest that the model can be used by inexperienced surgeons to improve their decision-making and that an evidence-based decision analytical tool can increase the quality of clinical decisions. They further suggest that any discrepancies between the decisions clinicians make and the recommendations the decision aid makes can be used to teach clinicians to make better decisions. A decision analysis based support tool was developed for use of warfarin for patients in AF (Thomson et al., 2002). This was developed with the aim of supporting better shared decisions in an area which they say has suffered from lack of implementation of the evidence base. Thomson et al. (2002) state that use of such a tool can help incorporating the patient in decision-making under uncertainty, whilst also bringing the evidence base to the consultation.

Patient decision aids

Patient decision aids are designed to improve sharing of information and decision-making between clinician and patient, an area which has been shown to be suboptimal (Holmes-Rovner et al., 2007). Patient decision aids can help reduce decisional conflict so that patients are more comfortable with their choices and decisions match more closely with their personal values (Barnato et al., 2007). Decision aids help to provide a structure for making a choice and present patients with information on the available options and the risks and benefits those options bring with them. Evidence-based decision aids provide a synthesis of up to date evidence on the risks and benefits of each available option (Graham et al., 2003). Some have raised concerns though about the quality of patient decision aids, especially with regard to them being updated with new information about treatment options, benefits and risks (Deyo, 2001). This, state Barnato et al. (2007), is particularly important in an area like cancer screening and treatment, where new technologies are constantly emerging. Patient decision aids had tended to be

focused on single-event decision-making, such as choice of surgery, although more recently more decision aids have been produced for chronic care (Holmes-Rovner et al., 2007).

It has been suggested that the usefulness of patient decision aids remains to be tested (O'Connor et al., 2004). Incorporating patient decision aids into medical care could require much reengineering of the processes of care through the health system (Blumenthal, 2004). In order to support patient welfare by using good quality decision aids such decision aids must be disseminated and research carried out on the best ways to develop cost-effective and feasible mechanisms for disseminating the aids into daily clinical practice (Barnato et al., 2007). However, a symposium held by the International Patient Decision Aid Standards in 2006 failed to determined whether or not patient decision aids are the best way to improve clinical decisions or whether they might become the best way (Holmes-Rovner et al., 2007).

A review of patient decision aids (O'Connor et al., 1999) showed that decision aids improved the patients' average knowledge score of options and outcomes by 13 to 25 points, whilst patient decision aids have been shown to have a positive impact on decisional conflict in many studies (Murray et al., 2001b, O'Connor et al., 1999, Molenaar et al., 2000, Barry, 2002, Murray et al., 2001a). O'Connor et al. (1999) also assessed the impact of the decision aids on patients' decisions about major surgery, showing that the decision aids reduced patients' preference for more intensive surgery by 21-42%. They also discovered that three of the decision aids increased the proportion of participants taking a more active part in the decision-making, a finding echoed in two trials of interactive multimedia decision aids (Murray et al., 2001a, Murray et al., 2001b). O'Connor et al.'s (1999) review showed that patient decision aids were better than usual care for improving patients' knowledge about options and reducing decisional conflict, as well as encouraging patients to play a more active role in decision-making. Molenaar et al.'s (2000) review described a need for more and better controlled studies of the effectiveness of decision aids. The studies of interactive multimedia

decision aids also showed that using web-based technology would reduce the cost of intervention and could be delivered cheaply over the internet (Murray et al., 2001a, Murray et al., 2001b).

Graham et al. (2003) assessed physicians' attitude towards decision aids to gauge their acceptability and the factors that influence their interest in using them with patients. They assessed three decision aids with 141 clinicians and identified factors such as the content and format of the decision aid, their patients' abilities to use the decision aid and the extent to which the aid might facilitate or impact on their work as factors which would influence their decision to use the aid with patients. A study carried out with patients assessing the usefulness of a decision aid for hypertension (Thomson et al., 2006) showed that patients found the decision aid useful for providing individualised information, taking account of their own values and preferences for different treatment options. Some patients felt this approach was not particularly helpful and patients varied in the amount of information which they wanted and the extent to which they wanted to be involved in the decision-making process. It has been shown that some patient groups, such as the elderly, may not always want to be involved in shared decision-making (McKinstry, 2000). Thomson et al. (2006) however, found that the decision aid could be a useful way to provide patients with individualised information in order to promote shared decision-making.

COMPUTER DECISION SUPPORT SYSTEMS (CDSS)

Evidence shows that CDSSs are a valuable tool for fostering the process of dissemination and uptake of clinical guidelines, which can improve medical decision-making and clinical outcomes (Coiera, 2003, Kotze and Brdaroska, 2004). Use of CDSS has increased as they are able to provide clinicians with patient-specific recommendations which can aid with clinical decision-making (Kawamoto et al., 2005, Sucher et al., 2008). CDSS have been considered to increase healthcare quality (Sim et al., 2001).

Use of CDSS can mean better access to and improved use of clinical evidence, as well as more appropriate clinical decision-making and an improvement in the quality of care, and also improving clinical performance and very often patient outcomes (Galanter et al., 2008, Sintchenko et al., 2007). CDSS offer a method of implementing a broad range of evidence based guidelines so that patients receive the best care available (Sucher et al., 2008). One study showed that a CDSS could successfully be used to adapt national clinical guidelines to local needs in an outpatient setting (Steele et al., 2005). However, to develop more effective CDSSs there is a need to develop more high quality useful clinical research evidence that is easily accessible and machine interpretable (Sim et al., 2001). Evidence at the point of care can lead to positive outcomes in the use of evidence and for teaching and learning (Christakis et al., 2001, Ghali et al., 2000, Sackett and Straus, 1998).

Evidence-based medicine has been promoted as a means of improving clinical outcomes. As CDSS have been recognised for their potential to reduce medical errors and improve healthcare quality and efficiency, using CDSS to facilitate evidence-based medicine could substantially improve healthcare quality (Sim et al, 2001). CDSS provide a powerful method of implementing a broad range of evidence-based guidelines (Sucher et al., 2008). A study carried out in Hong Kong (Leung et al., 2003) showed that medical students given a CDSS improved their education experience of EBM. One review of CDSS found that they improved clinician performance in 40% of diagnostic systems, 76% of reminder systems, 62% of disease management systems and 66% of prescribing systems, although the improvement in patient outcomes was less than anticipated, particularly for chronic diseases (Garg et al., 2005).

One review looked at the use of CDSS in prescribing for older adults (Yourman et al., 2008) and found that CDSS generally had a positive effect, such as by lowering rates of prescribing inappropriate drugs and greater adherence to better drug choices or dosages, although the effect on patient outcomes was less clear. At the other end of the age spectrum, a review of

CDSS for neo-natal care (Tan et al., 2005) found that there was only limited data from randomised clinical trials of CDSS on which to assess their effect in neo-natal care.

CDSS incorporated into computerised physician order entry systems have been shown to reduce medication errors and improve the quality and efficiency of medication use (Bates et al., 2001). They have also been shown to reduce the use of antimicrobials and improve prescribing of antimicrobials (Sintchenko et al., 2008, Samore et al., 2005, McGregor et al., 2006, Sintchenko et al., 2005, Thursky et al., 2006) demonstrating that CDSS can be a useful tool for the optimisation of antibiotic use and the improvement of patient care (Shebl et al., 2007, Sintchenko et al., 2008).

CDSS are also considered to be potentially useful for the Medicare program in the United States as a means of minimising inappropriate use and overuse of drugs, particularly for newly approved drugs (Clancy and Cronin, 2005).

An early review of CDSS showed that whilst some CDSSs had a positive effect on patient outcomes others had a lack of effect on patient outcomes (Johnston et al., 1994). However, the review authors state that this lack of effect could be because of inappropriate study design or failure to measure outcomes that would be responsive to the use of CDSSs. Another review (Kaplan, 2001) suggested that there was a lack of useful information for understanding why CDSSs were or were not effective and whether they affected patient outcomes. Kaplan's (2001) review also suggested that many systems are often not used that much despite their benefits. A further review (Kawamoto et al., 2005) found four features of CDSSs that were associated with improved clinical practice: automatic provision of decision support as part of clinicians' workflow; provision of a CDSS at the time and place of the decision-making; provision of a recommendation rather than an assessment; and the decision support system being computer based. The authors suggest that the common theme of these four features is that they make a CDSS easier for clinicians to use and that for a CDSS to be effective the effort

required by a clinician to receive and act on the system's recommendations should be minimal.

An article looking at CDSSs in electronic prescribing (Teich et al., 2005) identified four barriers to the adoption and effectiveness of CDSSs. These were limited functionality or usability problems; lack of data integration; uneven availability, standards and management of best-practice knowledge and costs of implementation and ongoing use. A survey of factors examining clinicians' acceptance of CDSSs (Sittig et al., 2006) identified that patient characteristics were often associated with a decision to either accept or ignore CDSS features. For instance, clinicians were more likely to use CDSS support if the patient was elderly, had multiple medications or a chronic condition, but less likely to use it for acute patients. Clinicians were also less likely to accept alerts from a CDSS if they were behind schedule, although those who were behind schedule were also more likely to have less access to computers in their examining rooms. Another three barriers which were identified in the use of a CDSS as a computer-based prescription reminder (Agostini et al., 2008) were demands of reading the reminder, in the time it took to read it and having to view an additional screen whilst prescribing; the role of clinical experience, in that the CDSS was seen as possibly intrusive and eroding clinicians' autonomy; and the information content of the CDSS, where some clinicians disagreed with the content of the CDSS. The literature shows, therefore, that different barriers have been identified to the implementation and adoption of CDSSs in clinical practice. Although Kawamoto's (2005) review identified features associated with improvements in clinical practice through the use of CDSS, subsequent literature shows these may not be being put into practice or that there may be further factors involved that limit the uptake of CDSSs.

A pyramid of the '5S' levels of organisation of evidence from healthcare research, puts 'systems', such as computer decision support systems, at the top of the pyramid as the most compiled source of evidence available to clinicians (Haynes, 2006). This, suggests Haynes (2006), means that clinicians searching for evidence to guide their clinical decisions can use

CDSS as a system integrated with electronic medical records which links the patient's characteristics with evidence-based guidelines, meaning that they need look no further for the best evidence than using the CDSS. CDSSs that give patient-specific recommendations in such a way that clinicians save time have been shown to be effective and sustainable tools for changing clinicians' behaviour (Payne, 2000). If CCDSs are designed to implement and refine evidence-based protocols they can provide standardized decision-making that will decrease variability, test interventions and validate whether quality of care has been improved (Sucher et al., 2008). It has also been suggested (Chaudhry, 2008) that a greater understanding is needed of the complex dynamics underlying system adoption and that future research should focus on the effectiveness of adopted systems.

CONCLUDING REMARKS

This critical review of the literature has shown that traditionally in medicine decision-making was intuitive and based on the paternalistic model where the clinician made the decision and the patient was told what treatment they would receive. Intuitive decision-making has been shown to often be lacking in evidence, incorporating too much uncertainty and with too much potential for bias, particularly from the use of heuristics.

Evidence-based medicine has been in common use since it was popularised around 1992. However, it has not always been as widely used as it could be, due to various barriers to implementation, either real or perceived. This is despite the fact that it provides a sounder method for making medical decisions than intuition or pure personal experience.

Decision analysis has been shown to be a way of implementing evidence-based medicine, which, as an approach based on rationality, excludes intuitive decision-making and the bias that goes with it, but which also incorporates human values and provides a means of implementing evidence into everyday clinical practice. The use of decision aids has also been shown

to be an effective method of incorporating shared decision-making, particularly as many decision aids are developed solely for patients' use.

In recent years CDSSs have become more widely available and more widely used in medicine and have shown themselves to be useful tools for implementing evidence-based medicine and incorporating an element of shared decision-making, whilst also reducing the amount of time practitioners need to spend on searching for and evaluating evidence.

This review has shown that evidence-based medicine and decision analysis are the way forward for medical decision-making and that CDSSs are a useful means of implementing the two together. There is a need for more CDSSs to be developed using decision analysis in order for a broader range of areas within medicine to have such useful tools. New CDSSs will need to be quick to use, provide comprehensive functionality and implementation of evidence-based medicine. Therefore, the subject of this thesis will incorporate the development of a new CDSS using decision analysis.

STUDY AIMS AND OBJECTIVES

The overall aim of this research was to develop a model and electronic decision aid (CDSS) to help practitioners choose the most effective drug treatments for a particular medical condition.

Objectives:

- To develop a model using a form of decision analysis called 'Multi-criteria decision analysis' to be applied to Parkinson's disease
- To develop a computer system to implement the model's functions

CHAPTER 2

Study Rationale and Methodological Framework

"Make decisions from the heart and use your head to make it work out."
Sir Girad

STUDY RATIONALE

Decision making, states (Coiera, 2003), is rarely a clear cut affair. Decisions do not just concern evidence, logic and probability, but also the goals, values and available resources of the people making them. Decisions are nearly always compromised by uncertainty and by people's in-built cognitive biases. Yet medical practitioners are expected to make complex and often difficult decisions on patients' treatment options with the aim of maximising the benefit to the patient whilst minimising the risks. In times of financial restraints and the constraint of guidelines and policies at both local and national levels, choosing the most effective treatment for a patient is not always a straightforward affair. Practitioners face an overwhelming volume of information from clinical trials and new research articles. As the review in chapter one showed, medical decision making has moved from its traditional position of using intuition and personal experience to the use of evidence-based medicine. Decision aids, and in more recent years CDSSs, have been shown to help incorporate evidence-based medicine into daily clinical practice.

METHODOLOGICAL FRAMEWORK

The Need For Decision Analysis

Coiera (2003) describes the process of decision making as firstly, identifying the problem, defining it, determining whether it needs to be solved and its relevant importance, as this process determines what the next steps are. Secondly, the alternative solutions need to be considered, by creating a list of alternatives to be selected from. The final step is to actually make the decision. The list of competing solutions is examined, supported by their evidence, and the most appropriate one is chosen.

Scientific evidence on clinical practice and cost-effectiveness is increasingly being used by health care purchasers as the criteria by which resources are allocated, with NHS trusts and GP practices being encouraged to adopt more cost-effective and clinically effective practices. Physicians, however, are constantly faced with complex, involved decision-making on patients' treatment. They are currently encouraged to make their decisions on the basis of evidence-based medicine, yet with the volume of information that must be assimilated and processed, making such decisions is not easy and there is little available to aid practitioners in their decision-making. Cost-effectiveness issues are also becoming of paramount importance in health care today, with NHS Trusts and GP practices having to justify their use of drug treatments. Alongside this, involvement of the patients themselves, and the patient's subjective interpretation of their condition, for example through health-related quality of life (HRQoL) assessment, in the decision-making process is ever more a consideration for practitioners. Using decision analysis to aid decision-makers with their clinical treatments means that the complexity and volume of information are removed, leaving the practitioner with clearer guidance on the suitability and relevance of individual treatments and more time for the patient.

Decision Analysis Models

A model is created as part of decision analysis to define the predicted health outcomes that are associated with each option being considered. This means that modelling allows issues to be fully explored rather than automated decisions being made (Waller et al, 2003). The process of developing a model begins with the creation or design of the model followed by the construction or instantiation of the model, where the model is used as a template to build an artefact that is an instance of the model in the physical world. Before a model can be used it is necessary to be clear about what has been modelled, as the circumstances at the time the model is developed can influence the final value of the model. The model needs to be designed with the environment in which it will be used in mind (Coiera, 2003).

The advantages of modelling include increased transparency, explicit reasoning, limitations on evidence and uncertainty clearly identified, assessment of the impact of all assumptions and better justified decisions. The disadvantages include the time taken for the modelling, additional resources and expertise and the possibility of the model itself becoming the focus of debate (Waller et al, 2003).

Among the types of model one may use for decision analysis are Markov models, decision trees, Bayesian networks, Artificial Neural Networks and Multi-Criteria Decision Analysis (MCDA). Each of these will be looked at in turn and a more detailed analysis will be given of MCDA.

Markov models

A Markov model consists of a finite number of health states which are defined by the disease severity. The progression of the disease is represented by patients progressing from one health state to another. The time horizon of the model is divided into Markov cycles, which are equal increments of time. The length of each cycle is a time interval that is clinically meaningful for the disease and represents the time that a patient spends in one health state before progressing to the next (Kamal et al., 2006). In each cycle it is assumed that a patient transfers from one health state to another and the net probability of making a transition is called the transition probability. The model can be evaluated by using a first-order Monte Carlo simulation or by using a cohort design. Markov models can be used to model stochastic processes which evolve over time and can therefore be useful for modelling chronic diseases.

Decision trees

A decision tree is a simple structure used to represent possible treatment and progression pathways. It starts with a treatment decision then branches out to look at all the potential health outcomes and costs that can arise from a decision between two alternative treatments. The pathways can be modelled using probabilities of events and relevant outcomes measures such as costs and effectiveness measures. The advantage of using decision trees is that

missing or incomplete data can be easily identified and can be replaced by expert opinion or assumptions. The effect of this data can then be tested using sensitivity analysis (Kamal et al., 2006).

Bayesian networks

A Bayesian network, a type of expert system, is a probabilistic model that consists of a dependency structure and local probability models. The dependency structure specifies how the variables relate to each other, with each variable depending on a possibly empty set of other variables called the parents (Gevaert et al., 2006). The variables are visualised in a graph, with each attribute being visualised by a node and a direct dependency by an arc. The local probability model specifies how the variables depend on their parents.

Artificial neural networks (ANN)

Artificial neural networks, another expert system, are an interconnected group of artificial neurons inspired by the way biological nervous systems process information(www.doc.ic.ac.uk/~nd/surprise_96/journal/vol14/cs11/report.html). ANNs are able to adapt their structure based on internal or external information flowing through the network and thus learn a new process by example. They can model complex relationships between inputs and outputs and learn to find patterns in data and model these. A trained neural network is considered to be an 'expert' in the category of information it is analysing. It can therefore provide projections for new situations or answer 'what if' questions.

Other advantages of an ANN are that it can learn how to do tasks based on training or experience, can create its own organisation or representation of information and it can carry out parallel computations.

As neural networks cannot be programmed to perform a task a disadvantage can be that unless examples are carefully selected for them to learn from useful time may be wasted or the network might not function correctly. ANNs can be unpredictable as they work out how to solve a problem themselves.

Multi-criteria decision analysis (MCDA)

MCDA is a way of breaking complex problems into manageable pieces, allowing data and judgement to bear on them, then reassembling them to present an overall picture of the problem. It can be used either retrospectively to evaluate things which have already had resources allocated to them, or prospectively to evaluate things which are proposed. The main role of such a technique is to enable decision-makers to be able to handle large volumes of complex information in a consistent way (Department of Transport, 2000).

Development of the model involves seven stages:

1. The context needs to be established; the aims of the MCDA, the decision makers and other key players are established.
2. The options are next identified.
3. The objectives and criteria then need to be established and the objectives organised as a value tree by clustering them under higher-level and lower-level objectives.
4. The options are each scored from 0 to 100. Each option's performance against the criteria is assessed as well as the value associated with the consequences of the option for each criterion (Department of Transport, 2000). The consequences of the options are described and the options then scored.
5. Weights are then assigned to the criteria as a reflection of their importance to the decision problem.
6. The weight and score of each option is then derived as an overall value; the weighted scores are calculated at each level of the hierarchy and the overall weighted scores then calculated.
7. The final step is to carry out a sensitivity analysis, by considering whether other preferences or weights affect the ordering of the options, looking at the advantages and disadvantages of selected options and comparing pairs of options and creating possible new options that could be better than the original. These three steps are repeated until a 'requisite' model has been obtained.

There are many different procedures in MCDA which will each be examined here in turn.

Analytical Hierarchy Process (AHP)

The AHP is a linear additive model which uses a procedure to make pair-wise comparisons between criteria and options in order to derive weights and scores. The decision-maker makes a pair-wise comparison by assessing how important one criterion is against another, which is generally a straightforward and convenient process. Some doubts have been raised about the theoretical basis of AHP (Department of Transport, 2000).

Outranking

Outranking may be used as a methodology to eliminate 'dominated' alternatives. Weights are used to give more influence to some criteria than others. One option outperforms another if it outranks it on enough important criteria and is not outperformed by the other option. The options are then assessed on how they outrank all of the options being considered, by measuring them against a pair of threshold parameters. Two options can be considered either incomparable or difficult to compare. This methodology has shown some cause for concern in respect of its dependence on arbitrary definitions of what constitutes outranking and how the threshold parameters are set and manipulated by the decision-maker. However, it can be effective in exploring how preferences between options are formed (Department of Transport, 2000).

Multi attribute utility theory (MAUT)

This is the methodology which is considered to have the widest acceptance and was developed by Keeney and Raiffa in 1976. There are three building blocks to this methodology; the performance matrix, the procedures that determine whether criteria are independent of each other or not and the ways that estimate parameters in a mathematical formulation to allow a single number index to be estimated to represent the decision-maker's valuation of an option by the value of its performance on each criterion (Department of Transport, 2000). This is a relatively complex procedure which takes

uncertainty formally into account and builds it into decision support models, allowing attributes to interact with each other. It does not assume, however, mutual independence of preferences.

Fuzzy sets

Fuzzy sets were developed from the idea that language used in discussing issues is imprecise, such as 'rather attractive' or 'fairly expensive'. Fuzzy arithmetic captures these elements using membership function, so that an option would belong to a set of say 'attractive' options with a degree of membership between 0 and 1. Fuzzy models then use weights, often represented as fuzzy quantities, to aggregate fuzzy performance levels. Such a method can be difficult to understand, has no clear theoretical foundation for modelling decision-maker's preferences and no clear advantages over other models that have been established (Department of Transport, 2000).

Linear Additive Models

This particular type of model is applicable where it has been established that criteria are preferentially independent of each other and uncertainty is not built into the model. The values of an option on the criteria can be combined into one value. The score on the value of each of the criteria are then multiplied by a criterion's weight and the weighted scores are added together. This methodology has a well-established record for providing robust and effective support for decision-makers (Department of Transport, 2000).

Key features of MCDA

- It establishes preferences between the options by referring to an identified set of objectives and establishes measurable criteria to assess the extent to which the objectives have been achieved;
- It enables the data on individual criteria to be aggregated to provide an indicator of the overall performance of options;

- It emphasises the judgement of the decision-making team to establish objectives and criteria, estimate the weights and judge the contribution of each option,

- It brings a degree of structure, analysis and openness to classes of decision (Belton and Stewart, 2002).

Advantages of MCDA

- It is open and explicit;
- The objectives and criteria are open to analysis and will be changed if they are considered inappropriate;
- The scores and weights are explicit, if they are used and developed according to established techniques, and they can be cross-referenced and amended if necessary;
- Performance management can be sub-contracted, if required, so it does not have to be left to the decision making body;
- It can provide a means of communication within the decision-making body itself and also between the decision-making body and the wider community;
- It provides an audit trail (Belton and Stewart, 2002),
- Criteria can be both financial and non-financial; therefore drug costings can be taken into account, as well as issues such as HRQoL.

Use of MCDA in practice

MCDA is well established and frequently used as a modelling technique in various fields, particularly in areas such as environmental management and operational research. For example, MCDA was used to support decisions on land use around chemical sites (Papazoglou et al., 2000), where the decision is complex due to the range of criteria that need to be considered such as economics, public health, environment etc. Similarly, MCDA was used to create a tool for people to assess the many available technologies for spent oil regeneration and select their preferred option (Khelifi et al., 2006).

In the last few years, MCDA has also started to be used as a modelling technique in medicine in a small number of cases. For example, MCDA was used to create a decision analysis tool to choose the most effective triptan in the treatment of migraine (Ferrari et al., 2005); an algorithm was developed for the optimal management of pharyngitis using MCDA (Singh et al., 2006) and MCDA was also used to evaluate the importance of treatment characteristics and the performance of different treatment approaches for people with tetraplegia (Hummel et al., 2005).

Application Of The Model

The model will need to be applied to a disease or condition and it was decided that it would be applied to Parkinson's disease (PD). The characteristics of the disease will be briefly discussed and the justification for applying the model to this disease elaborated on here.

Parkinson's disease

Parkinson's disease is a chronic, progressive neurodegenerative disease characterised by bradykinesia, tremor and rigidity (Saami et al., 2004). Other motor and non-motor symptoms may also be present. Currently, symptomatic treatments of the disease are the only effective treatments offered. These include pharmacotherapy, such as the gold-standard levodopa, or dopamine agonists such as ropinirole, as well as surgical treatments such as deep-brain stimulation (Thobois et al., 2005).

Advanced stage PD patients tend to present with complications of the disease which are generally classified as motor abnormalities and behavioural disorders. Chronic levodopa therapy can lead to motor response complications, with motor fluctuations appearing in relation to the timing of levodopa dosage, known as wearing-off phenomenon. Responses to levodopa can also manifest as the "on-off" phenomenon, shifting between an under-treated state to an over-treated state (Waters, 2002). Advanced PD patients may also suffer from symptoms not present in the early stages of the disease such as freezing spells, falls and neuro-psychiatric problems, with advanced-stage treatment problems advancing as the disease progresses.

The complications of PD mean that treating the disease effectively is a constant challenge for practitioners, from the decisions in the early stages of the disease of which drug to use and when, to the problems in the later stages of the disease of managing the complications resulting from long-term drug therapy (Stocchi, 2003).

The difficulties of treating PD mean that a decision analysis tool could aid practitioners in their decision making. A decision tool does not make the decision for the practitioner, but aids them in their decision-making. By implementing guidelines, such as the NICE guidelines and research evidence from trials into the model it will be possible to incorporate evidence-based medicine in the tool, enabling practitioners to apply the theory. Use of a model such as this would also ensure that current NHS policies and guidelines, such as the National Service Framework (NSF) for Older People, the NSF for long-term conditions and the NICE guidelines would be adhered to, as would be applicable for a disease such as PD. This could be particularly useful for practitioners with little or no experience of treating such a complicated condition as PD.

Computer Decision Support Systems

Having a model to aid in decision-making is not enough on its own however. By implementing a model in a computer decision support system (CDSS) practitioners will be able to apply the model quickly and effectively in clinical practice. CDSS have been defined as knowledge systems using two or more items of patient data to generate case-specific advice. The key components of CDSS are medical knowledge, patient data and specific design (Kotze and Brdaroska, 2004).

Electronic access to the model means it could be applied through a web connected desktop PC, a laptop or a hand-held computer such as a personal digital assistant (PDA) for example. A decision support system being computer-based is considered to be one of the main features of a system's ability to improve clinical practice (Kawamoto, 2005).

Development of CDSS

CDSSs began to be developed from the 1950s, although it was not until the 1970s that research in this area began to really take form, along with the implementation of medical diagnostic systems (Kotze and Brdaroska, 2004). CDSSs were developed to improve healthcare quality by providing accurate and timely diagnostic information to clinicians. Systems can be programmed to provide a range of patient-centred actions such as management plans, reminders, prompts and record-keeping (Kotze and Brdaroska, 2004).

Advantages of CDSS

They have been shown to be very helpful to medical practitioners (Achour et al., 2001). Coiera (2003) suggests the benefits fall into three broad categories. Firstly, that they improve patient safety, by reducing medication errors and adverse events and also improve medication and test ordering. Secondly, they improve the quality of care, by increasing clinicians' time for patient care, increasing the application of clinical guidelines and pathways, facilitate the use of up-to-date clinical evidence and improve clinical documentation and patient satisfaction. Lastly, they improve the efficiency of health care delivery, by reducing costs through faster order processing, reduce test duplication, decrease adverse events and change patterns of drug prescribing by favouring cheaper generic brands.

OUTLINE OF THE CHAPTERS

Chapter three will look at establishing the decision context for the decision problem, establishing the options available and developing the criteria. In order to establish what criteria practitioners use to decide on treatments a survey will be developed and sent to practitioners in the field of PD. These will include geriatricians, neurologists and Parkinson's disease nurse specialists. The results of the practitioner survey will be entered into the spreadsheet package Excel and the statistical package SPSS for frequency analysis. From the survey responses that are received a list of all criteria mentioned by practitioners will be compiled and this will be sent as a second survey to the same practitioners to elicit which of the listed criteria are used.

The data from this survey will again be entered into Excel and to SPSS for frequency analysis. A list of eight considerations will then be applied to all the criteria from the second survey in order to establish which of the criteria are feasible to be used in the model. Finally, the remaining list of criteria will be divided into 'risk' and 'benefit' criteria and a decision tree developed.

Once the criteria have been established, the model will then be developed. This will be discussed in chapter four where the options will need to be scored and weights developed for the criteria. Data will be collected on all the available options using Phase III clinical trial data and measurement scales will be developed for the scoring on each of the options, with 'least' and 'most' preferred scales developed for each of the criteria scores. The options will be scored on a scale from 0 to 100 against the criteria, with each option being allocated a number to produce a preference order on the alternatives. Weights will be calculated on the criteria. Importance weights will be assigned to the criteria, and the weights combined with the scores to find the overall value for each option.

Once developed, the model will then need to be implemented by developing a software system, in order to develop the model into a computer decision support system; this process will be described in chapter five. Chapter six will then describe the process of testing that the user's data is in the correct format by incorporating data validation methods. The software will then need to be thoroughly tested to ensure that it performs the way that it is expected to, this too will be described in chapter six.

Chapter seven will look at validating the model and CDSS as a whole. This will involve an expert panel using the model and comparing the results it produces for certain patient scenarios against the choices they would have made themselves for the patients. They will also assess the CDSS for its ease and practicality of use. The final chapter will discuss the project as a whole and discuss future work.

DATA PROCESSING AND ANALYSIS

Data processing will be exploratory, by means of a written survey to establish any protocol practitioners use, the criteria they use to decide on treatment and their views on whether they think an electronic decision aid would be useful. Data from the survey will be entered into SPSS and simple descriptive analysis will be carried out. A further survey will be sent to the same practitioner with a list of criteria from the first survey, asking them to select all the criteria from the list that they use. A survey will also be given to practitioners involved in the validation exercise of the model and CDSS to assess their views of both aspects of the project.

POTENTIAL BENEFITS OF THE STUDY

The intention of this study is to produce an aid for practitioners in the field of PD which helps them to choose the most effective drug treatment for Parkinson's disease and encourages the use of evidence-based medicine. Producing such a decision aid could ensure equity of access to the most effective PD medications for all patients, where the decision aid is used in clinical practice.

It would make decisions simpler, rationalised and explicit, bringing particular benefits for new or less experienced practitioners, and those such as GPs who may not come into contact with many PD patients. This would also be beneficial for Parkinson's disease nurse specialists who are new to prescribing Parkinson's medications. It could also be used as a teaching aid in medical schools for newly qualified doctors or medical students.

Developing a CDSS would mean that the model could be used anywhere by anyone with access to a computer where the software had been installed. Such an electronic decision aid would be unique for the field of PD, where only paper-based algorithms have been developed so far. To date, none of the models which has been developed using MCDA has been incorporated into a CDSS. Therefore, this would also be a unique development with MCDA in the field of medicine by incorporating the model into a CDSS.

SUMMARY

- This chapter has explored the rationale and methodology for the project.
- Decision analysis and the benefits of using it have been discussed.
- The basis of what a model is and the advantages of using them have been discussed and the different types of models have been discussed, with Multi-criteria decision analysis being discussed in more depth and detail. The different types of MCDA have also been discussed.
- The key features of MCDA and the benefits of using it have been discussed, as well as some applications of MCDA in medicine.
- An outline was given of Parkinson's disease and the rationale for using this form of decision analysis with Parkinson's disease was discussed.
- The background of CDSSs has been discussed, as well as the rationale for using them in clinical practice.
- An outline has been given of the chapters for the rest of this thesis and the potential benefits of the study discussed.

CHAPTER 3

Development of the Decision Context and Criteria for a Prescribing Support System In Parkinson's Disease

INTRODUCTION

The process of developing a MCDA model consists of seven stages. The first of these is to establish the decision context. Once this is established one must then identify the options to be appraised. The third, and perhaps most important stage, is to establish the criteria. The options then need to be scored for their performance against the criteria and the criteria themselves weighted for their importance to the decision problem. The scores and weights are then combined as an overall value. The final stage is to carry out a sensitivity analysis of the model. Stages one to three will be discussed in this chapter, with the remaining stages covered in the following chapter.

DECISION CONTEXT

For this project the decision context quite simply was to select the most effective treatment for a patient with Parkinson's disease.

THE OPTIONS

In terms of the options to be appraised, for Parkinson's disease this consisted of six groups of drug treatments comprising a total of 19 different drugs. The drug groups consist of levodopa, dopamine agonists, catechol-o-methyl transferase (COMT) inhibitors, glutamate antagonists, monoamine oxidase type B (MAOB) inhibitors and anticholinergics (Table 3.1).

Levodopa is an amino-acid precursor of dopamine which replenishes depleted striatal dopamine. It is administered alongside a dopa-decarboxylase inhibitor (benserazide hydrochloride in co-beneldopa and carbidopa in co-careldopa) which reduces the peripheral conversion of levodopa to dopamine and limits levodopa side-effects. Effective brain-dopamine concentrations can then be achieved with lower doses of levodopa (www.bnf.org/bnf/bnf/54/129828.htm, www.thebnf.org).

Dopamine agonists act directly on dopamine receptors and can be used alone or alongside levodopa (www.bnf.org/bnf/bnf/54/129827.htm). Apomorphine is administered by subcutaneous injection or continuous subcutaneous infusion, whilst rotigotine

Table 3.1 Parkinson's disease medications

Drug group	Drug name	Brand name
Levodopa	Co-Beneldopa	Madopar
	Co-Careldopa	Sinemet
	Levodopa/Carbidopa/ Entacapone	Stalevo
	Duodopa	Duodopa
Dopamine Agonists	Apomorphine	Apo-go
	Bromocriptine	Parlodel
	Cabergoline	Cabaser
	Pergolide	Celance
	Pramipexole	Mirapexin
	Ropinirole	Requip
	Rotigotine	Neupro
COMT Inhibitor	Entacapone	Comtess
	Tolcapone	Tasmar
Glutamate Antagonist	Amantadine	Symmetrel
MAOB Inhibitor	Selegiline	Eldepryl
	Rasagiline	Azilect
Anticholinergics	Trihexyphenidyl	Broflex
	Orphenadrine	Biorphen
	Orphenadrine Hydrochloride	Disipal

is administered as a 24 hour self-adhesive patch. All other dopamine agonists are administered orally.

COMT inhibitors prevent the peripheral breakdown of levodopa which allows more levodopa to reach the brain. They are used as an adjunct to co-beneldopa or co-careldopa (www.bnf.org/bnf/bnf/54/129830.htm).

The Glutamate antagonist amantadine is believed to enhance the release of dopamine and to delay its reuptake into synaptic vesicles. It may also exert anticholinergic activity. It can be administered alone or as combination therapy (www.alliancepharma.co.uk).

MAOB breaks down dopamine in the brain, therefore the MAOB inhibitor selegiline works by blocking the MAOB. Selegiline is administered as an adjunct to levodopa. Rasagiline can be administered alone or in combination with other therapy and works by slowing the breakdown of dopamine in the brain (www.parkinsons.org.uk).

The anticholinergic drugs, or antimuscarinic drugs, work by reducing the effects of the central cholinergic excess which occurs because of a deficiency in dopamine (www.bnf.org/bnf/bnf/56/2057.htm?q=%22anticholinergics%22#hit). These drugs are used for broader forms of parkinsonism, but are not now generally recommended for idiopathic Parkinson's disease and were therefore excluded from this model.

THE CRITERIA

For the third stage of the process one needs to establish the criteria. This is the basis from which the rest of the model will be developed. In order to establish the criteria for the model, two surveys were sent to PD practitioners. The process for surveying the practitioners will now be discussed in detail.

Methods

First survey

The first survey was sent to over 300 clinical practitioners working with PD patients in the UK. These included neurologists, geriatricians and Parkinson's disease nurse specialists (PDNSs). Details of neurologists were obtained from the British Association of Neurologists website (www.theabn.org). Details of geriatricians could not be obtained directly, as no list of UK geriatricians was publicly available, so a geriatrician in Cardiff contacted all geriatricians across Wales through his own personal list of contacts. Unfortunately, details of geriatricians across other parts of the UK could not be obtained. Neurologists were contacted by means of a confidential postal survey and geriatricians by email. It was not possible to obtain a list of

PDNSs to contact directly, so they were contacted by means of a short article published in their association newsletter with the survey attached. The nurses were then able to reply anonymously. Details of the types of practitioners the survey was sent to and their locations are outlined in Table 3.2.

Table 3.2 Type and location of practitioner the survey was sent to

Practitioner	Number sent	Location
Neurologists	304	Across the UK
Geriatricians	88	Wales
PDNSs	Unknown	Across the UK

The survey comprised of three questions (Figure 3.1). Practitioners were firstly asked whether they used a recognised algorithm, such as Olanow's, any algorithm or treatment protocol of their own to decide on treatments, or whether their decisions were based on personal experience. The second question asked them to list the criteria they use to decide on treatments for PD patients. The final question asked whether they would consider using an electronic decision aid for their treatment decisions if one were developed. Two subsequent follow-ups were sent to elicit further responses. The PDNSs were not able to be sent a follow-up as they could not be contacted directly.

The responses were entered into an Excel spreadsheet, where the criteria were extracted and listed individually in a separate worksheet. From this worksheet it was possible to compile a complete list of all the criteria. The data were subsequently entered into SPSS and frequency analyses carried out.

Second survey

A second survey was sent to the same practitioners as previously, excluding those who were known to be retired or who had moved workplace and for whom there was no change of address. This consisted of the compiled list of criteria from the previous responses (Figure 3.2). Respondents were asked to tick the criteria which they would use in their treatment decision making and add any further criteria not listed. The results were again entered in an Excel spreadsheet as they were received and then entered into SPSS for analysis.

Figure 3.1 First practitioner survey

DEVELOPMENT OF AN ELECTRONIC DECISION SUPPORT SYSTEM FOR PARKINSON'S DISEASE

1. Do you routinely use a protocol or algorithm for making decisions on drug treatment for PD, such as Olanow's algorithm? If so, what sort of protocol / algorithm do you use? Please send a copy or reference.

2. Have you seen any PD patients in the last month? If so, did you use any of the following to decide which treatment to use:

   Olanow's algorithm:

   Other algorithm – please specify:

   Personal experience:

   Any other criteria – please specify:

3. Whether or not you have seen any PD patients, what criteria would you consider appropriate for use in treatment decision making?

4. If an electronic treatment decision aid were to be developed, do you think you would use it?

Thank you for your time and help.

Figure 3.2 Second practitioner survey

Please tick all the criteria which you use when choosing a treatment for a patient with Parkinson's disease. Please add any additional criteria.

Drug response
Drug interactions
Patient's other current medication
Drug side effects
Adverse Drug Reactions
Drug contraindications
Is the medication of benefit?
Evidence of treatment efficacy
Cost-effectiveness of treatment
Literature and systematic reviews
Data from clinical trials
How the patient feels
The patient's choice
The nature of their deficits
Clinical guidelines
Hospital guidelines
NICE guidelines
Clinical appraisal / clinical state
PDMED/randomisation into trials
Functional assessment
Clinical assessment
Age
Life expectancy
Co-morbidities
ADLs
Severity of symptoms
Severity of disability
Stage of disease/H&Y score
American Association of Neurologists' guidelines
Risks/benefits
Keep medication low
Patient's occupation
Duration of disease
Predominant symptom
Type of symptom
Support/carer
Patient's understanding of condition
Patient's capacity to deal with simple/complex regimes
Neuro-psychiatric problems
Cognitive impairment
Mental state
Confusion
Hallucinations
MMSE score
Depression
Perceived disability
Motor fluctuations
Non-motor complications
Olanow's algorithm
HRQoL
Evidence
Nature of patient's symptoms
Underlying pathology
Postural hypotension

General recommendations - initially levodopa, stepwise introduction of other drugs
Dyskinesias
End of dose symptoms
Mobility
General health
Progression of symptoms
Avoid treatment until loss of function/patient request
Use dopamine agonists for as long as possible
Use amantadine / rasagiline in young patients
Age at onset
Functional impairment
Parkinson's Plus syndrome
Is the patient a wage earner?
Psychological response to diagnosis
Social circumstances

Criteria considerations

In order to establish a set of criteria which are fully relevant to the decision problem, one needs to incorporate the following eight considerations (Belton and Stewart, 2002).

1. Value relevance. The decision maker needs to be clear that the concept links to their goals, so that the specified preferences relate directly to the concept. This ensures that the criteria relate to their values. For example, if size is a criterion for a decision problem of choosing a new car, how does one define the importance of size? It could mean that the car should be small or should be big, or that it is the size of the boot that is important. Thus, the decision maker needs to be clear how the value is relevant to their goal (Belton and Stewart, 2002).

2. Understandability. The decision makers should have a shared understanding of the concepts being used in the analysis, to provide constructive discussion and mutual learning, rather than confusion and conflict (Belton and Stewart, 2002). There should be no ambiguity and no loss of information when decision makers interpret the criteria (Keeney, 1992). For example, similarly to the previous example, one decision maker may understand size to mean the people carrying capacity of the car, whereas another may understand it to relate to the status of the car.

3. Measurability. The performance of the alternatives against the criteria needs to be measured, and this must be done in a consistent way (Belton and Stewart, 2002). For example, it may be difficult to have a consistent and explicit measure of something such as a patient's life expectancy.

4. Non-redundancy. A factor should not be measured by more than one criterion. A concept may have been considered under different headings during the initial development, but if both are included in the analysis it may lead to a concept being attributed greater importance than it warrants. Generally, similar criteria should be incorporated into one concept. On occasion there may be a need to have similar factors considered separately if those factors reflect different values in different contexts (Belton and Stewart, 2002).

5. Judgemental independence. Criteria are considered to be judgementally independent if a criterion is not dependent on the level of another criterion. Judgemental dependence can be overcome by redefining criteria.

6. Balancing completeness and conciseness. A value tree should be complete, in that all the important aspects of the problem are captured, and also concise, in that the level of detail should be kept to a minimum (Keeney and Raiffa, 1976).

7. Operationality. Along with considering completeness and conciseness, one needs to ensure that the model is usable and that it does not place excessive demands on the decision makers. Thus, one needs to consider the context in which the model is being used in order to judge the usability (Belton and Stewart, 2002).

8. Simplicity versus complexity. Although the value tree is itself a simple representation of the essence of the problem, some representations will be simpler than others as a consequence of the amount of detail incorporated. The modeller should strive for the simplest value tree which captures the decision maker's problem. However, sometimes in practice the initial

representation may be more complex or detailed than is operationally desirable. It is through practical application of the model that this may become apparent, which should then lead to further refinement (Belton and Stewart, 2002).

These eight considerations were applied to all the criteria from the second survey in order to establish whether the criteria were suitable for inclusion in the model.

RESULTS

First Survey

A total of 153 practitioners responded to the first survey, including from the two follow-ups, giving a response rate of 43.9%. The results of the first survey showed that a staggering 93.5% of respondents used personal experience as the basis of their decision-making on choice of Parkinson's treatments. Of the criteria listed, age (32.1%) was the most common, with other common criteria including co-morbidities, patient's choice and neuro-psychiatric features. A total of 69 different criteria were established from the survey responses.

Second Survey

The second survey had a slightly lower response rate, with 135 (37.8%) responders, including the two follow-ups. This survey produced some interesting results. Respondents selected between 10 and 68 of the 69 criteria, giving a wide-ranging variation in responses, although there was little difference between groups of respondents. The mean number selected was 45 (range 10-68) overall, with the mean for the neurologists being 44 (range 10-68) and 47 (range 26-65) for the geriatricians. Only one response was received from a PDNS. Twenty-two (31.8%) criteria were selected by over 80% of respondents and eight (11.6%) by over 90%. The most selected criteria were 'motor fluctuations' (93.3%), 'drug side-effects' (93.3%) and 'cognitive impairment' (92.6%). The least selected criteria were 'health-related quality of life' (7.4%), 'American Association of Neurologists'

guidelines' (5.2%) and 'Olanow's algorithm' (3.7%). All of the criteria were selected at least once.

Development Of The Criteria

Once the results of the survey were established, it was then necessary to apply the considerations mentioned before: value relevance; measurability; usability; operationality; redundancy; completeness and conciseness, simplicity versus complexity and judgemental independence. Table 3.3 shows the results from these considerations being applied to the criteria. The application of the considerations meant that the number of criteria that could be included in the model had been considerably reduced, from 69 to 17.

Risks And Benefits

After these considerations had been applied the remaining criteria were then divided into two categories: 'benefit' and 'risk'. A criterion would fall into the 'risk' category if it could be shown to either cause or worsen a symptom. For example, 'motor fluctuations' could be considered a 'risk' because a drug might either cause the symptom of 'motor fluctuations' or worsen the symptom if the patient was already suffering from it. Conversely, with 'benefits' a criterion may be considered a 'benefit' if a drug were to improve the symptom, for example a drug might improve the patient's mobility, therefore 'mobility' would be considered a 'benefit'. Of these 17, only 14 could clearly be divided and these are listed below:

Risks:

- Motor fluctuations
- Cognitive impairment
- Confusion
- Hallucinations
- Dyskinesias
- Postural hypotension
- Depression
- Drug contraindications

- Drug interactions
- Adverse drug reactions

Benefits:

- Mobility
- Activities of daily living
- Cost-effectiveness
- Stage of disease (Hoehn &Yahr)

The criteria that fell under the 'risk' category were all considered to be potentially caused or worsened by PD treatments, with all the 'benefit' criteria being improved, with the exception of 'cost-effectiveness' which would equate to being a benefit if the drug were shown to be cost-effective.

The benefit and risk criteria can be organised into a value tree, so that the criteria are clustered in a hierarchical format, and the decision problem thus being represented clearly and simply. This was created with 'benefit' and 'risk' being established as the first level criteria, with the five 'benefit' and ten 'risk' criteria forming a second level of criteria clustered underneath their respective first level criteria. This is shown in Figure 3.3.

The remaining criteria were difficult to fit into either category, as they were considered to prompt questions to be asked of the clinician about their patient. These criteria are shown in Table 3.4 below with their respective questions.

It was decided then that the remaining criteria should form the basis of information gathering about the patient, with this information being used to inform the model in the way that the options would be included or excluded, or in the case of the criteria amended or excluded. For example, it would be necessary to know if the patient had previously had a poor response to a particular PD medication so that this could be excluded from the list of options. Likewise, it would be necessary to know the patient's co-morbidities in order to identify whether any of the options would be contraindicated.

Table 3.3 Considerations applied to criteria

Criterion	Problem	Consideration	Reason
Motor fluctuations	None		
Drug side effects	Same as 'Adverse drug reactions'	Redundancy	Another criterion already measures this factor
Cognitive impairment	None		
Drug response	(Information needed about individual patient)		
Severity of symptoms	Can be measured by UPDRS score	Operationality	If clinicians don't regularly record UPDRS score could mean extra time needed to do so to be able to input data for this criterion
Confusion	None		
Drug contraindications	None		
Hallucinations	None		
Neuro-psychiatric problems	General, covers hallucinations, confusion etc	Judgemental independence, redundancy	A general term that covers a number of individual criteria
Severity of disability	Similar/same as H&Y	Redundancy	Another criterion already measures this factor
Dyskinesias	None		
Evidence of treatment efficacy	Same as data from clinical trials	Redundancy	Another criterion already measures this factor
Age	(Information needed about individual patient)		
Is medication of benefit	How measured?	Measurability	How can this criterion be measured? Needs to be measured the same way by all clinicians using model to ensure consistency
Postural Hypotension	None		
End of dose symptoms	Incorporated under 'motor fluctuations'	Redundancy	Another criterion already measures this factor
Clinical assessment	General – meaningless	Understandability	Need to ensure all users of model have same understanding of what this entails
Patient's choice	Difficult to incorporate	Measurability	
Co-morbidities	(Information needed about individual patient)		

Table 3.3 Considerations applied to criteria (continued)

Criterion	Problem	Consideration	Reason
Mental state	Meaningless – not defined	Understandability, measurability	Do all model users have the same understanding of what this means? Are all model users measuring this in the same way?
Data from clinical trials	Forms part of evidence for scoring	Redundancy	Same as evidence that will be used to measure drugs against criteria
Predominant symptom	How can define how they affect treatment?	Measurability	Cannot be measured
Drug interactions	None		
Nature of deficits	What does this mean?	Understandability	Do model users have the same understanding of what this means?
Patients' other medication	Same as drug contraindications	Redundancy	Another criterion already measures this factor
Risks/benefits	General overview of s/e, contraindications, drug response etc	Redundancy	Another criterion already measures this factor
Mobility	None		
Non-motor complications	Sum of other criteria- neuro-psychiatric etc	Redundancy	Another criterion already measures this factor
How patient feels	Same as patient's choice	Redundancy	Another criterion already measures this factor
Adverse drug reactions	None		
Literature/systematic reviews	Same as evidence/clinical trials	Redundancy	Another criterion already measures this factor
Patient's capacity to deal with simple/complex regimes	How measured? Connected with cognitive impairment?	Measurability	Do all model users measure this in the same way? How is it defined?
Functional impairment	Generalised – what does it mean specifically?	Measurability/Understandability	How would this be measured? Do all model users have the same understanding of what this means?
Parkinson's plus syndrome	Type of parkinsonism, not idiopathic PD	Redundancy	
Type of symptoms	How can define how they affect treatment?	Measurability	Cannot be measured
Depression	None		
Nature of patient's symptoms	Generalised – meaning?	Understandability	Do all model users have the same understanding of what this means?

Table 3.3 Considerations applied to criteria (continued)

Criterion	Problem	Consideration	Reason
Age at onset	Might not be known, different to age?	Redundancy, judgemental independence to age, measurability	Could be considered redundant if same as patient's age. Is it judgementally independent of 'age' if it is the same as their age? Can this be measured, as their age at onset may not be known?
Progression of symptoms	How measured? Eg if H&Y score got worse, but is there evidence on how this is affected by drugs?	Measurability	Difficult to measure precisely. Could use H&Y score, but if this not recorded at previous stage would not know difference at current stage. Is there enough evidence on how progression affected by drugs?
General health	How defined?	Understandability/measurability	Do all model users have same definition of what this is? How is it measured?
Life expectancy	How measured? Evidence that this impacts on anything?	Measurability	How is this measured? Is there evidence it should affect their treatment?
Clinical appraisal	Meaning? Definition? Generalised	Understandability/redundancy	Do all model users have the same understanding of what this entails? Redundant because covers several individual criteria
Functional assessment	Similar to above, generalised	Understandability, redundancy	Do all model users have the same understanding of what this entails? Redundant because covers several individual criteria
Keep medication low	Irrelevant to model	Redundancy	
Patient's occupation	Difficult to define effect for purposes of model?	Measurability	How can the effect of this be measured?
Avoid treatment until loss of function	Irrelevant to model	Redundancy	
Activities of Daily Living	None		
Use dopamine agonists as long as possible	Cannot be defined	Measurability	How do you define as long as possible?

Table 3.3 Considerations applied to criteria (continued)

Criterion	Problem	Consideration	Reason
Clinical guidelines	Depend on individual trusts/hospitals/Drs? Whose guidelines?	Value relevance/understandability Measurability	Do users have same goal if depends who sets clinical guidelines? Do all users understand the same thing from guidelines? Can the guidelines be measured?
Perceived disability	Meaning? How defined?	Measurability, understandability	How can this be measured? Do all users have same interpretation of what it means?
Cost-effectiveness of treatment	None		
Stage disease/H&Y	None		
Underlying pathology	Relevance/meaning?	Understandability	Do all users have same understanding of how it affects model/patient?
Duration of disease	Doesn't tell us about individual patients – one patient could be much more advanced after 5 years than another	Measurability	Can't tell how patient affected by this
Evidence	Will already be incorporated into model	Redundancy	Another criterion already measures this factor
NICE guidelines	Incorporated into evidence?	Redundancy	Becomes redundant because already part of evidence
MMSE score	Definition of whether cognitive impairment or not	Redundancy	Another criterion already measures this factor
Social circumstances	Same/similar to "support/carer"	Redundancy	Another criterion already measures this factor
Support/carer	Cannot tell how this affects treatment	Measurability	Difficult to measure this
Patient's understanding of condition	How measured?	Measurability	Difficult to measure this
Psychological response to diagnosis	How measured?	Measurability	Difficult to measure this
Is patient wage earner?	Cannot tell how this affects treatment	Measurability	Difficult to measure this
General recommendations	What does this mean? Who from?	Understandability, measurability	
Hospital guidelines	Cannot be incorporated into model because would have individual model for each hospital	Measurability/ Value relevance	
PDMED/trials	Would /could the model be used for these patients? Just used to choose a drug within a group?	Redundancy	

Table 3.3 Considerations applied to criteria (continued)

Criterion	Problem	Consideration	Reason
Use amantadine/rasagiline in young patients	Can this be included? How would it be defined?	Measurability/understandability	
HRQoL	How measure? Which scale? Time	Measurability	
AAN guidelines	Wouldn't be applicable to geriatricians	Value relevance	
Olanow's algorithm	Could not be incorporated into model	Redundancy	

Figure 3.3 'Benefit' / 'Risk' value tree

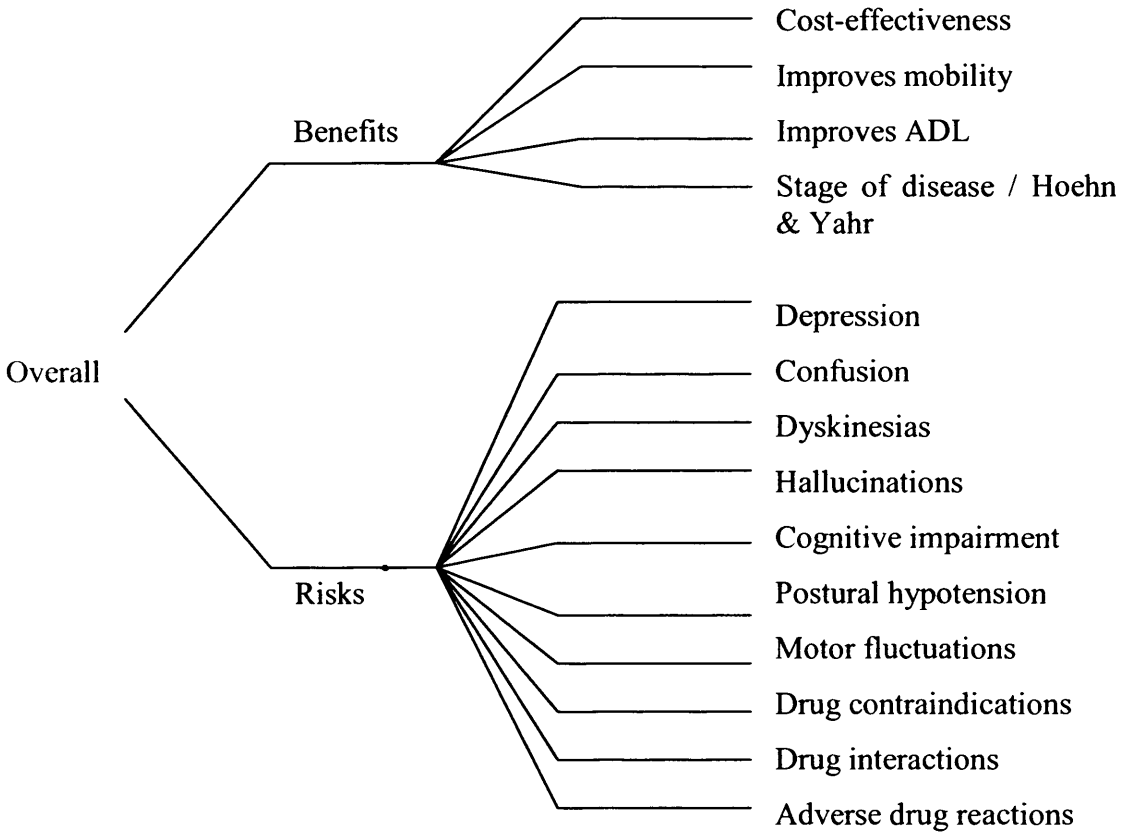


Table 3.4 Criteria with questions

Criterion	Question
Age	How old is the patient?
Previous drug response	What PD medications has the patient had previous poor response to?
Co-morbidities	What co-morbidities does the patient have?

Finally, it would also be necessary to establish what non-PD medication the patient was currently taking, in order to know any interactions that might occur with whichever PD medication was to be prescribed. Although this was not one of the criteria mentioned in the survey, it would be necessary information to be obtained.

DISCUSSION

In this chapter the first three stages of developing the model with MCDA were completed. The decision context was simple and straightforward to establish. The options were also straightforward to establish, as the available drug treatments for Parkinson's disease were already well known and the three anticholinergic were straight away excluded from the model, as per current recommendations for treatment of PD.

Establishing the criteria was a lengthier and more complex process in terms of the detail involved. For the first practitioner survey that was carried out it was difficult to obtain details of many of the practitioners, which meant that it was not possible to contact people across the UK for all the practitioner groups. It was difficult to be sure how many PDNSs were contacted and what geographical areas they responded from. Also, the fact that only geriatricians in Wales were contacted meant that the survey results obtained may not have been representative of geriatricians across the UK. The results showed that a wide number of different criteria were being considered by practitioners, meaning that a huge volume of information must be considered and remembered in each consultation.

The conclusion we can draw from the results of the two surveys together is that there is no clear treatment protocol for Parkinson's disease in the UK. In fact, treatment can vary not only from hospital to hospital, but from consultant to consultant within a hospital. We would therefore have to question whether practitioners are using evidence-based medicine in their clinical practice. The human short-term memory is considered to be capable of remembering seven plus or minus two items, but some of the consultants we surveyed were considering up to 68 criteria for their treatment decisions. This is an incredible volume of information to be considered, and one would have to question whether anyone is capable of considering so much information in medical decision making and whether in fact they are able to make the best decisions from such information. A clinical decision support system could therefore be a valuable tool for helping clinicians to consider large volumes of information

and could improve the decisions that are made. A decision aid would also help to ensure that evidence-based medicine was being incorporated into decision making.

Applying the considerations to the original list of criteria meant that criteria which were redundant or meaningless and so forth were able to be eliminated, so that a rationalised list of criteria which were meaningful and coherent was established. However, it also means that the criteria which are included in the model can be clearly established as being pertinent and relevant for the model.

Dividing the criteria in to 'risk' and 'benefit' categories meant that the criteria could be clearly divided. Using a value tree also meant that the decision problem was presented more clearly. This process showed a few of the criteria (age, previous drug response and co-morbidities) did not fit clearly into the 'risk'/'benefit' division and needed to be dealt with in a different way. Formulating them as information gathering questions rather than standard criteria meant that the information about the patient could still be included providing additional information to inform the model. This extra information could also mean that the model would incorporate more individualised information about each patient, helping to provide a model that would be suitable for each unique patient. Ultimately, a finished list of 14 criteria was developed, with the three additional criteria being transformed into questions for data to be elicited about the patient. These criteria were then able to provide the basis for developing the rest of the model. This will be discussed in chapter four.

SUMMARY

In this chapter the first three of seven stages for developing the model were covered.

- The decision context was established.
- The options to be appraised were established.

- The criteria were developed firstly by sending two surveys to practitioners, the first of which asked for all the criteria practitioners use to choose drug treatments for PD. The second of these used a compiled list of all criteria from the first survey to ascertain which criteria were used in practice.
- The results from the second survey were whittled down by applying the considerations value relevance; understandability; measurability; non-redundancy; judgemental independence; completeness and conciseness; operationality, and simplicity versus complexity, to rule out unnecessary or impractical criteria.
- A list of 14 suitable criteria was established.
- Three remaining criteria were transformed into questions to be asked of patients to establish individual data.

CHAPTER 4

Development of the Model using the Multi-Criteria Decision Analysis Technique

INTRODUCTION

In the previous chapter the methodology for the development of the model using MCDA was outlined, the decision context defined, the options identified and the criteria were developed. In this chapter the process for the development of the rest of the model will be discussed. This involves four steps: scoring the options against the criteria; developing weights for the criteria in respect of their importance to the decision problem and combining the scores and weights as an overall value. The final stage in the development of a model is to carry out a sensitivity analysis. That stage will be discussed in chapter seven. The aim of this chapter, therefore, is to develop a model to choose the most effective drug treatment for PD based on the criteria previously developed.

METHODS

Developing The Scores

Once the criteria have been established the next stage in the development of a model using MCDA is to establish the scores for the options.

Scoring is carried out by deriving a value for each option on how it performs against the criteria. When criteria are structured as a value tree the alternatives are scored against the bottom-level criteria of the tree. The values are assessed on an interval scale where the importance of the score is based on the difference between points. Two reference points are defined and numerical values assigned to each. These are generally taken as the top and bottom of the scale, with scores of 100 and 0 being assigned respectively (Belton and Stewart, 2002).

Scales can be either 'local' or 'global'. A 'local' scale refers to the set of options under consideration. The option which performs best on a given criterion is assigned a score of 100, and that which does least well is allocated a score of 0. The remaining options receive scores in between the two figures, reflecting their performance relative to each end of the scale. A 'local'

scale allows for a fairly speedy assessment of values and can be used for 'roughing out' a problem, or where time constraints are tight (Belton and Stewart, 2002).

A 'global' scale, on the other hand, refers to a wider set of possibilities. The two extremes of the scale can be defined by the ideal and worst conceivable performance on a given criterion, or by the best and worst performance that could occur. A 'global' scale has the advantage over a 'local' scale of being more general and can be defined before the options have been considered (Belton and Stewart, 2002).

Collecting the data

The list of drug treatment options available for PD was outlined in chapter three. Data from Phase III pivotal trials was collected for all the drugs. Where the pivotal trial data could not be collected, for example with older drugs such as Madopar, literature searches were carried out using databases such as PubMed to find trials which contained the data that would provide information for all the criteria. The data was then examined for information relevant to the model criteria. For each drug a table was constructed listing all of the model criteria in one column and the variables that were used to establish the relevant information on each drug in the other columns (Appendix I). These consisted of the following:

- Comparator
- Stage of disease
- Primary/Secondary outcome measures
- Significance level
- How the drug performed.

Different approaches were used to calculate the scores for different criteria. For example, the majority of the criteria, such as 'hallucinations' and 'dyskinesia' were relatively straightforward to score, based on the data that was obtained from trials and other publications. However, two criteria were an exception to this and proved to be more complex and needed a more detailed

scoring methodology. These two were: adverse drug reactions and drug interactions. The methodologies for all the criteria will now be described in detail.

Defining the measurements

Firstly, a set of measurements for each of the criteria was defined. A global scoring scale was used, meaning that individual end points were defined on a basis of the best and worst possible cases. These were allocated scores of 100 and 0, respectively. Each of the criteria needed to be examined individually and a point defined that best described the least and most preferred scores.

'Risk' criteria

Motor fluctuations

For 'motor fluctuations' it was known that many drugs caused or worsened motor fluctuations for Parkinson's patients, so the best possible case that could be expected for a drug would be to improve the level of motor fluctuations. On the other hand, the worst case would be that a drug caused a high degree of worsening of motor fluctuations. The least and most preferred points for 'motor fluctuations' were therefore set as 'high level of worsening of motor fluctuations' and 'improved level of motor fluctuations' respectively. Most of the other 'risk' criteria followed in the same vein.

'Benefit' criteria

The 'benefit' criteria had to be treated slightly differently, however. For example, 'stage of disease' was likely to be demonstrated in the trials as either an improvement or no improvement, therefore, the scales were set as 'no improvement in stage of disease' for the least preferred end and 'improved stage of disease' for the most preferred end.

Adverse drug reactions

Defining a scale of preference for 'adverse drug reactions' proved to be more complicated. There are several aspects to consider when looking at the occurrence of adverse drug reactions, namely the frequency of occurrence, the severity of the ADRs and the number of patients who withdrew from a trial

because of ADRs directly related to the study drug. Therefore, it was decided that each of these points would need to be assessed, resulting in the least preferred end of the scale being defined as 'high level of serious ADRs, high number of frequencies of ADRs and high number of withdrawals due to ADRs'. The most preferred point was defined as 'incidence of adverse events is similar to placebo'. A full list of the least and most preferred definitions is shown in Table 4.1.

Developing the scoring scales

Once the measurements were established, the actual scoring scale was developed. This meant a scale from 0 to 100 was broken down into tenths and a definition allocated to each tenth. The majority of the criteria were scored from the same scale, as shown in Table 4.2, where 0 equated to the worst possible score and 100 to the best possible score. The midpoint was given a score of 50 which equated to a drug having no effect on the criterion, neither improving the condition, nor worsening it. Where there was no data for a particular drug on any criterion a score of 50 was also allocated, as it could not be known whether the drug would have a positive or negative effect. For the scores 10 to 40, which were deemed to have a negative effect, each tenth equated to a frequency of occurrence as an ADR, for example a common ADR scored 10. On the other hand, the scores 60 to 90, which were deemed to have a positive effect, were assessed by the degree to which they improved the condition, for example a small improvement equated to a score of 60, whereas a large improvement equated to a score of 80. The score definitions are shown in Table 4.3.

Motor fluctuations

One exception to the scoring scales discussed above was the criterion 'motor fluctuations'. The results of analysing the data on 'motor fluctuations' showed that there were three main outcomes that were used consistently through the

Table 4.1 Least and most preferred definitions for criteria scores

Criterion	Least preferred	Most preferred
Motor fluctuations	High level of worsening of motor fluctuations	Improves levels of motor fluctuations
Cognitive impairment	High incidence of cognitive impairment as ADR	No incidence of cognitive impairment as ADR or effect similar to placebo
Confusion	High incidence of confusion as ADR	No incidence of confusion as ADR or effect similar to placebo
Hallucinations	High incidence of hallucinations or caused as ADR	No incidence of hallucinations as ADR or effect similar to placebo
Dyskinesias	High incidence of dyskinesias or caused as ADR	No incidence of dyskinesias as ADR or effect similar to placebo
Depression	High incidence of depression or caused as ADR	No incidence of depression as ADR or effect similar to placebo
Postural Hypotension	High incidence of postural hypotension or caused as ADR	No incidence of postural hypotension or effect similar to placebo
Stage of disease	No improvement in stage of disease	Improves stage of disease
ADL	No improvement in ADL	Improves ADL
Adverse drug reactions	High level of serious adverse events, high number of frequencies, high number of withdrawals due to ADR	Incidence of adverse effects is similar to placebo
Drug interactions	Unmanageable interactions with other drugs	No clinically significant interactions with other drugs
Contraindications	High level of serious contraindications	Incidence of contraindications similar to placebo

trials, namely: the Unified Parkinson's Disease Rating Scale (UPDRS) part III; the amount of time 'on' and the amount of time 'off'. The UPDRS (Fahn et al., 1987) is a multi-dimensional assessment tool used to measure severity of disease, with part three measuring motor examination. Time 'on' describes the periods when the patient is receiving benefit from the anti-PD medication and time 'off' the converse. These three assessments (UPDRS III, time 'on' and time 'off') were therefore scored separately, following the methods discussed above, and a mean obtained from the three results which became

Table 4.2 Definitions of scores scale

0	10	20	30	40	50	60	70	80	90	100
Worst possible score	Common ADR / very large worsening	Less common ADR / large worsening	Rare ADR / medium worsening	Very rare ADR / small worsening	Lack of effect/ no change	Small improvement	Medium improvement	Large improvement	Very large improvement	Best possible score

Table 4.3 Definition of scores

0	10	20	30	40	50	60	70	80	90	100
High incidence	Common ADR	Less Common ADR	Rare ADR	Very rare ADR	'No data therefore neither improves nor worsens' / 'no effect'	Small improvement	Medium improvement	Large improvement	Very large improvement	No incidence or effect similar to placebo

the overall score. The definitions are shown in Table 4.4.

Adverse drug reactions

Further exceptions were the criteria 'adverse drug reactions' and 'drug interactions'. 'Adverse drug reactions', similarly to 'motor fluctuations' was broken down into three categories and each category scored before the mean of the three was calculated. These categories were the frequency of occurrence of the ADR, the severity of the ADR and the number of patients withdrawn from a trial because of the ADR.

Frequency of occurrence

The frequency of occurrence of the ADR was broken down into a further five categories, determining whether the occurrence was 'common', 'less common', 'rare', 'very rare' or 'also reported' (Table 4.5). These data were taken from the British National Formulary (www.bnf.org, 2008). The drugs were scored on the basis of the number of ADRs they had in each category. Each grade of occurrence was scored on a different scale. It was decided that a form of weighting needed to be allocated to the grades to distinguish the importance of, for example, common against rare occurrences. Therefore, for common occurrences the worst score, i.e. a score of 0, was allocated to an occurrence of ≥30 different ADRs for any drug. A score of 100 was obtained if there were no occurrences of ADRs for a particular drug. The highest number of occurrences for less common frequencies was set at 40 for a score of 0, with the score increasing as the occurrences decreased. The categories 'very rare' and 'also reported' were allocated the same scores, both having the highest number of occurrences for the lowest score, with an occurrence of 60 equalling a score of 0. Again, the mean was calculated from the five categories.

Severity of ADRs

To calculate the severity of the ADRs the trial data was examined for the number of serious ADRs that were reported. Many of the trials only reported that the 'majority' of the ADRs were mild or moderate or used terms such as 'overall' or 'mainly'. It was therefore decided to class all these general terms

Table 4.4 Motor fluctuations score definitions

UPDRS scores										
0	10	20	30	40	50	60	70	80	90	100
≥0	≤ -2	-5	-8	-10	-12	-14	-17	-20	-23	-25
Time 'on' scores										
0	10	20	30	40	50	60	70	80	90	100
0 hours	2 hours	5 hours	8 hours	10 hours	12 hours	15 hours	17 hours	19 hours	22 hours	24 hours
Time 'off' scores										
0	10	20	30	40	50	60	70	80	90	100
0 hours	2 hours	5 hours	8 hours	10 hours	12 hours	15 hours	17 hours	19 hours	22 hours	24 hours

Table 4.5 ADR frequency score definitions

Common										
0	10	20	30	40	50	60	70	80	90	100
≥30	27	24	21	18	15	12	9	6	3	0
Less Common										
0	10	20	30	40	50	60	70	80	90	100
≥40	36	32	28	24	20	16	12	8	4	0
Rare										
0	10	20	30	40	50	60	70	80	90	100
≥50	45	40	35	30	25	20	15	10	5	0
Very rare										
0	10	20	30	40	50	60	70	80	90	100
≥60	54	48	42	36	30	24	18	12	6	0
Also reported										
0	10	20	30	40	50	60	70	80	90	100
≥60	54	48	42	36	30	24	18	12	6	0

together and allocate the same score to them, rather than try to distinguish, perhaps pedantically, any differentiation between them. They were allocated a score of 75, as this was judged to be roughly between a midpoint of no effect and the highest possible score. The worst possible score was deemed to be 50% of all ADRs being serious, and the scores between 10 and 40 were divided into tenths between 40% and 10%. The ADR severity score definitions are shown in Table 4.6.

Withdrawals from trial

The withdrawals from trial were calculated with 0 relating to 0% withdrawals and 100 relating to 40% withdrawals, which was deemed to be a high figure. The midpoint of 50 related to 20%, with the points 10 to 40 and 60 to 90 filling in the percentages in between (Table 4.7).

Drug interactions

To determine the scores for the criterion 'drug interactions' a panel of experts was consulted. This panel consisted of ten doctors, neurologists, geriatricians and academics, who were all experienced practitioners with PD patients. A table was compiled (Table 4.8) listing all the interactions for each of the drugs. For each drug the interactions were grouped together according to their effect, for example a number of drugs all caused a hypotensive effect if taken with co-beneldopa, so these were listed together as one interaction. The expert panel were then asked to complete a column headed 'Seriousness', giving their opinion on whether the interactions were 'most serious' (MS), 'very serious' (VS), 'fairly serious' (FS) or 'not serious' (NS). When the responses were received a score was allocated to each category, with the least preferred category 'most serious' having a score of 0 and the most preferred category 'not serious' having a score of 100. 'Very serious' and 'fairly serious' were given scores of 30 and 65 respectively as two roughly mid-points between 0 and 100. The responses from the panel were totalled up as means for each category and the overall mean score calculated for each drug.

Table 4.6 ADR severity score definitions

0	10	20	30	40	50	60	70	75	80	90	100
Highest level of occurrence / Highest number of patients =50% patients	40% occurrence	30% occurrence	20% occurrence	10% occurrence	No data therefore neither improves nor worsens			'overall' 'low intensity' 'generally' 'mainly' 'most'			No pts affected/ no occurrences

Table 4.7 ADR withdrawal score definitions

0	10	20	30	40	50	60	70	80	90	100
40% patients withdrawn from trial	36%	32%	28%	24%	20% / No data available	16%	12%	8%	4%	0% / same as placebo

Table 4.8 Interactions of all the PD drugs

Drug	Interaction	Seriousness: Most serious (MS)/very serious (VS)/fairly serious (FS)/not serious (NS)
Co-beneldopa	Enhanced hypotensive effect with ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside	
	Amisulpiride	
	Absorption of levodopa possibly reduced by: antimuscarinics, oral iron, phenytoin;	
	Effects of levodopa antagonised by: antipsychotics, possibly benzodiazepines;	
	Agitation, confusion & hallucinations with baclofen	
	Increased risk side effects with buproprion, moclobemide	
	Risk hypertensive crisis with MAOIs	
	Enhanced effect and increased toxicity with selegiline (reduce dose levodopa)	
Co-careldopa	Enhanced hypotensive effect with ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside	
	Amisulpiride	
	Absorption of levodopa possibly reduced by: antimuscarinics, oral iron, phenytoin;	
	Effects of levodopa antagonised by: antipsychotics, possibly benzodiazepines;	
	Agitation, confusion & hallucinations with baclofen	
	Increased risk side effects with buproprion, moclobemide	
	Risk hypertensive crisis with MAOIs	
	Enhanced effect and increased toxicity with selegiline (reduce dose levodopa)	
Stalevo	Enhanced hypotensive effect with ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside	
	Amisulpiride	
	Absorption of levodopa possibly reduced by: antimuscarinics, oral iron, phenytoin;	
	Effects of levodopa antagonised by: antipsychotics, possibly benzodiazepines;	
	Agitation, confusion & hallucinations with baclofen	
	Increased risk side effects with buproprion, moclobemide	

	Risk hypertensive crisis with MAOIs	
	Enhanced effect and increased toxicity with selegiline (reduce dose levodopa)	
Duodopa	Enhanced hypotensive effect with ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside	
	Amisulpiride	
	Absorption of levodopa possibly reduced by: antimuscarinics, oral iron, phenytoin;	
	Effects of levodopa antagonised by: antipsychotics, possibly benzodiazepines;	
	Agitation, confusion & hallucinations with baclofen	
	Increased risk side effects with buproprion, moclobemide	
	Risk hypertensive crisis with MAOIs	
	Enhanced effect and increased toxicity with selegiline (reduce dose levodopa)	
Ropinirole	Avoid antipsychotics, metoclopramide	
	Metabolism inhibited by ciprofloxacin	
	Plasma concentration increased by oestrogens	
Pramipexole	Amantadine – may slightly decrease the oral clearance of pramipexole	
	Cimetidine – caused a 50% increase in pramipexole AUC and 40% increase in half-life	
	Drugs secreted by cationic transport system (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine & quinine)	
Rotigotine	Manufacturer of rotigotine advises avoid concomitant use of antipsychotics (antagonism of effect)	
	manufacturer of rotigotine advises avoid concomitant use of metoclopramide (antagonism of effect)	
Pergolide	effects of pergolide antagonised by anti-psychotics	
	Anti-parkinsonian effect of pergolide antagonised by metoclopramide	
Bromocriptine	Hypoprolactinaemic and antiparkinsonian effects of bromocriptine antagonised by antipsychotics	
	Hypoprolactinaemic effect of bromocriptine possibly antagonised by domperidone and metoclopramide	
	Plasma concentration of bromocriptine increased by erythromycin (increased risk of toxicity) and octreotide and possibly increased by macrolides (increased risk of toxicity),	
	Risk of toxicity when bromocriptine given with isometheptene and phenylpropanolamine	
Cabergoline	Hypoprolactinaemic and antiparkinsonian effects antagonised by antipsychotics	
	Hypoprolactinaemic effect of cabergoline antagonised by metoclopramide and possibly domperidone,	
	Plasma concentration of cabergoline increased by erythromycin (increased risk of toxicity) and possibly macrolides	

Apomorphine	Effects of apomorphine antagonised by antipsychotics	
	Effects of apomorphine possibly enhanced by entacapone	
Selegiline	CNS toxicity: tricyclics	
	Risk serotonin syndrome: citalopram	
	Risk hypertensive crisis: dopamine	
	Increased risk hypertension and CNS excitation: fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine	
	Enhanced effect and increased toxicity: levodopa	
	Enhanced hypotensive effect: MAOIs	
	Effects selegiline enhanced: Memantine	
	Avoid use: moclobemide	
	Plasma concentration increased: oestrogens, progesterone	
	Hyperpyrexia and CNS toxicity (avoid use): pethidine	
	Manufacturer advises caution: tramadol	
Rasagiline	Avoid dextromethorphan and sympathomimetics	
	Increased risk of CNS toxicity with antidepressants (SSRIs & Tricyclics)	
	Wait 2 weeks before using: fluoxetine, fluvoxamine, MAOIs, pethidine	
	Plasma concentration of rasagiline reduced by entacapone	
Amantadine	Increased risk of antimuscarinic side-effects when given with antimuscarinics	
	Increased risk of side-effects when given with bupropion	
	Increased risk of CNS toxicity when given with memantine (manufacturer of memantine advises avoid concomitant use)	
	Increased risk of extrapyramidal side-effects when given with methyldopa, metoclopramide, tetrabenazine, antipsychotics, domperidone	
Entacapone	Possibly enhances effects of: adrenaline, apomorphine, dobutamine, dopamine, methyldopa, noradrenaline	
	Manufacturer advises caution with: tricyclics, moclobemide, paroxetine, venlafaxine	
	Absorption of entacapone reduced by oral iron	
	Avoid use with non-selective MAOIs	
	Possibly reduces plasma concentration of rasagiline	
	Enhances anticoagulant effect of warfarin	
Tolcapone	Avoid MAOIs	

Contraindications

'Contraindications' proved to be a difficult criterion to try to score. Whilst definitions such as frequency or severity could be used to determine the scores, it was felt that neither of these definitions would be applicable. For

example, although frequency of occurrence of a contraindication would give some idea of the effect this particular criterion would have on the PD drugs, this alone would not give a true picture of the impact. For instance, a higher number of minor contraindications should not necessarily receive a worse score than a low number of serious contraindications. However, if one took severity into account as well as frequency this would not give a true reflection of the impact of the drug either. For example, many of the drugs are contraindicated for pregnancy, which, whilst a serious contraindication is only relevant to the female half of the population, but also only a small proportion of female PD patients, as the age of PD patients is on average well above the age range for conception. Therefore, it was decided not to score 'contraindications' as a criterion, but to show a list of all contraindications for the recommended drugs which the model chose.

Total scores

The mean score for each drug was calculated and the overall mean of all the drugs calculated to give an idea how each drug had performed before the weights were calculated.

Developing The Weights

In evaluating a decision problem it is generally clear that not all criteria will carry the same weighting, or importance, therefore the relative importance of each of the criteria should be assessed. Decision makers are able to respond to a question such as: 'What is more important to you when buying a car: safety or comfort?'. They are also able to respond to questions that ask them to rate the relative importance of the criteria 'safety' and 'comfort' against a numerical or verbal scale. However, it has been argued that responses to questions such as these are essentially meaningless. The questions can be interpreted in many different ways, people's responses may not be consistent and their responses may not relate to the way in which weights are used to synthesise information (Belton and Stewart, 2002).

Swing weighting

However, weights used in a multi-criteria decision model are well defined. Weights are essentially scaling factors that relate scores on one criterion to scores on all the other criteria. This means that if criterion one has a weight that is twice that of criterion two this signifies that the decision maker values ten value points on criterion one the same as 20 value points on criterion two and would be willing to trade one for the other. This form of weighting is referred to as 'swing weighting', which is distinct from the less well defined concept 'importance weighting'. 'Swing weighting' is considered to capture both the psychological concept of 'importance' as well as the extent to which the measurement scale used discriminates between the alternatives. The weights and the measurement scale used are intimately connected (Belton and Stewart, 2002).

The swing is from the worst value to the best value on each criterion. If the value tree is small the decision maker may consider all bottom-level criteria simultaneously and assess the swing which gives the greatest increase in overall value; this criterion will then be given the highest weight. The process is then repeated on the remaining set of criteria, until a swing from worst to best has been determined on each criterion, defining a ranking of the criteria weights. In order to assign values to the weights the decision maker has to assess the relative value of the swings. For example, a swing from worst to best on the highest weighted criterion is assigned a value of 100; the decision maker must then decide what the relative value of a swing from worst to best on the second ranked criterion is. The decision maker must remember that the weights are dependent on the scales used for scoring as well as the importance of the criteria. This means that swing weights cannot be assigned until the scales for each criterion are defined. If a criterion that is considered intrinsically important does not differentiate much between the options, that is to say, if the difference between the minimum and maximum points is only small, then that criterion may be given quite a low weight (Belton and Stewart, 2002).

Once the rank order for the weights has been established, values can be assigned to them. For each criterion the decision maker assesses the increase in overall value which results from an increase from 0 to 100 on that criterion as a percentage of the increase in overall value resulting from an increase from 0 to 100 on the most highly ranked criterion (Belton and Stewart, 2002).

Weights within value trees

If the decision problem is structured as a multi-level value tree, weights should be considered at different levels of the tree. Relative and cumulative weights should be defined. Relative weights are assessed within criteria sharing the same parent and the weights in each family are normalised to sum to 1 (or 100). The cumulative weight of a criterion is the product of its relative weight compared to the siblings and the relative weights of the parent, parent's parent and so on, up to the top of the tree. The cumulative weights of all bottom-level criteria must sum to 1 (or 100). The cumulative weight of a parent criterion is the sum of the cumulative weights of its children.

On the other hand, if there are not too many leaves in the value tree the weights can be assessed by directly comparing all the bottom-level criteria to calculate the cumulative weights. The higher level weights are then calculated by adding the cumulative weights of all members of the family to determine the cumulative weight of the parent. The cumulative weights of family members are normalised to sum to one in order to determine the relative weights (Belton and Stewart, 2002).

The bottom-up approach assesses relative weights within families which only contain bottom-level criteria. Cross family comparisons are carried out using one criterion from each family and comparisons with any unitary bottom-level criteria. This process gives the cumulative weights of bottom-level criteria which can then be aggregated to higher levels of the value tree (Belton and Stewart, 2002).

Phrasing the weightings

To develop the weights using swing-weighting a series of phrases were developed based on the results from the criteria scores. These were developed for the user to be able to choose their own weighting relevant to the patient's particular condition, based on whether, for example, 'hallucinations' was a relevant criterion for that particular patient or not. This would mean that the weights would change with each new user of the model. Although the phrasing would be the same for each user, as they were based on the highest and lowest score ranges, the figures allocated for the weights would vary from user to user, thus producing in effect a new model with each use. Evidence-based medicine encourages physicians to involve patients in the decision making process as shared decision making ensures the patient's voice is heard when choices are made (Whitney, 2003). Thus, the physician and patient choosing the weights together would ensure the patient was involved in the decision-making as the model is effectively reproduced anew with each use.

To choose the wording for the weights for each of the criteria the lowest and highest scores were taken, representing either end of the scale for that criterion's scores. For example, for 'motor fluctuations' the lowest score was represented by 'no improvement in motor fluctuations' and the highest score by 'a big improvement in motor fluctuations'. The weighting for 'motor fluctuations' therefore read as 'The drugs cause from 'no improvement in motor fluctuations' to 'a big improvement in motor fluctuations'. This was considered to represent the full range of effects that the PD drugs caused for that criterion. As there was not a large number of criteria they were all taken as the same level in the value tree and weighted all together.

Normalisation

Weights are usually normalised to sum to 1 or 100. Normalisation allows decision makers to interpret the original weight of say 0.6 to be normalised to 19% of the total importance weight, giving a useful interpretation. In some cases decision makers may find it more intuitive to specify a reference criterion which is weighted at one and which all the other criteria are

compared against (Belton and Stewart, 2002). The weights for this model were not normalised as the user would be choosing one criterion as the reference criterion and comparing all the other criteria against it.

Consistency checks

In order to specify the set of criteria weights it is considered good practice to carry out more than the minimum number of comparisons necessary. This builds in a check on how consistent the decision makers' judgements are. The assessment of weights is implicitly a process of pair-wise comparison. This may be carried out by specifying a reference criterion against which all other criteria are compared, which requires the minimal number of comparisons, or each criterion can be compared with all the others, giving a full specification which would require $m(m - 1)/2$ comparisons (Belton and Stewart, 2002). This would mean if there were for example ten criteria the number of comparisons needed would be 10(10-1)/2. This would equal 10 (9)/2, or 90 divided by 2, which equals 45. Thus the total number of comparisons needed for 10 criteria would be 45.

For this model, carrying out consistency checks in this fashion would not have been possible, as the user would define the weights themselves. Therefore, only the user would be able to determine how many comparisons were made between criteria at the point of use. However, a help facility was installed in the application designed to run the model, which is discussed in chapter five. This explained the process for carrying out swing weighting to ensure that the user used the correct methodology for choosing the weights. This provided an alternative safeguard to ensure consistency in the choice of weights.

Combining The Scores And Weights

In order to combine the scores and weights the score for each option on each criterion is first multiplied by the weight for the criterion. For instance, if co-beneldopa scored 50 for 'dyskinesia' which was given a weight of seven the combined result would be 350. The scores and weights of the rest of the criteria are each multiplied and the results for each of the options then summed.

This is represented by the following algorithm, where 'S' represents the score for each option, 's_{ij}' represents the score for option 'i' on criterion 'j' and the weight by 'w_j', so for 'n' criteria the overall score for each option 's_i' is shown underneath (DTLR, 2000):

$$S_i = w_1 s_{i1} + w_2 s_{i2} + \ldots\ldots + w_n s_{in} = \sum_{j=1}^{n} w_j s_{ij}$$

This would mean that, for example, if there were ten criteria the weight of criteria one and score of option one would be multiplied together; these would be added to the multiplication of the weight of criteria two and score of option two and so on until the multiplication of all ten criteria weights and option scores were added together.

RESULTS

Calculating The Scores

Motor fluctuations

As mentioned in the methods sections of this chapter, 'motor fluctuations' was scored on three different aspects: the change in UPDRS score; time spent 'on' and time spent 'off'. The results of each of these will now be described in turn.

The UPDRS scores were assessed on whether the drug caused an improvement or worsening in score, with a reduction of the score by 25 points taken as the best possible scenario. All the drugs bar three (Duodopa, pramipexole and amantadine) had data from the trials on their UPDRS scores. Two drugs scored 90 or higher, namely pergolide and apomorphine. One drug, entacapone, scored 0. The other drugs all scored between ten and 30.

Fewer trials recorded time 'on' and 'off'. Only six trials recorded time 'on', with a mean score of 26 (range 0 to 100). Duodopa was the only drug to score 100, whilst both co-careldopa and amantadine scored 0. The remaining drugs

scored between five and 40. There was slightly more data for time 'off', with seven trials recording data with a range of scores between 10 and 55. The mean was 20.

The total score for each drug was calculated by taking the mean of the scores available for the three categories (Table 4.9). If data was only available for one or two categories then the mean was calculated accordingly, eg for co-careldopa there was a score for two categories (UPDRS score and time 'on') so the mean was calculated for the two categories and the third category (time 'off') was ignored as there was no data. The overall scores for the drugs for 'motor fluctuations' ranged between five and 100, with the mean score being 28. Amantadine scored the lowest (5), whilst Duodopa scored the highest with the top score of 100. Five drugs had a low score of 10 and three other drugs scored less than 20.

Cognitive impairment

The scores for 'cognitive impairment' (Table 4.10) were much more even, as there was little data about this criterion in the trials. All but three of the drugs were therefore allocated a score of 50, although cabergoline was also allocated 50 as it was reported in the trials as having no change over time. Both co-beneldopa and duodopa were given a score of 10, as 'cognitive impairment' was a common ADR for both drugs.

Confusion

Both co-careldopa and rotigotine scored 50 as trials claimed no effect for either of them. Ropinirole had one trial reporting 'confusion' as a serious ADR and the BNF reporting it is as common, which gave it scores of 5 and 10, the mean of which was rounded down to seven. Bromocriptine had one trial reporting a serious ADR and another an ADR at high doses only, leading to scores of five and 15, the mean of which being ten. Nine drugs had confusion as a common ADR, either from trial data or the BNF, which merited them a score of ten (Table 4.11).

Table 4.9 'Motor fluctuations' scores

Drug	UPDRS score	Time 'on' score	Time 'off' score	Total Score	Overall benefit or risk
Co-beneldopa	10	No data	No data	10	Risk
Co-careldopa	20	0	No data	10	Risk
Stalevo	15	No data	No data	15	Risk
Duodopa	No data	100	No data	100	Benefit
Ropinirole	10	No data	No data	10	Risk
Pramipexole	No data	No data	10	10	Risk
Rotigotine	25	5	10	13	Risk
Pergolide	95	No data	20	57	Benefit
Bromocriptine	25	No data	No data	25	Risk
Cabergoline	30	No data	55	42	Risk
Apomorphine	90	No data	No data	90	Benefit
Selegiline	17	No data	No data	17	Risk
Rasagiline	10	No data	No data	10	Risk
Amantadine	No data	0	10	5	Risk
Entacapone	0	10	10	7	Risk
Tolcapone	12	40	28	27	Risk

Hallucinations

A total of nine drugs listed 'hallucinations' as a common ADR (Table 4.12), either from BNF or trial data, and were therefore allocated a score of ten. All the drugs scored poorly, with bromocriptine scoring the highest with a total of 15, as it was only listed as causing hallucinations as an ADR at high doses. Cabergoline scored a mean of 12, from a score of 10 for causing a common ADR and 15 for ADR at high doses. One drug, entacapone, scored nine, five trials and the BNF reporting it as a common ADR and one trial reporting a higher percentage of occurrences meriting a score of five. The remaining four drugs (ropinirole, pramipexole, amantadine and tolcapone) all scored seven from having a mean calculated from mainly higher scores as well as being a common ADR.

Table 4.10 'Cognitive impairment' scores

Drug	Benefit/risk/neutral	Scores	Total (mean) Score	Overall benefit or risk
Co-beneldopa	Risk – common ADR	10	10	Risk
Co-careldopa	Neutral - no data	50	50	Neutral
Stalevo	Neutral - no data	50	50	Neutral
Duodopa	Risk – common ADR	10	10	Risk
Ropinirole	Neutral - no data	50	50	Neutral
Pramipexole	Neutral - no data	50	50	Neutral
Rotigotine	Neutral - no data	50	50	Neutral
Pergolide	Neutral - no data	50	50	Neutral
Bromocriptine	Neutral - no data	50	50	Neutral
Cabergoline	Neutral – no change over time (non-significant)	50	50	Neutral
Apomorphine	Neutral - no data	50	50	Neutral
Selegiline	Neutral – MMSE score worsened but non-significant	50	50	Neutral
Rasagiline	Neutral – MMSE score improved but on-significant	50	50	Neutral
Amantadine	Neutral – no data	50	50	Neutral
Entacapone	Neutral - no data	50	50	Neutral
Tolcapone	Neutral - no data	50	50	Neutral

Dyskinesia

'Dyskinesia' produced more varied results, ranging from means of three to 75,with a mean total score of 22. Two drugs produced a low mean score of

Table 4.11 'Confusion' scores

Drug	Benefit/risk/neutral	Scores	Total (mean) Score	Overall benefit or risk
Co-beneldopa	Risk – common ADR	10	10	Risk
Co-careldopa	Neutral – no data	50	50	Neutral
Stalevo	Risk – common ADR	10	10	Risk
Duodopa	Risk – common ADR	10	10	Risk
Ropinirole	Risk – relatively high incidence, common ADR	5, 10	7	Risk
Pramipexole	Risk – common ADR	10	10	Risk
Rotigotine	Neutral – no data	50	50	Neutral
Pergolide	Risk – common ADR	10	10	Risk
Bromocriptine	Risk – relatively high incidence, between common and less common ADR	5, 15	10	Risk
Cabergoline	Risk – between common and less common ADR	15	15	Risk
Apomorphine	Risk – common ADR	10	10	Risk
Selegiline	Risk – common ADR	10	10	Risk
Rasagiline	Neutral – no effect	50	50	Neutral
Amantadine	Neutral – no data	50	50	Neutral
Entacapone	Risk – common ADR	10	10	Risk
Tolcapone	Risk – common ADR	10	10	Risk

three, co-beneldopa and tolcapone, due to a high percentage of patients occurrences during the trial. Pergolide scored the highest, due to a reduction in UPDRS IV score and a reduction in hours per day producing dyskinesias. Amantadine also scored well, with a total mean of 65, produced from a reduction in dyskinesia score and small improvements in duration and

disability and UPDRS scores. Similarly, rasagiline scored 60 from a small reduction in UPDRS IV score, as shown in Table 4.13.

Depression

The results for 'depression' were fairly evenly split between those scoring around the middle mark, to those with fairly low scores. The mean total score was 27 (range 5 to 65). Pramipexole scored highest, with a medium improvement and a small improvement in depression combining to form a mean of 65. Pergolide also had a positive result, with two small improvements resulting in a score of 60. There was no data for rotigotine, and both apomorphine and selegiline showed non-statistically significant results, giving all three drugs a score of 50. Ropinirole showed the poorest result, with two trials showing depression as a more serious ADR, meriting a mean score of five. Four drugs scored ten from having depression as a common ADR (Table 4.14).

Postural hypotension

'Postural hypotension' scored poorly for all the drugs. The lowest score was nine and the highest only a rather poor 20. Six drugs scored a mean of ten, mainly from having 'postural hypotension' as a common ADR, with three drugs having a slightly lower mean score of nine because of slightly higher occurrences of the condition as an ADR. Apomorphine had the top score of 20, with both a trial and the BNF reporting 'postural hypotension' as a less common ADR.

Activities of daily living

Most of the drugs scored better on ADL, with a mean total score of 58 (range 50 to 80). A few of the drugs (four) did not have ADL reported on in their trials, or had non-significant results and therefore scored 50. The majority of the drugs that showed some improvement had only a small improvement and therefore scored between 52 and 60. The exceptions to this were Duodopa and cabergoline, which both showed a large improvement.

Table 4.12 'Hallucinations' scores

Drug	Benefit/risk/neutral	Scores	Total (mean) Score	Overall benefit or risk
Co-beneldopa	Risk –common ADR	10	10	Risk
Co-careldopa	Risk – common ADR	10	10	Risk
Stalevo	Risk – common ADR	10	10	Risk
Duodopa	Risk – common ADR	10	10	Risk
Ropinirole	Risk – common ADR, relatively high occurrence	10, 5	7	Risk
Pramipexole	Risk – common ADR, relatively high occurrence	10, 5	7	Risk
Rotigotine	Risk – common ADR	10	10	Risk
Pergolide	Risk – common ADR	10	10	Risk
Bromocriptine	Risk – ADR – high doses only	15	15	Risk
Cabergoline	Risk – common ADR, ADR at high doses	10, 15	12	Risk
Apomorphine	Risk – common ADR	10	10	Risk
Selegiline	Risk – common ADR	10	10	Risk
Rasagiline	Risk – common ADR	10	10	Risk
Amantadine	Risk – common ADR, relatively high occurrence	10, 5	7	Risk
Entacapone	Risk – common ADR, common ADR, common ADR, common ADR, common ADR, common ADR, relatively high occurrence	10, 10, 10, 10, 10, 10, 5	9	Risk
Tolcapone	Risk – common ADR, relatively high occurrence	10, 5	7	Risk

Table 4.13 Scores for 'dyskinesias'

Drug	Benefit/risk/neutral – trial results	Scores	Total (mean) Score	Overall benefit or risk
Co-beneldopa	Risk – relatively high occurrence as ADR, relatively high occurrence as ADR	3, 4	3	Risk
Co-careldopa	Risk – common ADR, relatively high occurrence as ADR	10, 5	7	Risk
Stalevo	Risk – less common ADR, relatively high incidence, common ADR	20, 3, 10	16	Risk
Duodopa	Neutral - no change, Risk-common ADR, common ADR	50, 10, 10	35	Risk
Ropinirole	Risk – less common ADR, common ADR, relatively high incidence, less common ADR	20, 10, 4, 20	13	Risk
Pramipexole	Risk – common ADR	10	10	Risk
Rotigotine	Risk – common ADR, relatively high incidence	10, 5	7	Risk
Pergolide	Benefit – reduction UPDRS IV score, reduction hours per day producing dyskinesia	80, 70	75	Benefit
Bromocriptine	Risk – less common ADR, common ADR	20, 10	15	Risk
Cabergoline	Benefit – medium improvement, Risk – common ADR, less	70, 10, 20, 10	27	Risk

	common ADR, common ADR			
Apomorphine	Risk – less common ADR, not suitable for severe dyskinesia, common ADR	20, 5, 10	11	Risk
Selegiline	Risk – relatively high incidence occurrence, common ADR	5, 10	7	Risk
Rasagiline	Benefit – reduction UPDRS IV score	60	60	Benefit
Amantadine	Benefit – reduction dyskinesia score, improvement duration, improvement disability, improvement UPDRS IV score,	80, 60, 60, 60	65	Benefit
Entacapone	Risk – relatively high occurrence, common ADR, relatively high occurrence, relatively high occurrence, relatively high occurrence, relatively high occurrence, common ADR	5, 10, 3, 4, 4, 5, 10	6	Risk
Tolcapone	Risk – relatively high occurrence as ADR, relatively high occurrence as ADR, relatively high occurrence as ADR	2, 3, 3	3	Risk

Stage of disease

The criterion 'stage of disease' was the only one on which all the drugs bar one scored the same. The one exception was rasagiline, which showed a tiny improvement and therefore merited a score of 52. Of the drugs scoring 50,

Table 4.14 'Depression' scores

Drug	Benefit/risk/neutral – from trial data	Scores	Total (mean) Score	Overall benefit or risk
Co-beneldopa	Risk – relatively high incidence ADR, common ADR	5, 10	7	Risk
Co-careldopa	Risk – common ADR, relatively high incidence ADR, relatively high incidence ADR	10, 5, 5	7	Risk
Stalevo	Risk – common ADR	10	10	Risk
Duodopa	Risk – common ADR, common ADR	10, 10	10	Risk
Ropinirole	Risk – relatively high incidence as ADR, relatively high incidence as ADR	5, 5	5	Risk
Pramipexole	Benefit – medium improvement, small improvement	70, 60	65	Benefit
Rotigotine	Neutral – no data	50	50	Neutral
Pergolide	Benefit – small improvement, small improvement	60, 60	60	Benefit
Bromocriptine	Risk – common ADR	10	10	Risk
Cabergoline	Risk – common ADR	10	10	Risk
Apomorphine	Neutral – no change, (result non-significant)	50	50	Neutral
Selegiline	Neutral – hardly any change (non-significant)	50	50	Neutral
Rasagiline	Benefit – small improvement, Risk –	55, 10	32	Risk

	common ADR			
Amantadine	Risk – relatively high incidence, common ADR	5, 10	7	Risk
Entacapone	Risk – common ADR, relatively high incidence as ADR, common ADR	10, 5, 10	8	Risk
Tolcapone	Neutral – no data	50	50	Neutral

there was no data for 11 of them, with the remaining four (pergolide, bromocriptine, selegiline and entacapone) being either unchanged (entacapone), having non-significant results (selegiline) or having a positive result counterbalanced by a negative result (pergolide). The result for bromocriptine gave no detail of the amount the stage of disease was improved by, stating only that the score was lower than for the comparator; therefore this was given a neutral score of 50.

Adverse drug reactions

To calculate the frequency of occurrence of ADRs for each drug, the occurrences were divided into five categories, namely: 'common'; 'less common'; 'rare'; 'very rare' and 'also reported'. When the scores for the number of occurrences in each group was totalled up it was shown that the mean score was 46 (range 0 to 83) for 'common', with stalevo scoring 0 and two drugs, bromocriptine and cabergoline, both scoring 83. No drug scored 100. The mean was 82 for 'less common' (range 40 to 100), with six drugs (pramipexole, pergolide, selegiline, amantadine, entacapone and tolcapone) scoring 100. 72 (range 20 to 100) was the mean for 'rare', all the levodopa drugs scoring in the 20s, and six drugs (ropinirole, pramipexole, pergolide, rasagiline, amantadine and tolcapone) having the top score of 100. The mean was 97 for 'very rare' (range 89 to 100), only two drugs, bromocriptine and cabergoline, scoring less than 90. The mean for 'also reported' was 93 (range 60 to 100), with again six drugs (rotigotine, bromocriptine, apomorphine, rasagiline, amantadine and tolcapone) scoring 100 and seven drugs (co-beneldopa, co-careldopa, Duodopa, ropinirole, pramipexole,

Table 4.15 'Postural hypotension' scores

Drug	Benefit/risk/neutral – results from trial data	Scores	Total (mean) Score	Overall benefit or risk
Co-beneldopa	Risk – common ADR, common ADR	10, 10	10	Risk
Co-careldopa	Risk – common ADR, common ADR, common ADR	10, 10, 10	10	Risk
Stalevo	Risk – common ADR	10	10	Risk
Duodopa	Risk – common ADR, common ADR	10, 10	10	Risk
Ropinirole	Risk – common ADR, common ADR, relatively high incidence as ADR	10, 10, 8	9	Risk
Pramipexole	Risk – common ADR, common ADR, relatively high incidence as ADR	10, 10, 8	9	Risk
Rotigotine	Risk – common ADR	10	10	Risk
Pergolide	Risk – common ADR, common ADR	10, 10	10	Risk
Bromocriptine	Risk – relatively high incidence, less common ADR	8, 20	14	Risk
Cabergoline	Risk – less common ADR, relatively high incidence	20, 5	12	Risk
Apomorphine	Risk – less common ADR, less common ADR	20, 20	20	Risk
Selegiline	Risk – common ADR,	10, 20	15	Risk

	less common ADR			
Rasagiline	Risk – common ADR	10	10	Risk
Amantadine	Risk – between common and less common	15	15	Risk
Entacapone	Risk – common ADR, common ADR, relatively high incidence as ADR	10, 10, 8	9	Risk
Tolcapone	Risk – between common and less common	15	15	Risk

selegiline and entacapone) scoring in the 90s. The scores for each drug were then totalled for each category and the mean calculated for each drug. The range for the totals was 52 to 92, with the mean 77. Apomorphine had the top score, with amantadine a close second on 90 and stalevo the lowest on 52.

Severity

The mean score for 'severity' was 53 (range 32 to 83). Co-careldopa scored the lowest and stalevo the highest. Duodopa was the only other drug to score more than 70, with a score of 73. Co-beneldopa, bromocriptine and amantadine all scored 50 as there was no data on any of them for severity.

Withdrawal

The scores for 'withdrawal' ranged from 18 to 91, with a mean of 66. Co-beneldopa scored the lowest and rasagiline the highest. Co-beneldopa had a score considerably lower than the second lowest, ropinirole, on 48, scoring only 18. The other scores were more evenly spaced. Two drugs (amantadine and tolcapone) scored in the 50s, four drugs (bromocriptine, cabergoline, selegiline and entacapone) in the 60s, five (duodopa, pramipexole, pergolide, rotigotine and rasagiline) in the 70s and three (co-careldopa, stalevo and apomorphine) in the 80s.

Table 4.16 'Activities of daily living' scores

Drug	Benefit/risk/neutral – results from trial data	Scores	Total (mean) Score	Overall benefit or risk
Co-beneldopa	Neutral – improvement but non-significant	50	50	Neutral
Co-careldopa	Benefit – small improvement, small improvement, Risk – small worsening	60, 55, 40	52	Benefit
Stalevo	Benefit – small improvement	60	60	Benefit
Duodopa	Benefit – large improvement	80	80	Benefit
Ropinirole	Risk – small worsening, Benefit – small to medium improvement	40, 65	52	Benefit
Pramipexole	Benefit – small improvement	60	60	Benefit
Rotigotine	Benefit – small to medium improvement, medium improvement, very small improvement	65, 70, 55	63	Benefit
Pergolide	Benefit – large improvement, Risk – medium worsening	90, 30	60	Benefit
Bromocriptine	Benefit – small improvement	60	60	Benefit
Cabergoline	Benefit – medium improvement, very large improvement	70, 90	80	Benefit
Apomorphine	Neutral – no data	50	50	Neutral
Selegiline	Neutral – small change	50	50	Neutral

	but non-significant			
Rasagiline	Benefit – very small improvement, very small improvement, very small improvement, Risk – very small worsening	55, 55, 55, 45	52	Benefit
Amantadine	Benefit – small improvement	60	60	Benefit
Entacapone	Benefit – very small improvement, small improvement, very small improvement, very small improvement, Neutral – no change non-significant, slight improvement non-significant, improvement non-significant	55, 60, 55, 55, 50, 50, 50	53	Benefit
Tolcapone	Benefit – very small improvement, Risk – very small worsening	55, 45	50	Neutral

Total scores for ADRs

For the total score for ADRs, the mean for 'frequency' and the scores for 'severity' and 'withdrawal' were totalled and the overall mean calculated, yielding a mean of 65 (range 43 to 76). However, the ergot dopamine agonists pergolide, bromocriptine and cabergoline are only recommended by National Institute for Clinical Excellence (NICE, 2006) as second choice drugs to the non-ergot dopamine agonists because of their serious potential cardiovascular side-effects. It was therefore felt that this should be acknowledged in some way in the scoring, as the criteria scores thus far had not been able to take account of this aspect. The overall scores for the non-ergot dopamine agonists were therefore reduced to ten, which would reflect

Table 4.17 'Stage of disease' scores

Drug	Benefit/risk/neutral – results from trial data	Scores	Total (mean) Score	Overall benefit or risk
Co-beneldopa	Neutral – no data	50	50	Neutral
Co-careldopa	Neutral – no data	50	50	Neutral
Stalevo	Neutral – no data	50	50	Neutral
Duodopa	Neutral – no data	50	50	Neutral
Ropinirole	Neutral – no data	50	50	Neutral
Pramipexole	Neutral – no data	50	50	Neutral
Rotigotine	Neutral – no data	50	50	Neutral
Pergolide	Benefit – small improvement, Risk -	55, 45	50	Neutral
Bromocriptine	Neutral – result better for comparator but amount not stated therefore judged as neutral	50	50	Neutral
Cabergoline	Neutral – no data	50	50	Neutral
Apomorphine	Neutral – no data	50	50	Neutral
Selegiline	Neutral – non-significant result	50, 50	50	Neutral
Rasagiline	Neutral – no change, small improvement	50, 54	52	Benefit
Amantadine	Neutral – no data	50	50	Neutral
Entacapone	Neutral – no change	50	50	Neutral
Tolcapone	Neutral – no data	50	50	Neutral

what was effectively a 'penalty' against them. The mean score overall therefore became 54 (range 10 to 76). All the results for ADRs are shown in Table 4.18.

Table 4.18 Scores for 'ADRs'

Drug	Frequency					Frequency Total	Severity	Withdrawal	Total (penalty score in brackets)
	Common	Less common	Rare	Very rare	Also reported				
Co-beneldopa	23	62	24	99	93	60	50	18	43
Co-careldopa	23	62	24	99	93	60	32	84	59
Stalevo	0	62	20	91	87	52	83	85	73
Duodopa	23	62	24	99	93	60	73	70	68
Ropinirole	54	90	100	99	99	54	35	48	46
Pramipexole	44	100	100	100	93	88	62	70	73
Rotigotine	33	40	96	100	100	74	46	70	63
Pergolide	67	100	100	100	60	85	75	60	73 (10)
Bromocriptine	83	78	88	89	100	88	50	66	68 (10)
Cabergoline	83	78	88	89	75	83	47	72	67 (10)
Apomorphine	80	90	92	100	100	92	48	88	76
Selegiline	57	100	90	100	99	89	49	66	68
Rasagiline	44	90	100	100	100	87	43	91	74
Amantadine	50	100	100	100	100	90	50	50	63
Entacapone	47	100	96	93	93	86	46	67	66
Tolcapone	20	100	100	100	100	84	57	52	64

Drug interactions

Six out of the ten experts consulted responded to the short questionnaire sent out. The mean score overall was 71 (range 59 to 82). Pramipexole scored the highest with 82, whilst pergolide and rotigotine both scored the lowest on 59. The scores for the vast majority of the drugs fell in the 60s and 70s, suggesting that the average severity was 'fairly serious' for most of the interactions. The responses of the expert panel were fairly varied, with all the experts only agreeing on their response for a small number of interactions. For several interactions the responses encompassed 'not serious' to 'very serious', covering all the grades of severity per interaction. The results for all the interactions are shown in Table 4.19.

Contraindications

There were no results for 'contraindications' as this was not being used as a criterion anymore, as mentioned in the methodology section. However, both the contraindications and cautions for all the drugs were taken from the BNF to be displayed to the user alongside the recommended treatments by the computer decision support system which is discussed in chapter five. Tables 4.20 and 4.21 show the contraindications and the cautions respectively.

Total scores

The mean scores for all the drugs ranged between 28 and 48, with co-beneldopa scoring the lowest and apomorphine the highest. The overall mean was 39. Although co-beneldopa had a low score the scores for the other levodopa based drugs were fairly similar, ranging between 37 and 44. Besides co-beneldopa all the other drugs scored in the 30s and 40s. The mean score for all the dopamine agonists was 40 (range 32 to 48). The total scores and means are shown in Table 4.22.

Working out the weights

'Adverse drug reactions' and 'drug interactions' were the only criteria to be pre-weighted, as it was assumed that both were essential criteria to consider for all patients. They were both given a weight of 10, this being the highest

Table 4.19 Scores for 'Interactions'

Drug	Interaction Seriousness: Most serious (MS)/very serious (VS)/fairly serious (FS)/not serious (NS)	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
Co-beneldopa	Enhanced hypotensive effect with ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside	65	65	65	65	65	65	65	67
	Amisulpiride	65	100	30	65	Not completed	65	65	
	Absorption of levodopa possibly reduced by: antimuscarinics, oral iron, phenytoin;	100	100	100	100	65	100	94	
	Effects of levodopa antagonised by: antipsychotics, possibly benzodiazepines;	100	65	30	65	30	65	59	
	Agitation, confusion & hallucinations with baclofen	65	65	30	65	30	65	53	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
	Increased risk side effects with buproprion, moclobemide	65	100	65	65	65	100	77	
	Risk hypertensive crisis with MAOIs	65	100	30	30	30	30	47	
	Enhanced effect and increased toxicity with selegiline (reduce dose levodopa)	100	100	65	65	65	100	82	
Co-careldopa	Enhanced hypotensive effect with ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside	65	65	65	65	65	65	65	70
	Amisulpiride	65	100	30	65	Not completed	65	65	
	Absorption of levodopa possibly reduced by: antimuscarinics, oral iron, phenytoin;	100	100	100	100	65	100	94	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
	Effects of levodopa antagonised by: antipsychotics, possibly benzodiazepines;	100	65	30	65	30	65	59	
	Agitation, confusion & hallucinations with baclofen	100	65	30	65	30	65	59	
	Increased risk side effects with buproprion, moclobemide	100	100	65	65	65	100	82	
	Risk hypertensive crisis with MAOIs	100	100	30	30	30	30	53	
	Enhanced effect and increased toxicity with selegiline (reduce dose levodopa)	100	100	65	Not comleted	65	100	86	
Stalevo	Enhanced hypotensive effect with ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside	65	65	65	65	65	65	65	73
	Amisulpiride	100	100	30	65	Not completed	65	72	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
	Absorption of levodopa possibly reduced by: antimuscarinics, oral iron, phenytoin;	100	65	100	100	65	100	88	
	Effects of levodopa antagonised by: antipsychotics, possibly benzodiazepines;	100	65	30	65	30	65	59	
	Agitation, confusion & hallucinations with baclofen	100	65	30	65	30	65	59	
	Increased risk side effects with buproprion, moclobemide	100	100	65	65	65	100	82	
	Risk hypertensive crisis with MAOIs	100	100	30	30	30	30	53	
	Enhanced effect and increased toxicity with selegiline (reduce dose levodopa)	100	100	65	65	65	100	82	
	Possibly enhances effects of: adrenaline, apomorphine, dobutamine, dopamine, methyldopa, noradrenaline	100	100	65	65	65	65	77	
	Manufacturer advises caution with: tricyclics, moclobemide, paroxetine, venlafaxine	100	65	65	65	100	100	82	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
	Absorption of entacapone reduced by oral iron	100	65	100	100	100	100	94	
	Avoid use with non-selective MAOIs	100	65	65	65	65	65	71	
	Possibly reduces plasma concentration of rasagiline	100	100	100	100	100	100	100	
	Enhances anticoagulant effect of warfarin	65	65	30	30	30	65	47	
Duodopa	Enhanced hypotensive effect with ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside	65	65	65	65	65	65	65	64
	Amisulpiride	100	100	30	65	Not completed	65	60	
	Absorption of levodopa possibly reduced by: antimuscarinics, oral iron, phenytoin;	100	65	30	30	65	100	65	
	Effects of levodopa antagonised by: antipsychotics, possibly benzodiazepines;	100	100	30	65	30	65	65	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
	Agitation, confusion & hallucinations with baclofen	65	65	30	65	30	65	53	
	Increased risk side effects with buproprion, moclobemide	100	65	65	65	65	100	77	
	Risk hypertensive crisis with MAOIs	100	100	30	30	30	30	53	
	Enhanced effect and increased toxicity with selegiline (reduce dose levodopa)	100	100	65	65	65	100	82	
Ropinirole	Avoid antipsychotics, metoclopramide	100	65	30	65	30	65	59	80
	Metabolism inhibited by ciprofloxacin	100	100	100	65	65	100	88	
	Plasma concentration increased by oestrogens	100	100	100	65	100	100	94	
Pramipexole	Amantadine – may slightly decrease the oral clearance of pramipexole	65	100	100	100	100	100	94	82
	Cimetidine – caused a 50% increase in pramipexole AUC and 40% increase in half-life	100	100	65	65	47	65	74	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
	Drugs secreted by cationic transport system (cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine & quinine)	100	100	65	65	47	100	79	
Rotigotine	Manufacturer of rotigotine advises avoid concomitant use of antipsychotics (antagonism of effect)	100	65	30	65	30	65	59	59
	manufacturer of rotigotine advises avoid concomitant use of metoclopramide (antagonism of effect)	100	65	30	65	30	65	59	
Pergolide	effects of pergolide antagonised by anti-psychotics	100	65	30	65	30	65	59	59
	Anti-parkinsonian effect of pergolide antagonised by metoclopramide	100	65	30	65	30	65	59	
Bromocriptine	Hypoprolactinaemic and antiparkinsonian effects of bromocriptine antagonised by antipsychotics	65	65	30	65	30	65	53	65
	Hypoprolactinaemic effect of bromocriptine possibly antagonised by domperidone and metoclopramide	100	65	30	100	30	65	65	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
	Plasma concentration of bromocriptine increased by erythromycin (increased risk of toxicity) and octreotide and possibly increased by macrolides (increased risk of toxicity),	100	65	65	65	65	100	77	
	Risk of toxicity when bromocriptine given with isometheptene and phenylpropanolamine	65	65	65	65	30	100	65	
Cabergoline	Hypoprolactinaemic and antiparkinsonian effects antagonised by antipsychotics	100	65	30	65	65	65	65	75
	Hypoprolactinaemic effect of cabergoline antagonised by metoclopramide and possibly domperidone,	100	65	30	100	65	100	77	
	Plasma concentration of cabergoline increased by erythromycin (increased risk of toxicity) and possibly macrolides	100	65	65	100	65	100	82	
Apomorphine	Effects of apomorphine antagonised by antipsychotics	100	30	30	65	65	65	59	70
	Effects of apomorphine possibly enhanced by entacapone	100	65	65	100	100	65	82	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
Selegiline	CNS toxicity: tricyclics	65	65	65	65	65	65	65	69
	Risk serotonin syndrome: citalopram	65	30	65	65	30	65	53	
	Risk hypertensive crisis: dopamine	100	65	30	30	65	65	59	
	Increased risk hypertension and CNS excitation: fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine	65	65	65	65	30	65	59	
	Enhanced effect and increased toxicity: levodopa	100	100	100	65	100	100	94	
	Enhanced hypotensive effect: MAOIs	100	65	65	65	65	100	77	
	Effects selegiline enhanced: Memantine	100	65	65	65	65	100	77	
	Avoid use: moclobemide	100	100	30	65	30	65	65	
	Plasma concentration increased: oestrogens, progesterone	100	100	100	65	100	100	94	
	Hyperpyrexia and CNS toxicity (avoid use): pethidine	100	65	30	65	0	65	54	
	Manufacturer advises caution: tramadol	100	65	30	100	30	65	65	
Rasagiline	Avoid dextromethorphan and sympathomimetics	100	65	30	65	30	65	59	73

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
	Increased risk of CNS toxicity with antidepressants (SSRIs & Tricyclics)	65	65	65	65	82	65	68	
	Wait 2 weeks before using: fluoxetine, fluvoxamine, MAOIs, pethidine	65	100	65	65	65	65	71	
	Plasma concentration of rasagiline reduced by entacapone	100	65	100	100	100	100	94	
Amantadine	Increased risk of antimuscarinic side-effects when given with antimuscarinics	100	100	65	65	30	65	71	69
	Increased risk of side-effects when given with bupropion	100	100	65	65	65	100	82	
	Increased risk of CNS toxicity when given with memantine (manufacturer of memantine advises avoid concomitant use)	100	65	65	65	30	65	65	
	Increased risk of extrapyramidal side-effects when given with methyldopa, metoclopramide, tetrabenazine, antipsychotics, domperidone	100	65	30	65	30	65	59	

Table 4.19 Scores for 'Interactions' (continued)

Drug	Interaction seriousness: MS/VS/FS/NS	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5	Respondent 6	Mean	Overall mean
Entacapone	Possibly enhances effects of: adrenaline, apomorphine, dobutamine, dopamine, methyldopa, noradrenaline	100	100	65	65	65	65	77	78
	Manufacturer advises caution with: tricyclics, moclobemide, paroxetine, venlafaxine	100	65	65	65	100	100	82	
	Absorption of entacapone reduced by oral iron	100	65	100	100	100	100	94	
	Avoid use with non-selective MAOIs	100	65	65	65	65	65	71	
	Possibly reduces plasma concentration of rasagiline	100	100	100	100	100	100	100	
	Enhances anticoagulant effect of warfarin	65	65	30	30	30	65	47	
Tolcapone	Avoid MAOIs	100	100	30	65	100	Not completed	79	79

Table 4.20 Contraindications for all the drugs

Drug	Contraindications
Co-beneldopa	Breast-feeding
Co-careldopa	Breast-feeding
Stalevo	Breast-feeding; pregnancy; hepatic impairment; phaeochromocytoma; history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis
Duodopa	Breast-feeding,
Ropinirole	Breast-feeding; pregnancy
Pramipexole	Breast-feeding
Rotigotine	Breast-feeding; pregnancy; remove patch before MRI or cardioversion
Pergolide	History of fibrotic disorders; cardiac valve disease
Bromocriptine	Shouldn't be used in patients with a hypersensitivity to ergot alkaloids; avoid in pre-eclampsia
Cabergoline	Shouldn't be used in patients with a hypersensitivity to ergot alkaloids; avoid in pre-eclampsia; history of pulmonary, pericardial or retroperitoneal fibrotic disorders; cardiac valvulopathy
Apomorphine	Respiratory depression; hypersensitivity to opiods; not suitable if 'on' response to levodopa marred by severe dyskinesia, hypotonia or psychiatric effects; hepatic impairment; breast-feeding; not for IV administration
Selegiline	Pregnancy; breast-feeding
Rasagiline	None
Amantadine	Epilepsy; history of gastric ulceration; pregnancy; breast-feeding
Entacapone	Pregnancy; breast-feeding; hepatic impairment; phaeochromocytoma; history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis
Tolcapone	Hepatic impairment or raised liver enzymes; severe dyskinesia; phaeochromocytoma; previous history of neuroleptic malignant syndrome, rhabdomyolysis or hyperthermia; breast-feeding

Table 4.21 Cautions for all the drugs

Drug	Caution
Co-beneldopa	Severe cardiovascular or pulmonary disease, psychiatric illness (avoid if severe), endocrine disorders (including hyperthyroidism, Cushing's syndrome, diabetes mellitus, osteomalacia, and phaeochromocytoma), history of convulsions, malignant melanoma, or peptic ulcer. Use with caution in open-angle glaucoma and patients susceptible to angle-closure glaucoma, and in hepatic or renal impairment. Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis), be aware of the potential for excessive drowsiness and sudden onset of sleep. Use with caution in pregnancy
Co-careldopa	Severe cardiovascular or pulmonary disease, psychiatric illness (avoid if severe), endocrine disorders (including hyperthyroidism, Cushing's syndrome, diabetes mellitus, osteomalacia, and phaeochromocytoma), history of convulsions, malignant melanoma, or peptic ulcer. Use with caution in open-angle glaucoma and patients susceptible to angle-closure glaucoma, and in hepatic or renal impairment. Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis), be aware of the potential for excessive drowsiness and sudden onset of sleep. Use with caution in pregnancy
Stalevo	Severe cardiovascular or pulmonary disease, psychiatric illness (avoid if severe), endocrine disorders (including hyperthyroidism, Cushing's syndrome, diabetes mellitus, osteomalacia, and phaeochromocytoma), history of convulsions, malignant melanoma, or peptic ulcer. Use with caution in open-angle glaucoma and patients susceptible to angle-closure glaucoma, and in hepatic or renal impairment. Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis), be aware of the potential for excessive drowsiness and sudden onset of sleep. Use with caution in pregnancy
Duodopa	Severe cardiovascular or pulmonary disease, psychiatric illness (avoid if severe), endocrine disorders (including hyperthyroidism, Cushing's syndrome, diabetes mellitus, osteomalacia, and phaeochromocytoma), history of convulsions, malignant melanoma, or peptic ulcer. Use with caution in open-angle glaucoma and patients susceptible to angle-closure glaucoma, and in hepatic or renal impairment. Avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis), be aware of the potential for excessive drowsiness and sudden onset of sleep. Use with caution in pregnancy
Ropinirole	Severe cardiovascular disease, major psychotic disorders; hepatic impairment; renal impairment. Associated with more neuropsychiatric side-effects than levodopa. Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep. Hypotensive reactions can occur in some patients taking

	dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery. Doses of dopamine receptor agonists should be increased slowly according to response and tolerability. Treatment with dopamine receptor agonists should not be withdrawn abruptly.
Pramipexole	Psychotic disorders; ophthalmological testing recommended (risk of visual disorders); severe cardiovascular disease; renal impairment, pregnancy. Associated with more neuropsychiatric side-effects than levodopa. Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep. Hypotensive reactions can occur in some patients taking dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery. Doses of dopamine receptor agonists should be increased slowly according to response and tolerability. Treatment with dopamine receptor agonists should not be withdrawn abruptly.
Rotigotine	Ophthalmic testing recommended; avoid exposure of patch to heat; hepatic impairment. Associated with more neuropsychiatric side-effects than levodopa. Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep. Hypotensive reactions can occur in some patients taking dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery. Doses of dopamine receptor agonists should be increased slowly according to response and tolerability. Treatment with dopamine receptor agonists should not be withdrawn abruptly.
Pergolide	Associated with more neuropsychiatric side-effects than levodopa. Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep. Hypotensive reactions can occur in some patients taking dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery. Doses of dopamine receptor agonists should be increased slowly according to response and tolerability. Treatment with dopamine receptor agonists should not be withdrawn abruptly. Ergot-derived dopamine receptor agonists have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Before starting treatment with these ergot derivatives it may be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Arrhythmias or underlying cardiac disease; history of confusion, psychosis, or hallucinations, dyskinesia (may exacerbate); porphyria; pregnancy; breast-feeding
Bromocriptine	Associated with more neuropsychiatric side-effects than levodopa.

	Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep. Hypotensive reactions can occur in some patients taking dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery. Doses of dopamine receptor agonists should be increased slowly according to response and tolerability. Treatment with dopamine receptor agonists should not be withdrawn abruptly. Ergot-derived dopamine receptor agonists have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Before starting treatment with ergot derivatives it may be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. specialist evaluation—monitor for pituitary enlargement, particularly during pregnancy; monitor visual field to detect secondary field loss in macroprolactinoma; contraceptive advice if appropriate (oral contraceptives may increase prolactin concentration); avoid breast-feeding for about 5 days if lactation prevention fails; hepatic impairment
Cabergoline	Ergot-derived dopamine receptor agonists have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Before starting treatment with these ergot derivatives it may be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Associated with more neuro-psychiatric side-effects than levodopa. Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep. Hypotensive reactions can occur in some patients taking dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery. Doses of dopamine receptor agonists should be increased slowly according to response and tolerability. Treatment with dopamine receptor agonists should not be withdrawn abruptly. Severe hepatic impairment; monthly pregnancy tests during the amenorrhoeic period; advise non-hormonal contraception if pregnancy not desired
Apomorphine	Associated with more neuropsychiatric side-effects than levodopa. Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep. Hypotensive reactions can occur in some patients taking dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery. Doses of dopamine receptor agonists should be increased slowly according to response and tolerability. Treatment with dopamine receptor agonists should not be withdrawn abruptly. Pulmonary or

	cardiovascular disease, history of postural hypotension (special care on initiation); neuropsychiatric problems or dementia; hepatic, haemopoietic, renal, and cardiovascular monitoring; *on administration with levodopa* test initially and every 6 months for haemolytic anaemia (development calls for specialist haematological care with dose reduction and possible discontinuation); renal impairment; pregnancy
Selegiline	avoid abrupt withdrawal; gastric and duodenal ulceration (avoid in active ulceration), uncontrolled hypertension, arrhythmias, angina, psychosis, side-effects of levodopa may be increased, concurrent levodopa dosage can be reduced by 10–20%
Rasagiline	avoid abrupt withdrawal; hepatic impairment; pregnancy, breast-feeding
Amantadine	hepatic impairment; renal impairment (avoid if creatinine clearance less than 15mL/minute); congestive heart disease (may exacerbate oedema), confused or hallucinatory states, elderly; avoid abrupt withdrawal in Parkinson's disease
Entacapone	avoid abrupt withdrawal; concurrent levodopa dose may need to be reduced by about 10–30%
Tolcapone	Avoid abrupt withdrawal; most patients receiving more than 600mg levodopa daily require reduction of levodopa dose by about 30%; renal impairment; pregnancy. Potentially life-threatening hepatotoxicity including fulminant hepatitis reported rarely, usually in females and during the first 6 months, but late-onset liver injury has also been reported; test liver function before treatment, and monitor every 2 weeks for first year, every 4 weeks for next 6 months and every 8 weeks thereafter (restart monitoring schedule if dose increased); discontinue if abnormal liver function tests or symptoms of liver disorder (counselling, see below); do not re-introduce tolcapone once discontinued. Counselling: Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop

Table 4.22 Total scores for all the criteria

Drug name	Motor flucs	Cog impair	Confusion	Hallucns	Dyskinesia	Depression	Post Hypot	ADL	Stage disease	ADR	Interact	Total	Mean
Co-beneldopa	10	10	10	10	3	7	45	50	50	43	67	238	28
Co-careldopa	10	50	50	10	7	7	50	52	50	59	67	345	37
Stalevo	15	50	10	10	16	10	50	60	50	73	72	344	38
Duodopa	100	10	10	10	35	10	50	80	50	68	67	423	44
Ropinirole	10	50	7	7	13	5	47	52	50	46	79	287	33
Pramipexole	10	50	10	7	10	65	50	60	50	73	81	385	42
Rotigotine	13	50	50	10	7	50	50	63	50	63	58	406	42
Pergolide	57	50	10	10	75	60	47	60	50	10	58	429	44
Bromocriptine	25	50	10	15	15	10	50	60	50	10	61	295	32
Cabergoline	42	50	15	12	27	10	45	80	50	10	72	341	37
Apomorphine	90	50	10	10	11	50	60	50	50	76	72	457	48
Selegiline	17	50	10	10	7	50	55	50	50	68	68	367	39
Rasagiline	10	50	50	10	60	32	50	52	52	74	69	440	46
Amantadine	5	50	50	7	65	7	45	60	50	63	68	402	43
Entacapone	7	50	10	9	6	8	47	53	50	66	78	306	35
Tolcapone	27	50	10	7	3	50	50	50	50	64	79	361	40

possible weighting. As mentioned in the methodology, the model was designed for the users to be able to choose the weights themselves between 0 and 10, so only the phrasing of the weights was developed here. An example of the phrasing of the weights is shown for 'motor fluctuations' below:

> 'The drugs cause from 'no improvement in motor fluctuations' to 'a big improvement in motor fluctuations'.'

This was calculated from the lowest score for 'motor fluctuations' for all the drugs being five (i.e. virtually zero improvement) to the highest score obtained being 100 (i.e. the highest improvement). Table 4.23 shows the weight definitions.

Combining the scores and weights

It was not possible to combine the scores and weights at this stage to calculate overall values as the model was designed for the users to choose the weights themselves, as mentioned above. The advantage of the user choosing the weights though is that the patient can be fully involved in the decision-making process. The practitioner and patient choosing the weights together means that they would be involved in shared decision-making. This is one way of ensuring that the patient's voice is heard when the relevant choices are made (Whitney, 2003).

DISCUSSION

The aim of this chapter was to develop a model to choose the most effective drug treatment for Parkinson's disease, based on criteria developed in the previous chapter. This was achieved through the process of MCDA, by scoring the options and developing a system to enable the user to weight the criteria so that the scores and weights can then be combined to establish the overall values. A model for drug treatment choice has thus been developed for Parkinson's disease for the first time. It is also the first time that MCDA has been used for such a complicated disorder in medicine.

Table 4.23 Weight definitions

Criterion	Lowest score	Highest score	Weight
Motor fluctuations	5	100	From 'no improvement in motor fluctuations' to 'a big improvement in motor fluctuations'
Cognitive impairment	10	50	From 'cognitive impairment being a common occurrence' to 'no incidence of cognitive impairment'
Confusion	7	50	From 'a high incidence of confusion' to 'neither improving nor worsening confusion'
Hallucinations	7	15	From 'a high incidence of hallucinations' to 'a fairly common occurrence of hallucinations'
Dyskinesia	3	75	From 'a high incidence of dyskinesia' to 'a medium improvement of dyskinesia'
Depression	5	65	From 'a high incidence of depression' to 'a small improvement on depression'
Postural hypotension	9	20	From 'a common occurrence of postural hypotension' to 'a less common occurrence of postural hypotension'
Activities of daily living	50	80	'Neither improve nor worsen the stage of disease'
Stage of disease	50	50	From ' neither worsening nor improving ability to carry out ADL' to 'a large improvement in ability to carry out ADL'

A number of problems were encountered in scoring the options. Firstly, in obtaining data to establish the scores. Some drugs, such as Madopar and Sinemet, were very difficult to obtain any data on at all, mainly due to the age of them as they had been developed perhaps 30 or 40 years ago and therefore the original trial data was not easily obtainable any more. For the most recent drugs, such as duodopa, trial data was readily available and easily obtained. This, however, meant that there was a lack of consistency in the data obtained on the drugs. For the older drugs and also some other drugs, where there was a lack of data in the trials pertinent to the criteria required, it was necessary to obtain data by searching for relevant literature. Another problem with the trial data was the lack of uniformity in the data. For

example, in assessing the data on the criterion 'activities of daily living' it became clear that different trials used different assessment scales, typically either the UPDRS II or the Schwab and England scale. Although both these scales assess the same thing, that is the extent to which the patient's activities of living are affected by the disease, it is not possible to directly compare the results because the scales produce different results. Therefore, the solution had to be to solely use one scale, which in this case was the UPDRS as it was the most commonly used. This though meant that data was excluded and therefore the picture obtained of the drugs' performance was not as complete as it could have been.

This suggests that if clinical trial data is to be meaningfully compared it would be useful if drug companies had an established protocol for uniformity in all their trials. Although at the time older trials were carried out many of the assessment tools commonly used in current trials were not available, for more recent trials there are still discrepancies in the assessments used, despite all the tools being widely available. In recent trials, for example, it was interesting to note that the same assessment scales were not necessarily used nor indeed even that the same criteria were assessed. It would be interesting to ascertain why, for example, some trials did not assess cognitive impairment when there is a readily available tool, the MMSE, available for such a purpose. This is particularly pertinent in the case of anti-parkinsonian drugs as not only is cognitive impairment a problem for the main age group of Parkinson's patients, i.e. the over 65s, but also that the condition can be both brought on and aggravated by Parkinson's disease. Therefore, one would have to question why drug companies had not assessed such an important condition in their trials.

There were varying results from the scores of the individual criteria. 'Motor fluctuations' showed a wide variation in scores, with the mean being quite low. With only three drugs being shown to benefit the user for 'motor fluctuations' one can see a lack of choice available for prescribers for patients with this often debilitating symptom. One of these drugs, Duodopa, is particularly

expensive to prescribe, and another, pergolide, has some serious side-effects, meaning that options could be even more limited for prescribers.

The main conclusion one can draw about 'cognitive impairment' is that a lack of trial data gives no answers for prescribers. Two drugs were shown to have a negative effect, but prescribers would have no information to go on when making an informed choice for the other drugs.

A lack of data was also a problem for 'confusion', with several drugs having no data available. The majority of the drugs were shown to cause confusion, but as there was no data on the other drugs, prescribers would only have a choice of prescribing a drug that was known to cause confusion or one for which the effect was not known. Again, this shows an area that more researchers need to look at in clinical trials.

'Hallucinations' proved to be a problem for all the drugs, being a side-effect of all of them. This could perhaps be an area that needs looking at for future drug development, as an obvious niche exists for a drug that does not cause this side-effect.

There was a wide variation in the scores for 'dyskinesias', ranging almost from one end of the scale to the other. Only three drugs were shown to improve this symptom, and two of those only showed a small improvement.

'Depression' was another criterion that the drugs seemed to show little benefit for, with only two drugs exhibiting any improvement. Depression has been shown to be a major problem among Parkinson's patients and these results show there are little alternatives available for practitioners wishing to reduce the condition among their patients.

'Postural hypotension' was also a poorly scoring criterion, with all the drugs causing the condition as a side-effect, although this may be considered a less serious condition than some of the other criteria.

'Activities of daily living' on the other hand was the highest scoring criterion, with drugs at worst having a neutral effect, but many of the drugs showing a benefit for patients. This showed an encouraging aspect of the drug treatments.

There was a real lack of data for 'stage of disease', similarly to 'cognitive impairment'. Although this might be considered by the people running the trials to not be a particularly important aspect of the effects of the drug treatments in PD, it could be useful data if it were assessed more often. It would give a picture of the effect the drugs have on the patient's condition overall, with a clear comparison to be made if the patients have either reduced a stage or increased a stage by the end of their treatment period for example. The difficulty in scoring the ADRs was shown by the problems with the ergot dopamine agonists. It is unclear whether the seriousness of their potential cardiovascular side-effects is truly reflected in the 'penalty' score they were awarded for this criterion. They would otherwise have scored better than one might have imagined. Perhaps also surprising was the difference in the scores for the four levodopa drugs, which one might expect to score within a fairly close range.

The overall results from the scores showed some perhaps surprising results. Although one would perhaps expect drugs such as apomorphine and rasagiline to score well, one would not have expected the same for pergolide. This particular non-ergot dopamine agonist has generally been prescribed less in recent years due to the seriousness of the cardiovascular side-effects it can cause. The other non-ergot dopamine agonists bromocriptine and cabergoline did not fare quite so well with their scores, but still scored more highly than co-beneldopa, despite the fact that levodopa is still considered the 'gold standard' among anti-parkinsonian medications. It was also surprising that co-beneldopa scored so poorly, having the lowest overall score of all the drugs. As mentioned before, levodopa is the current 'gold standard', therefore one would expect all the levodopa drugs to score well.

Devising a means for the weights to be calculated was initially quite a difficulty. However, the resulting method of allowing the user to choose their own weights enabled a unique model to be developed for each user. The development of a generic 'one size fits all' model, with the weights pre-defined, would mean the model was not necessarily applicable to each individual patient. Developing the weights this way meant that the user, and by implication the patient, would be fully involved in the process and a unique model developed for each individual patient. Although the scores and weights could not be combined to form an overall result within the process of developing the model, the advantage of developing the weights in this way has meant that shared decision-making has become an integral part of the model. The aim of this is to give patients enough information about the treatments and their effects that they are able to make an informed choice(Schneider et al, 2008). This is particularly important for chronic long-term conditions such as Parkinson's disease where practitioners need to work closely with patients to choose the optimum pharmacological solution, which may take time, continuous monitoring and adjustment of medication type and level. The process works best where both practitioners and patients are involved in the management of medication regimens (Charles et al., 1997).

It should therefore be recognised that a model has been successfully developed for Parkinson's disease. This model must be considered as a prototype and as a proof of concept. Importantly, the model would aid clinicians to make drug treatment decisions using evidence-based medicine and could be particularly useful for inexperienced doctors and nurses with little experience of prescribing. It also incorporates shared decision-making and therefore includes what have been considered by some to be two of the most important aspects of medicine in recent years. The model will need to be validated by an expert panel and this will be examined in chapter seven. The model will also be implemented within a computerised decision support system in order for it to become an electronic decision aid and this will be discussed in the next chapter.

SUMMARY

In summary, in this chapter a model to choose the most effective drug treatment for Parkinson's disease was developed using the methodology of MCDA. The development of the model involved the following steps:

- Pivotal trials and other trial articles were examined to obtain data to score the options
- Scales were developed to define the least and most preferred points for each of the criteria, as well as the intermediary points
- The trial data was analysed to determine the scores for each drug
- Scores were developed for each of the drugs on each of the criteria
- The phrasing of the weights was developed
- The scores and weights could not be combined to form overall values as the users would be choosing the weights themselves

CHAPTER 5

Development of the Computer Decision Support System

INTRODUCTION

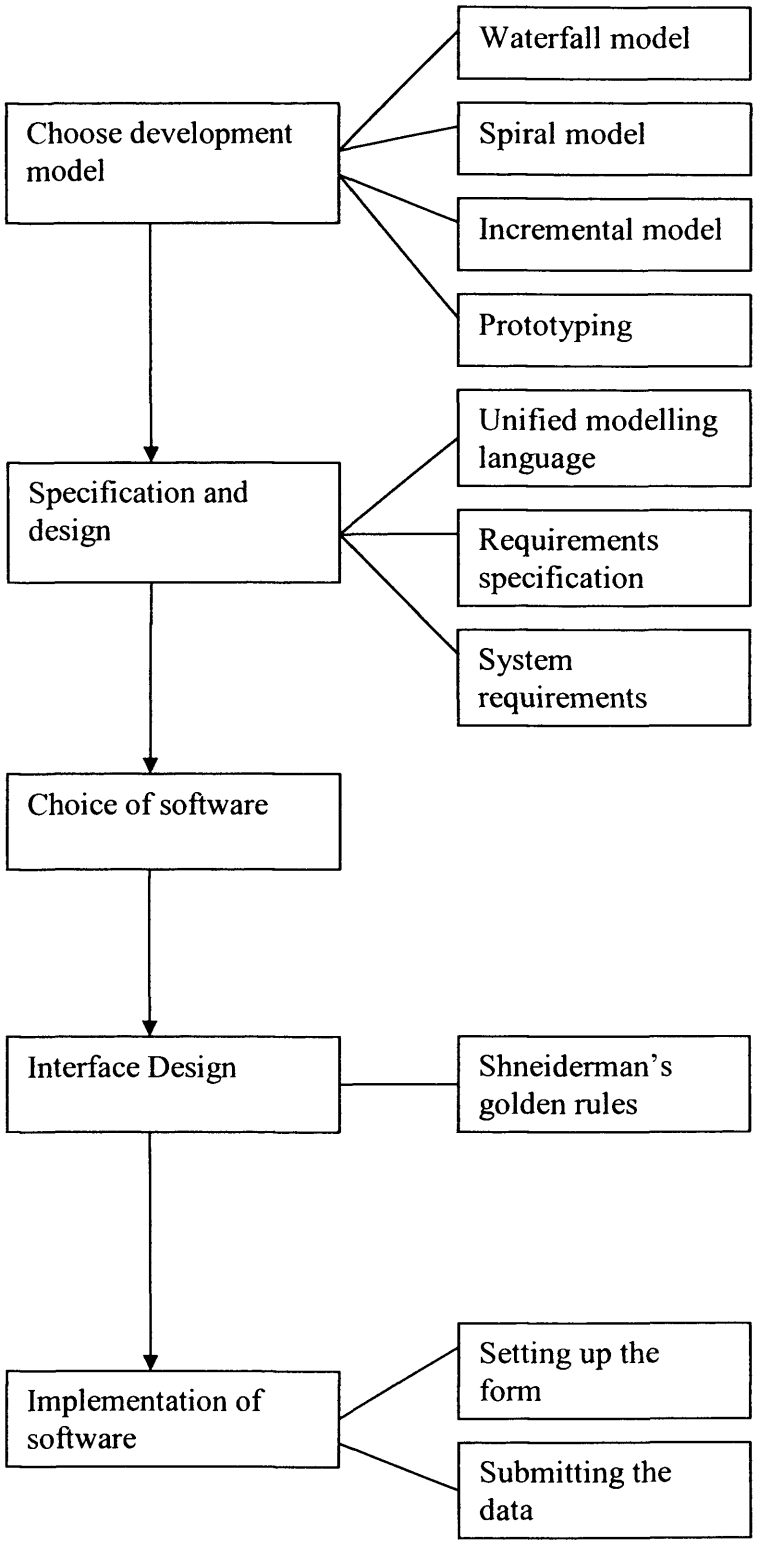
In chapter four the model was developed for Parkinson's disease using MCDA. In order to operationalise the model and carry out the mathematic calculations within the model it was deemed necessary to develop a software system. It was hoped that this system would enable the model to become an electronic prescribing decision aid.

The use of proprietary software developed for MCDA models was considered initially, but was considered to be unsuitable for the model developed here. Software was needed that would allow the user to enter information about the patient other than the criteria or weights, such as the patient's medication. Proprietary software, such as Hiview, would not provide this feature. Therefore, it was decided that it would be necessary to develop a bespoke piece of software to operationalise all the functions needed within the model. Deciding on all the issues involved with developing a new piece of software, such as choosing a suitable programming language can often be a difficult process. However, a methodology exists which gives a process to follow to ensure user requirements are established and met and that the software performs all the functions it is intended to. This process and the software developed will therefore be discussed in this chapter.

SOFTWARE DEVELOPMENT METHODS

A number of stages are involved in developing a new piece of software. Firstly, one chooses a software development model. The next stage is the specification and design, where Unified Modelling Language is used to model the requirements. The system requirements are also developed in this stage. The software or programming language is next chosen and the interface then designed. The final stage is the implementation of the software. These stages are represented diagrammatically in Figure 5.1. Each stage will now be described in detail.

Figure 5.1 Software development methods



Types of Software Development Models

The first stage when designing a new piece of software is to choose a development model. Several different kinds of development models exist and it is important to choose the right kind of model depending on the type of software that is being developed and the way that it will be used. The types of software development models consist of the four models listed below:

- Waterfall
- Incremental
- Spiral
- Prototyping

Waterfall model

This technique requires completion of one phase of the software development process before proceeding onto the next phase. The process of these phases is demonstrated graphically to resemble the downward flow of a waterfall (Sommerville, 2001), as shown in Figure 5.2. The model consists of five stages:

1. Requirements analysis and definition – the system's services, constraints and goals are established through consulting with the system's users. They are defined in detail and become the system specification.
2. System and software design – systems design separates the requirements for hardware and software systems. The overall system architecture is established. The software design process incorporates identification and description of the fundamental software system abstractions and their relationships.
3. Implementation and unit testing – the software design is realised as a set of program unit and each unit is tested to ensure it meets its specification.
4. Integration and system testing – the program units are integrated and tested together as a whole to ensure that the software requirements

have been met. The software system is then delivered to the customer.

5. Operation and maintenance – this is usually the longest life-cycle phase. The system is installed and put into operation. The maintenance phase includes correcting errors not previously discovered, improving the implementation of system units and enhancing the system as new requirements are uncovered.

Incremental model

The incremental model was developed as a means of reducing rework during the development process and also to give customers opportunities to delay decisions on their requirements until they had experience of using the system (Sommerville, 2001). It consists of three main stages:

1. Customers identify the services they want the system to provide. Several increments are defined, which each provide a subset of the system functionality. The highest priority services are the first to be delivered to customers.
2. The requirements for the first increment are next defined in detail and developed.
3. When each increment is completed and delivered the customers are able to put it straight into service. They can experiment with the system, allowing them to clarify requirements for later increments. Each new increment that is completed is integrated with existing increments (Sommerville, 2001). The graphic representation of an incremental model is shown in Figure 5.3.

Spiral model

For this model, as the name suggests, the software development process is represented as a spiral, with each loop in the spiral representing a phase of the process (Sommerville, 2001). There are four sections in each loop of the spiral:

1. Objective setting – objectives for each phase of the project are defined, constraints identified and a management plan drawn up.

Figure 5.2 Waterfall model (Sommerville, 2001)

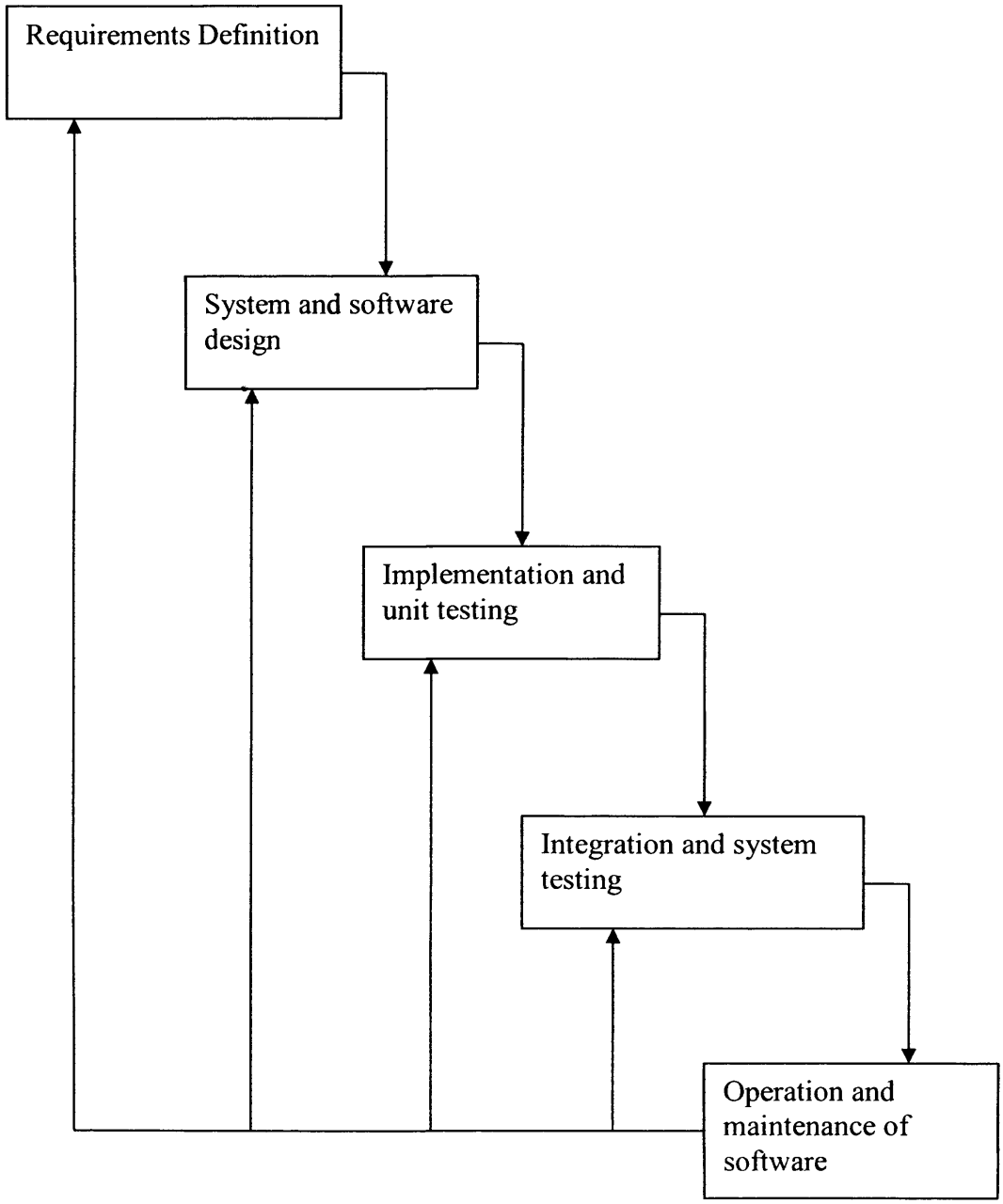
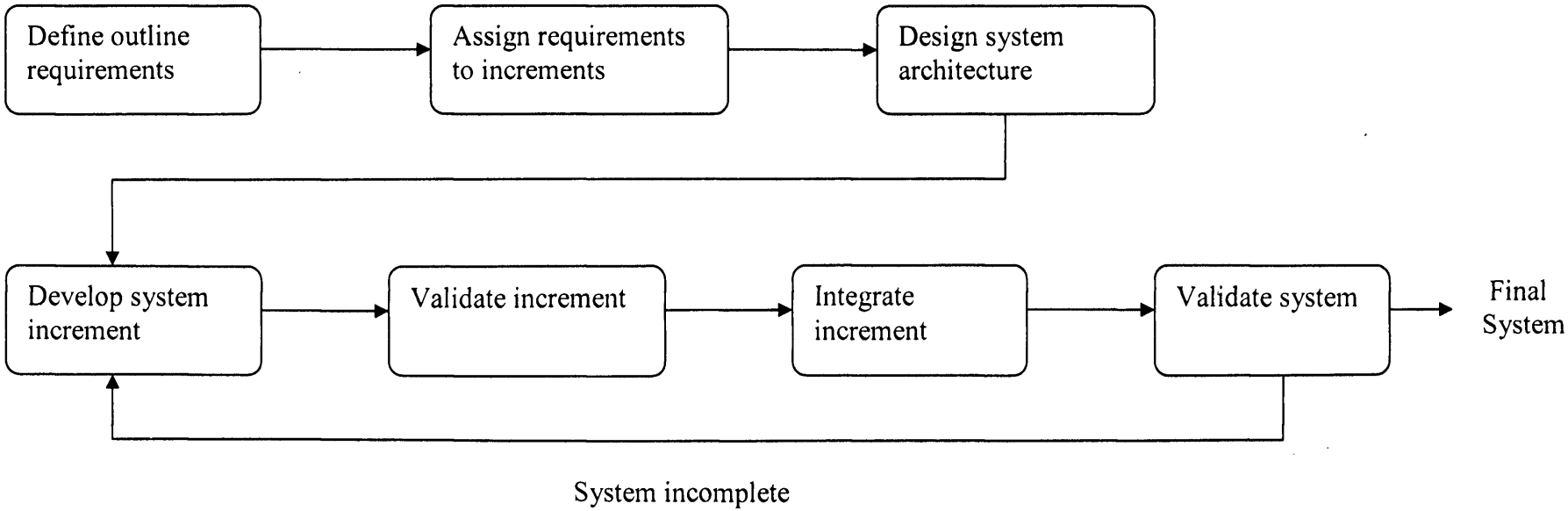


Figure 5.3 Incremental model (Sommerville, 2001)



3. Risk assessment and reduction – a detailed analysis is carried out for each risk identified in the project.
4. Development and validation – a development model for the system is chosen after the risks are evaluated. For example, if user interface risks are identified as the dominant ones an evolutionary prototyping model may be the most appropriate model.
5. Planning – the project is reviewed and decisions made whether to continue with another loop of the spiral.

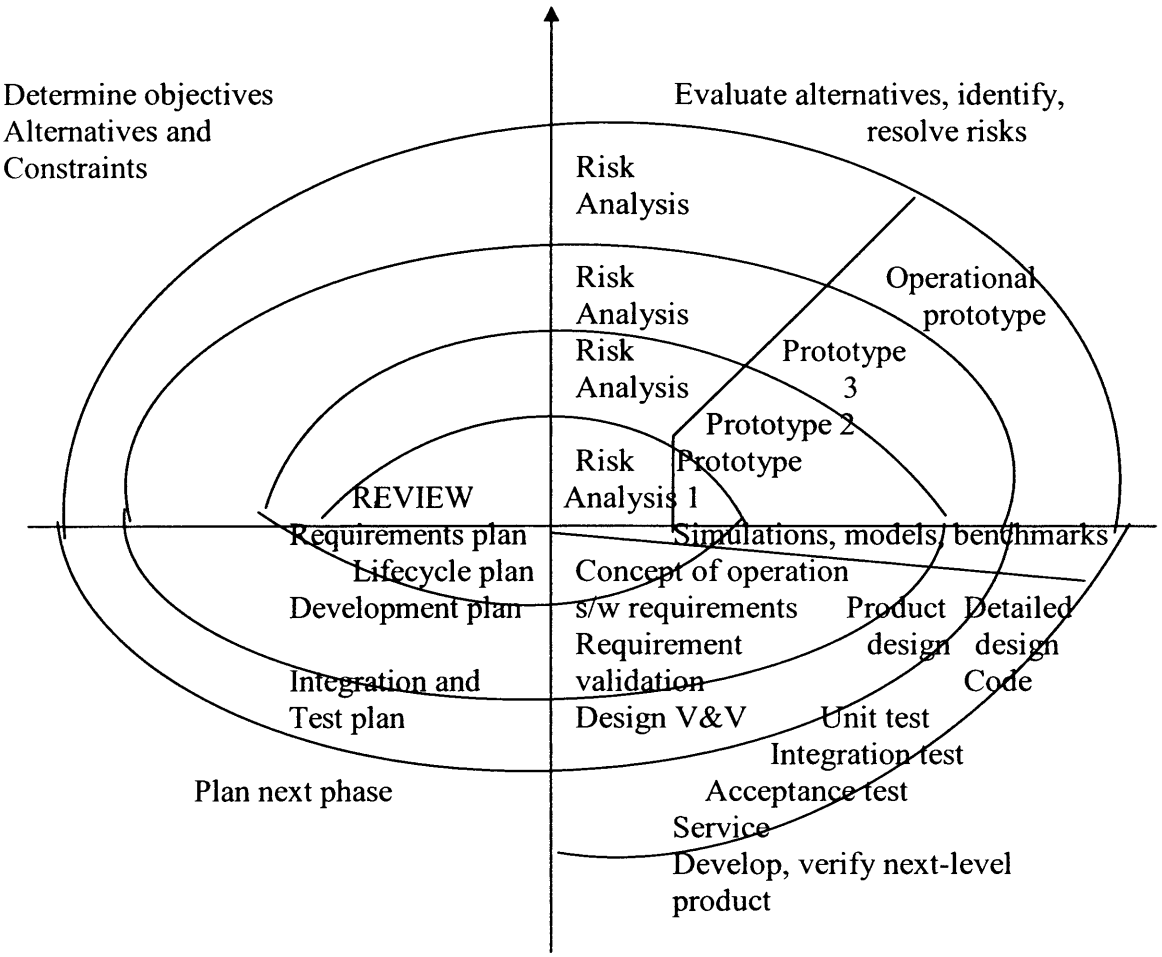
The spiral model is the only one to explicitly consider risks. The spiral model is demonstrated graphically in Figure 5.4.

Prototype model

Prototyping gives the client a working version of a system early on in the development lifecycle and the prototype is then amended until the client's requirements are fully met (Bell, 2000). Two types of prototyping exist; evolutionary and throwaway. Evolutionary prototyping involves the prototype becoming the final version after it has been transformed with new facilities or features added, according to the user's requirements. Throwaway prototyping, on the other hand, involves the system being implemented in a way which is distinct from the original version. A prototype model is demonstrated in Figure 5.5.

A prototype model was chosen for this particular software development, as it meant a system could be developed and refined according to what the user would be expecting to do with it. It would not be possible to consult with any users as to their requirements, but the software would be developed based on what the users' requirements were assumed to be. Using an evolutionary prototyping model would mean that the software could be continuously redeveloped until user requirements were completely met. This would allow for refinement and further development, but would also allow for a more or less finished product to be presented to users. The users would then be able

Figure 5.4 Spiral model (Sommerville, 2001)



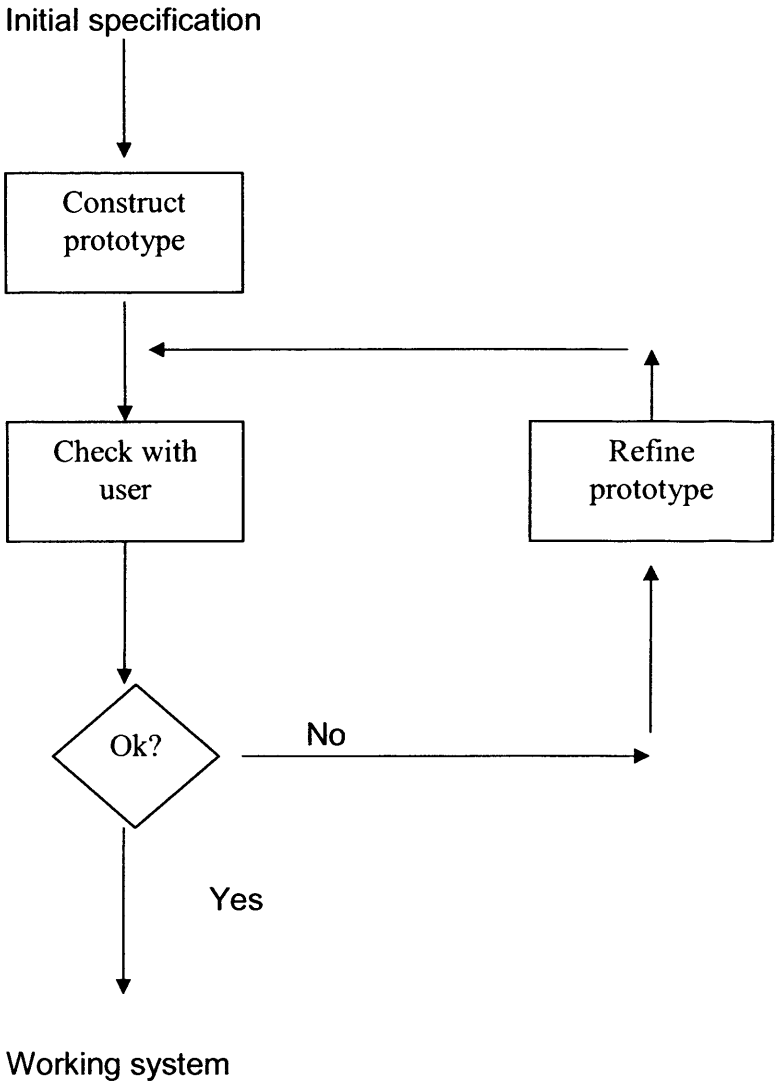
to see what the software was able to do and assess whether it suited their requirements.

SPECIFICATION AND DESIGN

Unified Modelling Language

The second stage in the software development process involves developing the requirements specification and system requirements. Unified Modelling System (UML) diagrams are used to illustrate the specification and design of the system. UML is not a way of designing a system, but of modelling a

Figure 5.5 Prototype model (Bell, 2000)



system. It can be broken down into two main aspects; structural diagrams and behavioural diagrams.

Structural diagrams

Structural diagrams include two types of diagram; class and implementation diagrams.

Class diagrams

This is used to represent the underlying pieces, or classes, of a system, their relationship to each other and which subsystem they belong to. They include

attributes and operations, as well as roles and associations. Object diagrams are similar except that they show objects that are instances of classes. Objects deal with individual unique things, whilst classes are more generic (Roff, 2003).

Implementation diagrams: component and deployment

Component diagrams illustrate how a system's components interact with each other and show the dependencies between source files and classes, along with the components they belong to. A deployment diagram models where the components will end up after they are installed on a system and how the systems interact.

Behavioural diagrams

These are used to show how a process flows between components, classes, users and the system. There are five different types, as detailed below.

Use Case diagrams

These contain use cases and actors and illustrate the relationship between the two sets. The use cases are joined by associations and linked to the actors to project the overall structure and availability in a system.

Activity diagrams

These are used to analyse the behaviour within more complex use cases and show their interaction. They can model business workflows during the design of use cases. They are usually used to represent more complicated business activities.

Sequence diagrams

These show the interaction between actors and objects and other objects. Messages are sent from actors to objects, between objects and from objects to actors to show how the flow of control progresses through the system. Sequence diagrams document how a use case is solved with the current system design. They can show every possible path through an interaction or show a single path through an interaction (Roff, 2003).

Collaboration diagrams

These help class diagrams progress to the next stage. They represent the interaction and relationship between objects created in earlier stages of the domain modelling process. Collaboration diagrams can also model messages between different objects.

Statechart diagrams

These diagrams model the behaviour of subsystems, the interaction with classes and the system interface and also realise use cases. They can help to visualise the flow of an application.

The functional requirements for the system will be illustrated by a Use Case Diagram. The system requirements will also be discussed and illustrated by an Activity Diagram to explain how the system functions.

Requirements Specification

The requirements of a system are the properties that the system should exhibit to meet particular needs. Requirements specification focuses on what is needed, rather than how it will be achieved. Requirements can be split into two distinct types: functional and non-functional. Functional requirements describe the system's services or functions, that is to say, what the system should do. Non-functional requirements, on the other hand, are the qualities of the system. These may relate to system properties such as reliability, response time and store occupancy. Failure to meet a non-functional requirement can make the whole system unusable. Therefore, they are often more critical than individual functional requirements (Sommerville, 2001).

Functional requirements

The functional requirements for this system are that it allows the user to do the following:

- User enters data about the patient
- User rates importance of criteria to doctor/patient
- User receives the recommended treatment

- User receives list of all the treatments with their overall result

Use Case diagrams

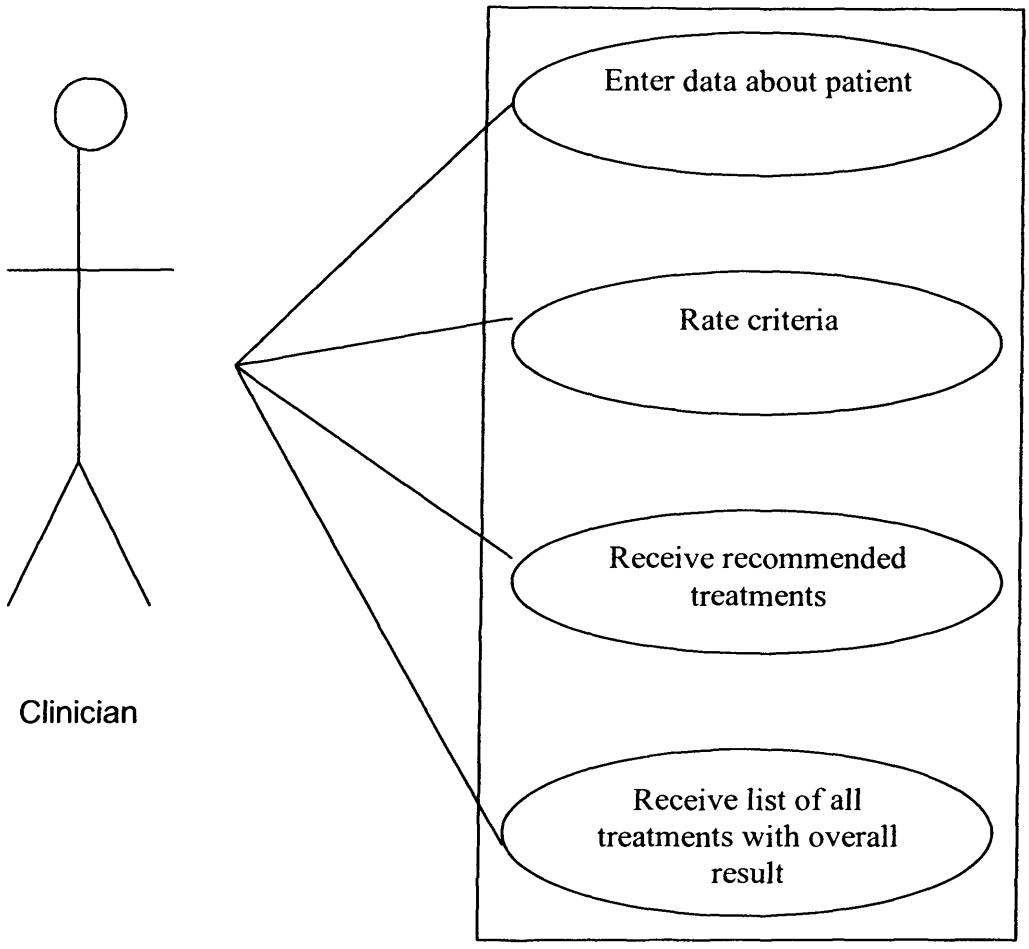
A Use Case Diagram shows how the system is intended to behave from the user's point of view and can be used in elicitation of the user's requirements. It is the highest form of details about a system and describes what the system does for the user, but not how it is done. The top level use case represents functionalities that the system provides for the user. This can then be further expanded into a lower level giving extra detail by means of the relationships 'includes', 'extends' and 'generalisation'. However, for this system a top level use case was considered sufficient to represent the functionalities of the system.

Use Case diagrams consist of four parts: the system, actors, use cases and relationships. A system is something that performs a function, eg a piece or multiple pieces of software. The system is generally not identified in a Use Case diagram and in this case there is only one overall system represented. The actors represent something or someone that uses the system, that is, either a person or another system. This is depicted by a stick figure with the user's name underneath. A use case is the action that a user makes by using the system. For example, a developer 'creates software'. This is represented by text in an oval for each use case and all the use cases displayed in a text box. Finally, the relationships are represented by a line connecting the actors to the use cases. This shows which actors relate to which use cases and vice versa. Actors can relate to multiple use cases and use cases to multiple actors (Roff, 2003). Figure 5.6 represents the Use Case diagram for the system.

System requirements

The system requirements demonstrate how the system will carry out the functional requirements that have been established.

Figure 5.6 Use Case Diagram



Activity diagrams

The behaviour of the system is demonstrated by use of an UML Activity Diagram. This type of UML diagram shows the procedural flow of control through the system as well as the dependencies between the activities. Activity diagrams allow the reader to see how the system executes and how it changes direction according to different conditions and stimuli. They also give an obvious start and end state (Roff, 2003).

Activity diagrams are represented by activities, states and transitions. Activities are actions that the system will carry out. These are depicted by rectangles with rounded corners. States, represented by rectangles with less

rounded corners than activities, use a word or phrase to indicate the current being of a system, such as 'stop'. There are two special states, 'start' and 'end'. The 'start' state is represented by a solid black circle and the 'end' state by a solid black circle with a white circle around it. Transitions show the control flow from one state to another and can show flow from a state to an activity, between activities and between states. They are depicted by an open arrow which points in the direction of the control flow. Figure 5.7 shows the Activity diagram for the CDSS.

Non-functional requirements

There were no non-functional requirements for this software development, as no specific users had been defined at this stage. Therefore, it was not possible to consider issues such as budget constraints, organisation policies or interoperability with other software systems and so on as none of these issues was applicable.

CHOICE OF SOFTWARE

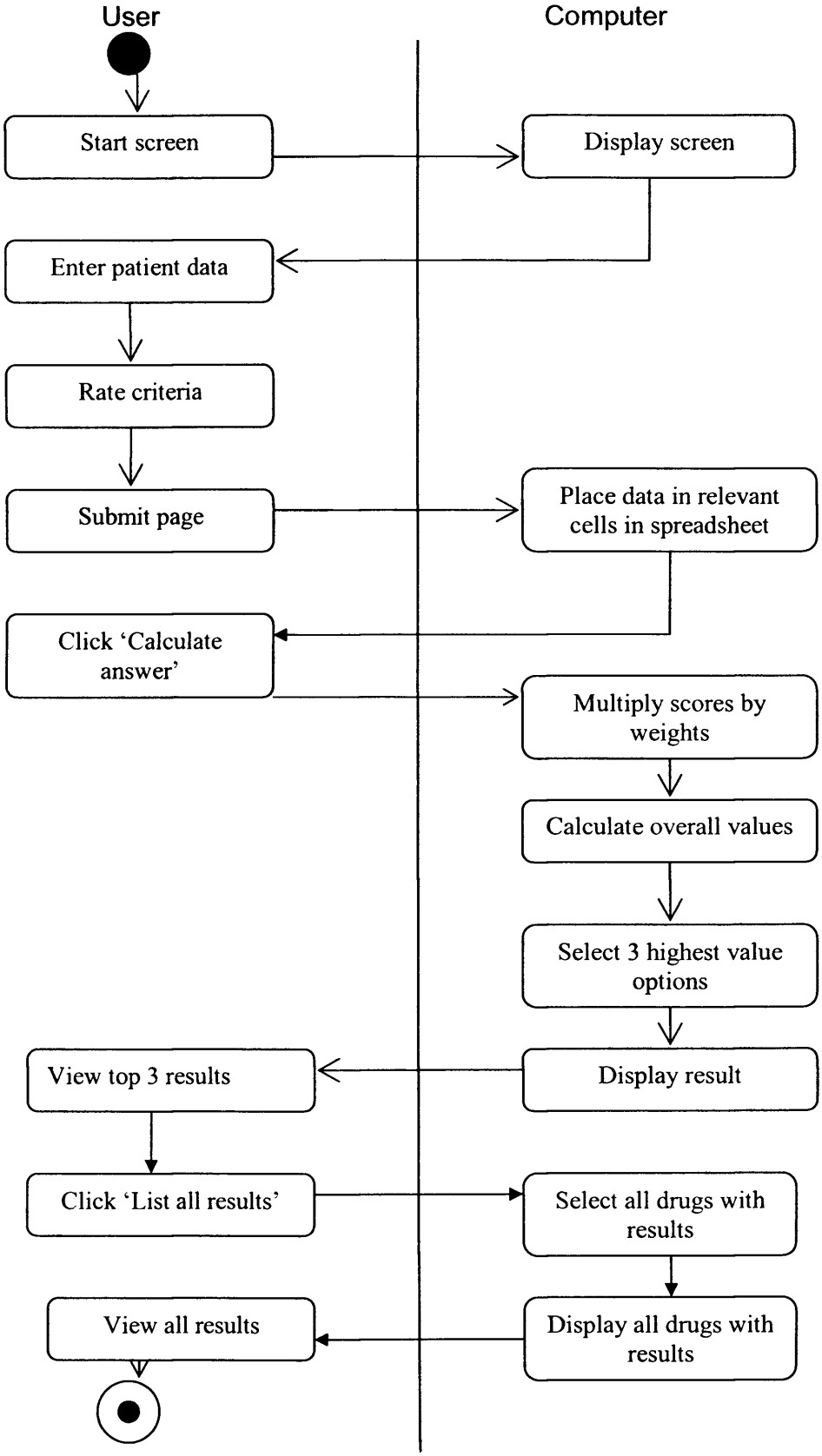
Excel

In order to develop the software for the decision support system, an Excel spreadsheet with Visual Basic for Applications (VBA) was chosen. Excel is an electronic spreadsheet program used for storing, organising or manipulating data (www.spreadsheets.about.com, 2008). The spreadsheet would provide the calculations and maths side of the Computer Decision Support System, whilst VBA would provide the user interface and data input side of the application. Excel is a widely available piece of software, which meant access would be easy for all users.

Visual Basic for Applications (VBA)

VBA is an embeddable programming environment which enables developers to build custom solutions (Microsoft, 2008). It allows the user to manipulate data in spreadsheets, whilst providing the user with a 'user-friendly' interface that avoids them seeing the calculations and manipulations being carried out by the spreadsheet. The coding for the software is detailed in Appendix II.

Figure 5.7 Activity diagram



INTERFACE DESIGN

Schneiderman's Golden Rules

A well designed interface is an important part of improving the usability of an application. Schneiderman's 'Eight Golden Rules of Interface Design' (http://faculty.washington.edu/jtenenbg/courses/360/f04/sessions/schneidermanGoldenRules.html, 2008) are a guide to good interface design. Schneiderman's collection of principles is derived heuristically from experience and is applicable in most interactive systems once it has been properly refined, extended, and interpreted. They consist of the following:

1. Strive for consistency – actions that are consistent in nature should be used in similar situations; with identical terminology used in prompts, menus and help screens and consistent commands used throughout.

2. Enable frequent users to use shortcuts – with increased frequency of use comes a user's desire to reduce the number of interactions and increase the pace of interaction. Functions such as abbreviations and command keys can be useful for an experienced user.

3. Offer informative feedback – there should be system feedback for every operator action. This could be a modest response for frequent or minor actions but a more substantial response for infrequent or major actions.

4. Design dialogue to yield closure – sequential actions should be designed in groups with a beginning, middle and end. Feedback at the completion of a group of actions gives the user the satisfaction of accomplishment and an indication that they are ready to prepare for the next group of actions.

5. Offer simple error handling – the system should be designed as much as possible so that the user cannot make a serious error. The system should detect any errors made and offer a mechanism for handling the error.

6. Permit easy reversal of actions – this enables users to know that errors can be undone and encourages them to explore unfamiliar options.

7. Support internal locus of control – experienced users need to know that they are in charge of the system and the system will respond to their actions. The system should be designed so that users are the initiators of actions not responders.

8. Reduce short-term memory load – displays should be kept simple, multiple pages consolidated, and window-motion frequency reduced due to the limitations of human information processing in short-term memory.

Application of the rules

Strive for consistency

A series of command buttons were used for the controls, and these were mainly added together at the bottom of the page. Only a small number of actions are needed from the user and these are consistent as far as they can be, as the user is either clicking a radio button, selecting from a list or entering a figure and clicking a 'submit' button where appropriate.

Enable frequent users to use shortcuts

The form is designed to be quick in use, so this is not really relevant for this application. A more lengthy and time-consuming application would necessitate shortcuts.

Offer informative feedback

Feedback is given to the user where necessary, for example a form displaying the results when they click 'calculate answer'. However, further feedback was not deemed appropriate as the user actions are so few and the form is so quick to use. Feedback for user errors, providing error message boxes where the incorrect type of data has been entered for example, will be looked at in chapter six where data validation is discussed.

Design dialogue to yield closure

The form was designed as a series of sequential actions, so the user is quickly through each stage and receiving the requested result.

Offer simple error handling

The system was designed to have little data input from the user so serious user errors would be extremely unlikely. However, as mentioned previously simple error handling, e.g. use of message boxes to give feedback to users, is discussed in chapter six under data validation.

Permit easy reversal of actions

A 'clear' button was added to the form so that users could clear all the data they had added if they had made a mistake.

Support internal locus of control

As this was a relatively small application this item was perhaps not so relevant for this development. The system did however allow users to proceed through the form on their own, only prompting where errors occur.

Reduce short-term memory load

The interface for the CDSS was designed to be simple and easy to use. Everything was put on one page so that the user did not have to move from page to page or to remember what was on one page when they were on another.

IMPLEMENTATION

A user form was developed for the user to enter data about the patient and select the weights. The data would then be submitted to Excel, where the calculations would be carried out and the results returned to the user.

Setting Up The Form

The form was to be divided into different sections for the user to complete. A label was therefore first of all added to the top of the form giving the user the

overall instruction for completing the form. Another label was then added underneath the first with the first question for the user asking them to answer the questions about the patient. A list box was next added to the form. The list box, which was named 'ListBoxPoorResp', was for users to select any Parkinson's disease drugs the patient had previously had a poor response to. A label alongside the text box displayed the statement 'Select any PD drugs the patient has previously had a poor response to'. This was set to null on initialisation of the form so that none of the options would be pre-selected. This was shown through the following code:

```
TxtName.Value = " ".
```

Data was added to the list box by means of the following code, which shows the example for the item 'not applicable':

```
.AddItem "Not applicable".
```

In section two of the form a label was added giving the instructions for completing the first section on the weightings. A frame was then added underneath with a series of nine option buttons. These provided a radio button for the user to tick by clicking on their mouse, where they chose the applicable criterion they wanted to give the highest weighting to. A frame was used here, because it contained all the options in one section and meant the user would only be able to select one option. If a frame had not been used, the user would have been able to have selected multiple options, rather than just the one that was required. Underneath this frame a label with the number '3' was added alongside a command button with the caption 'Submit section 2'.

Another label was added for section four, asking the user to complete the second section on the weightings. A second label was added underneath this one, giving an explanation of how to complete section four. Another frame was then added with the weighting labels alongside text boxes for the user to enter their figures for the weights. A frame was not necessary here to prevent

the user selecting more than one option, as in fact the user was required to complete all the boxes, but for design consistency with the weights section above it. As text boxes were added rather than option boxes the user was automatically able to add data into more than one box.

Command buttons were added for sections five 'Submit responses' and six 'Calculate answer' in the bottom left-hand corner of the form. A further two command buttons were added for 'List all responses' and 'Reset' next to these, whilst smaller command buttons were added in the bottom right-hand corner of the form for the commands 'Clear' and 'Close'. Finally, a command button titled 'Help' was added in the top right-hand corner of the form to provide a help facility for the user. The screenshot in figure 5.8 shows the full user form.

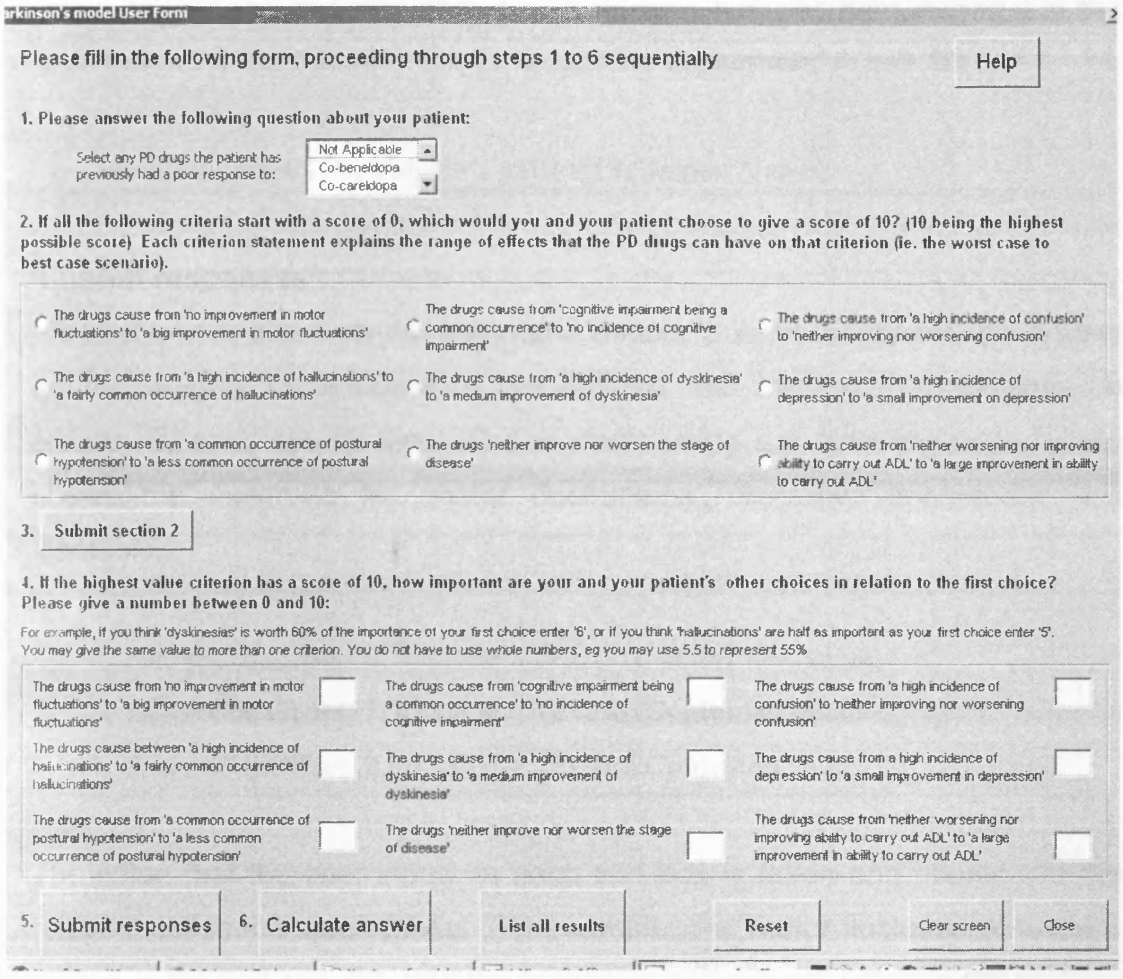
Submitting The Data

'Submit section two'

Once the user has clicked the command button 'Submit section 2', the criterion which has been chosen for a weight of 100 is entered into the relevant text box in section four. This was done by using the 'If Then Else' syntax and offsetting the selected value into the relevant text box, as the following code demonstrates for the options 'motor fluctuations' and 'cognitive impairment':

```
If OptMotorFlucs.Value = True Then
  ActiveCell.Value = 10
   TextBoxMotorFlucs.Value = 10
     Else If OptCogImpair.Value = True Then
       ActiveCell.Offset(1,0).Value = 10
         TextBoxCogImpair.Value = 10
```

Figure 5.8 Screenshot of the user form



Once section four is completed, when the user has selected the figures they want for the rest of the weights, the command button 'Submit responses' is clicked and the weights are submitted to an Excel spreadsheet. Initially, the cell 'A1' is selected as the active cell with the code:

```
Range("A1").Select
```

and the active cell offset by one row and one column to the cell 'B2', the cell for the weight of 'motor fluctuations':

```
ActiveCell.Offset(1, 1).Select.
```

The values for the rest of the weights were inserted below, offsetting the active cell by one row and zero columns each time, as demonstrated in the code below for the criterion weight 'cognitive impairment' in cell 'B3':

```
ActiveCell.Offset(1, 0).Value = TextBoxCogImpair.Value.
```

'Submit responses'

When the user clicks on the command button 'Submit responses' the figures for the weights in section four are entered into the Excel spreadsheet in column B, rows two to ten. This is done using the following code, which shows the examples for 'motor fluctuations', 'cognitive impairment' and 'confusion':

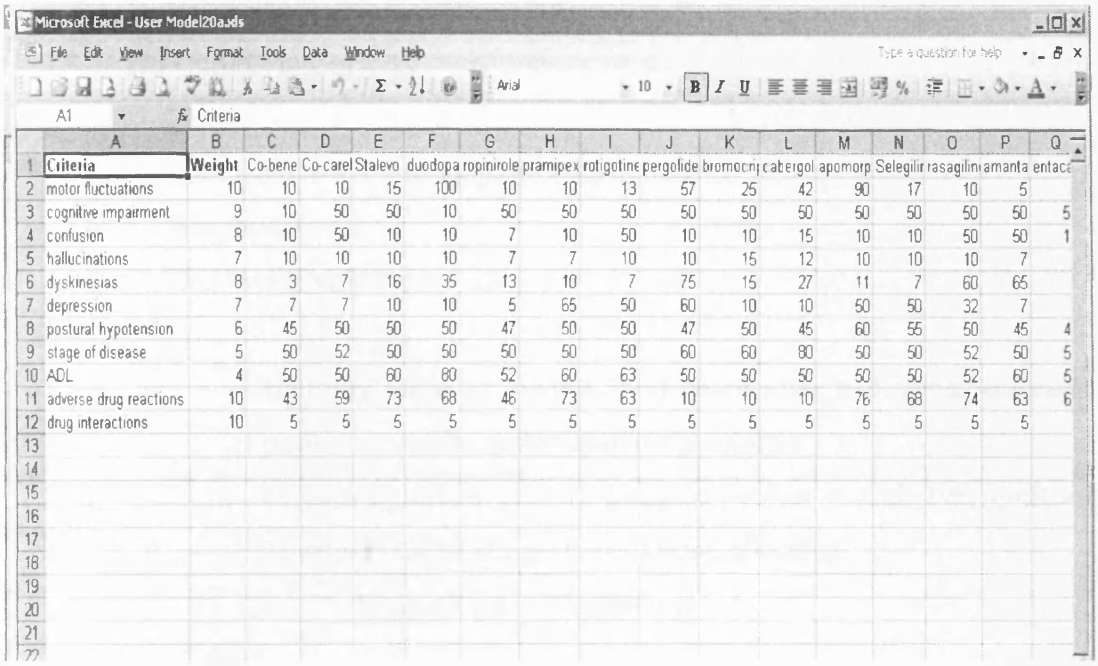
```
ActiveCell.Offset (0, 0).value = TextBoxMotorFlucs.value
ActiveCell.Offset (1, 0).value = TextBoxCogImpair.value
ActiveCell.Offset (2, 0).value = TextBoxConfusion.value.
```

The value that the user inputs in each text box is taken and copied into the relevant cell in the spreadsheet. For example, the 'motor fluctuations' value is placed in the first cell, B2, and the 'cognitive impairment' value in the cell one row underneath, C2.

'Calculate answer'

Once the weights have been placed in the spreadsheet, the calculations can be performed when the user clicks 'Calculate answer'. As discussed in chapter four, the scores and weights must be multiplied together and the results summed to find an overall value. These calculations are carried out by Excel according to the coding in VBA. This is carried out using nested loops. This involves one loop being implemented within another loop. For example, the outside loop starts from column C (column number three) and proceeds through to column R (column number 18). The loop stops when it gets to the column after the last one required:

Figure 5.9 Screenshot showing the weights added to column B, rows 2 to 10



Microsoft Excel - User Model20a.xls

File Edit View Insert Format Tools Data Window Help

A1 fx Criteria

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Criteria	Weight	Co-bene	Co-carel	Stalevo	duodopa	ropinirole	pramipex	rotigotine	pergolide	bromocry	cabergol	apomorp	Selegilir	rasagilin	amanta	entaca
2	motor fluctuations	10	10	10	15	100	10	10	13	57	25	42	90	17	10	5	
3	cognitive impairment	9	10	50	50	10	50	50	50	50	50	50	50	50	50	50	5
4	confusion	8	10	50	10	10	7	10	50	10	10	15	10	10	50	50	1
5	hallucinations	7	10	10	10	10	7	7	10	10	15	12	10	10	10	7	
6	dyskinesias	8	3	7	16	35	13	10	7	75	15	27	11	7	60	65	
7	depression	7	7	7	10	10	5	65	50	60	10	10	50	50	32	7	
8	postural hypotension	6	45	50	50	50	47	50	50	47	50	45	60	55	50	45	4
9	stage of disease	5	50	52	50	50	50	50	50	60	60	80	50	50	52	50	5
10	ADL	4	50	50	60	80	52	60	63	50	50	50	50	50	52	60	5
11	adverse drug reactions	10	43	59	73	68	46	73	63	10	10	10	76	68	74	63	6
12	drug interactions	10	5	5	5	5	5	5	5	5	5	5	5	5	5	5	
13																	
14																	
15																	
16																	
17																	
18																	
19																	
20																	
21																	

```
DrugCol = 3
Do Until DrugCol = 19
Loop.
```

The internal loop starts from row two of the weights column and loops down to row 12, again the loop stops at the row after the last required one:

```
WeightRow = 2
Do Until WeightRow = 13
Loop.
```

The scores and weights are then multiplied together, starting at column C, working down all the rows in that column then proceeding to each subsequent column until column R. The results for each column are posted two rows underneath the respective scores columns. The whole nested loop with calculations is represented in the following code, with comments explaining the code represented by sentences beginning with an apostrophe:

```
'start from column C and loop through to column R
  DrugCol = 3
  Do Until DrugCol = 19

    'start from row 2 and loop through to row 12
    WeightRow = 2
    Do Until WeightRow = 13

        'multiply score by weight, loop down rows and across columns,
        position results underneath each column
        Cells(WeightRow + 13, DrugCol).value = Cells(WeightRow,
        2).value * Cells(WeightRow, DrugCol).value
            WeightRow = WeightRow + 1
    Loop
    DrugCol = DrugCol + 1
Loop
```

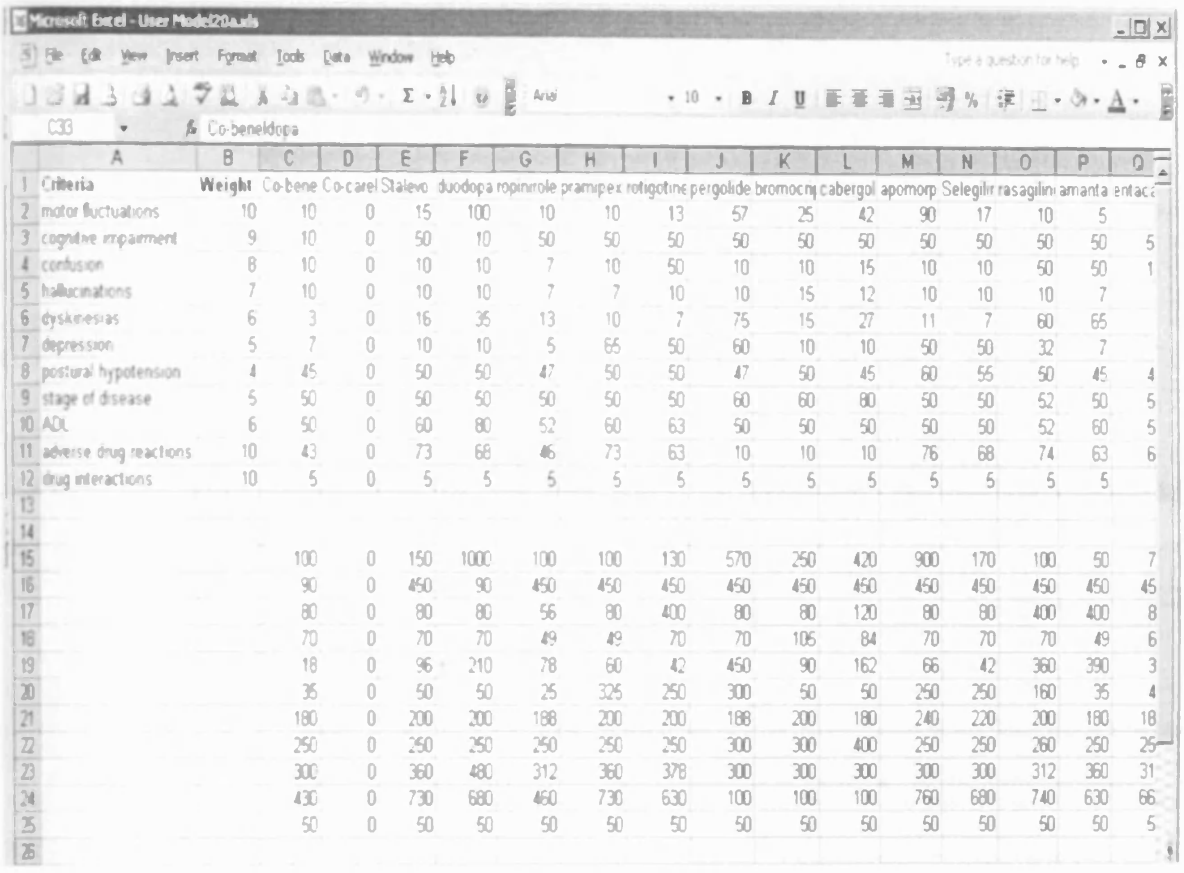
Figure 5.10 shows a screenshot of the results of the multiplication inserted underneath the scores columns.

The next step is for the multiplication results to be summed and the result entered three rows underneath the multiplication values. This is again carried out with a loop, working from column three onwards as shown by the code below:

```
'sum multiplication values - (no sum function)
'start from column C, loop through to column R
MultiCol = 3
Do Until MultiCol = 19

    'put result of addition 2 rows below scores
Cells(28, MultiCol).value = (Cells(15, MultiCol).value + Cells(16, MultiCol).value +
Cells(17, MultiCol).value + Cells(18, MultiCol).value + Cells(19, MultiCol).value +
Cells(20, MultiCol).value + Cells(21,
```

Figure 5.10 Screenshot showing the results of the multiplication



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Criteria	Weight	Co-bene	Co-carel	Stalevo	duodopa	ropinirole	pramipex	rotigotine	pergolide	bromocri	cabergol	apomorp	Selegilir	rasagilin	amanta	entaca
2	motor fluctuations	10	10	0	15	100	10	10	13	57	25	42	90	17	10	5	
3	cognitive impairment	9	10	0	50	10	50	50	50	50	50	50	50	50	50	50	5
4	confusion	8	10	0	10	10	7	10	50	10	10	15	10	10	50	50	1
5	hallucinations	7	10	0	10	10	7	7	10	10	15	12	10	10	10	7	
6	dyskinesias	6	3	0	16	35	13	10	7	75	15	27	11	7	60	65	
7	depression	5	7	0	10	10	5	65	50	60	10	10	50	50	32	7	
8	postural hypotension	4	45	0	50	50	47	50	50	47	50	45	60	55	50	45	4
9	stage of disease	5	50	0	50	50	50	50	50	60	60	80	50	50	52	50	5
10	ADL	6	50	0	60	80	52	60	63	50	50	50	50	50	52	60	5
11	adverse drug reactions	10	43	0	73	68	46	73	63	10	10	10	76	68	74	63	6
12	drug interactions	10	5	0	5	5	5	5	5	5	5	5	5	5	5	5	
13																	
14																	
15			100	0	150	1000	100	100	130	570	250	420	900	170	100	50	7
16			90	0	450	90	450	450	450	450	450	450	450	450	450	450	45
17			80	0	80	80	56	80	400	80	80	120	80	80	400	400	8
18			70	0	70	70	49	49	70	70	105	84	70	70	70	49	6
19			18	0	96	210	78	60	42	450	90	162	66	42	360	390	3
20			35	0	50	50	25	325	250	300	50	50	250	250	160	35	4
21			180	0	200	200	188	200	200	188	200	180	240	220	200	180	18
22			250	0	250	250	250	250	250	300	300	400	250	250	260	250	25
23			300	0	360	480	312	360	378	300	300	300	300	300	312	360	31
24			430	0	730	680	460	730	630	100	100	100	760	680	740	630	66
25			50	0	50	50	50	50	50	50	50	50	50	50	50	50	5
26																	

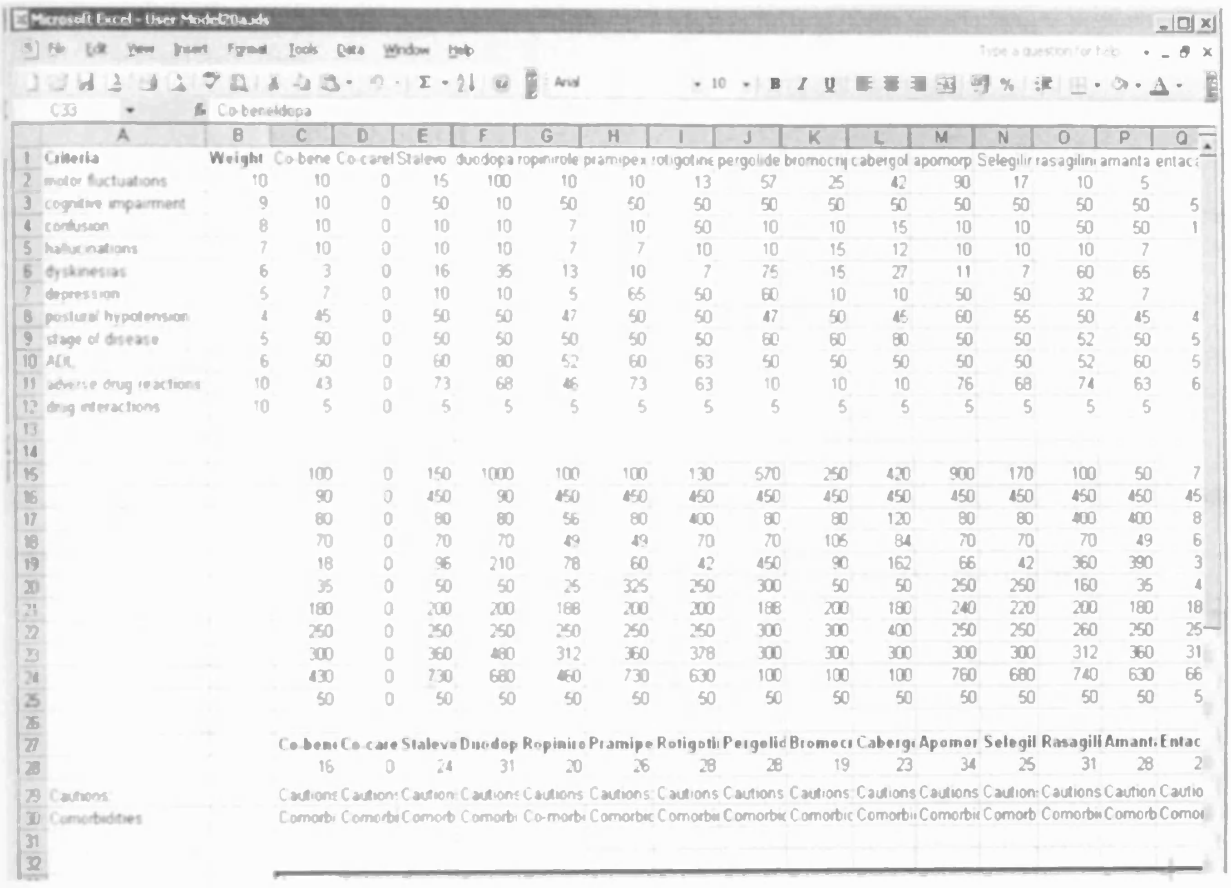
```
MultiCol).value + Cells(22, MultiCol).value + Cells(23, MultiCol).value +
Cells(24, MultiCol).value + Cells(25, MultiCol).value) \ 100

    MultiCol = MultiCol + 1
Loop
```

The drug names are already listed in a row below the multiplication results and the result of the sum are inserted in the row below this, as shown by the screenshot in Figure 5.11.

The final stage for 'Calculate answer' is to sort the results in ascending order so that the top three treatments can be returned to the user. First of all, the drug names, results and each drug's cautions and co-morbidities (which area already listed in the spreadsheet) are copied and pasted a few rows below:

Figure 5.11 Screenshot showing the results of the sum in row 28



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	Criteria	Weight	Co-bene	Co-carel	Stalevo	duodopa	ropinirole	pramipex	rotigotine	pergolide	bromocry	cabergol	apomorp	Selegilir	rasagilin	amanta	entac
2	motor fluctuations	10	10	0	15	100	10	10	13	57	25	42	90	17	10	5	
3	cognitive impairment	9	10	0	50	10	50	50	50	50	50	50	50	50	50	50	5
4	confusion	8	10	0	10	10	7	10	50	10	10	15	10	10	50	50	1
5	hallucinations	7	10	0	10	10	7	7	10	10	15	12	10	10	10	7	
6	dyskinesias	6	3	0	16	35	13	10	7	75	15	27	11	7	60	65	
7	depression	5	7	0	10	10	5	65	50	60	10	10	50	50	32	7	
8	postural hypotension	4	45	0	50	50	47	50	50	47	50	45	60	55	50	45	4
9	stage of disease	5	50	0	50	50	50	50	50	60	60	80	50	50	52	50	5
10	AER	6	50	0	60	80	52	60	63	50	50	50	50	50	52	60	5
11	adverse drug reactions	10	43	0	73	68	46	73	63	10	10	10	76	68	74	63	6
12	drug interactions	10	5	0	5	5	5	5	5	5	5	5	5	5	5	5	
13																	
14																	
15			100	0	150	1000	100	100	130	570	250	420	900	170	100	50	7
16			90	0	450	90	450	450	450	450	450	450	450	450	450	450	45
17			80	0	80	80	56	80	400	80	80	120	80	80	400	400	8
18			70	0	70	70	49	49	70	70	105	84	70	70	70	49	6
19			18	0	96	210	78	60	42	450	90	162	66	42	360	390	3
20			35	0	50	50	25	325	250	300	50	50	250	250	160	35	4
21			180	0	200	200	188	200	200	188	200	180	240	220	200	180	18
22			250	0	250	250	250	250	250	300	300	400	250	250	260	250	25
23			300	0	360	480	312	360	378	300	300	300	300	300	312	360	31
24			430	0	730	680	460	730	630	100	100	100	760	680	740	630	66
25			50	0	50	50	50	50	50	50	50	50	50	50	50	50	5
26																	
27			Co-bene	Co-care	Stalevo	Duodop	Ropinire	Pramipe	Rotigotii	Pergolid	Bromocı	Cabergo	Apomor	Selegil	Rasagili	Amant	Entac
28			16	0	24	31	20	26	28	28	19	23	34	25	31	28	2
29	Cautions		Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution	Caution
30	Comorbidities		Comorbi	Comorbi	Comorb	Comorbi	Co-morbi	Comorbi	Comorbi	Comorbi	Comorbi	Comorbi	Comorbi	Comorb	Comorbi	Comorb	Comor
31																	
32																	

'copy rows with names of drugs and results of multiplication and cautions and co-morbidities

```
Range("C27:R30").Select
Selection.Copy
```

'paste drug names into row 33, results to row 34, cautions to row 35 and co-morbidities to row 36

```
Range("C33:R36").Select
Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks
:=False, Transpose:=False
```

The results are then sorted in ascending order, along with the drug name, cautions and co-morbidities using the Excel 'sort':

'select drug names, results, cautions and co-morbidities and sort in ascending order

```
Range("C33:R36").Select
Selection.Sort Key1:=Range("C34"), Order1:=xlAscending, Header:=xlNo, _
    OrderCustom:=1, MatchCase:=False, Orientation:=xlLeftToRight, _
    DataOption1:=xlSortNormal
```

Finally, the results are returned to the user in a pop-up user form on screen, showing the top three recommended treatments and their respective cautions and co-morbidities:

```
'take top 3 results in columns R, Q and P and return their names in a message box
with their cautions and co-morbidities
'results 1, 2 and 3 return results for top drug with cautions and co-morbidities
SortResult1 = Cells(33, 18).value
SortResult2 = Cells(35, 18).value
SortResult3 = Cells(36, 18).value

'results 4, 5 and 6 return results for 2nd drug with cautions and co- morbidities
SortResult4 = Cells(33, 17).value
SortResult5 = Cells(35, 17).value
SortResult6 = Cells(36, 17).value

'results 7, 8 and 9 return results for 3rd drug with cautions and co-morbidities
SortResult7 = Cells(33, 16).value
SortResult8 = Cells(35, 16).value
SortResult9 = Cells(36, 16).value

'show results of sort in ResultsForm - top 3 recommended treatments
ResultsForm.TextBox1 = SortResult1 & vbCrLf & vbCrLf & SortResult2 &
vbCrLf & vbCrLf & SortResult3
ResultsForm.TextBox2 = SortResult4 & vbCrLf & vbCrLf & SortResult5 &
vbCrLf & vbCrLf & SortResult6
ResultsForm.TextBox3 = SortResult7 & vbCrLf & vbCrLf & SortResult8 &
vbCrLf & vbCrLf & SortResult9
ResultsForm.Show
```

The Excel results are demonstrated in Figure 5.12 and the user form results which the user sees in figure 5.13.

'List all results'

As well as viewing the top three results the user can see all the results by clicking the command button 'List all results'. This is coded in a similar way to 'Calculate answer'. The value of the drug name in row 33 is taken along with the value of the drug result in row 34 and these are displayed alongside each other in a message box. The message box lists all the drugs with their respective results in descending order. The code for the top scoring drug is shown below:

```
SortResult1 = Cells(33, 18).value
SortResult1Fig = Cells(34, 18).value
```

where 'SortResult1' is the name of the drug, and 'SortResult1Fig' is the associated result.

The code for the message box to display the results is as follows, which just shows the code for results one and two:

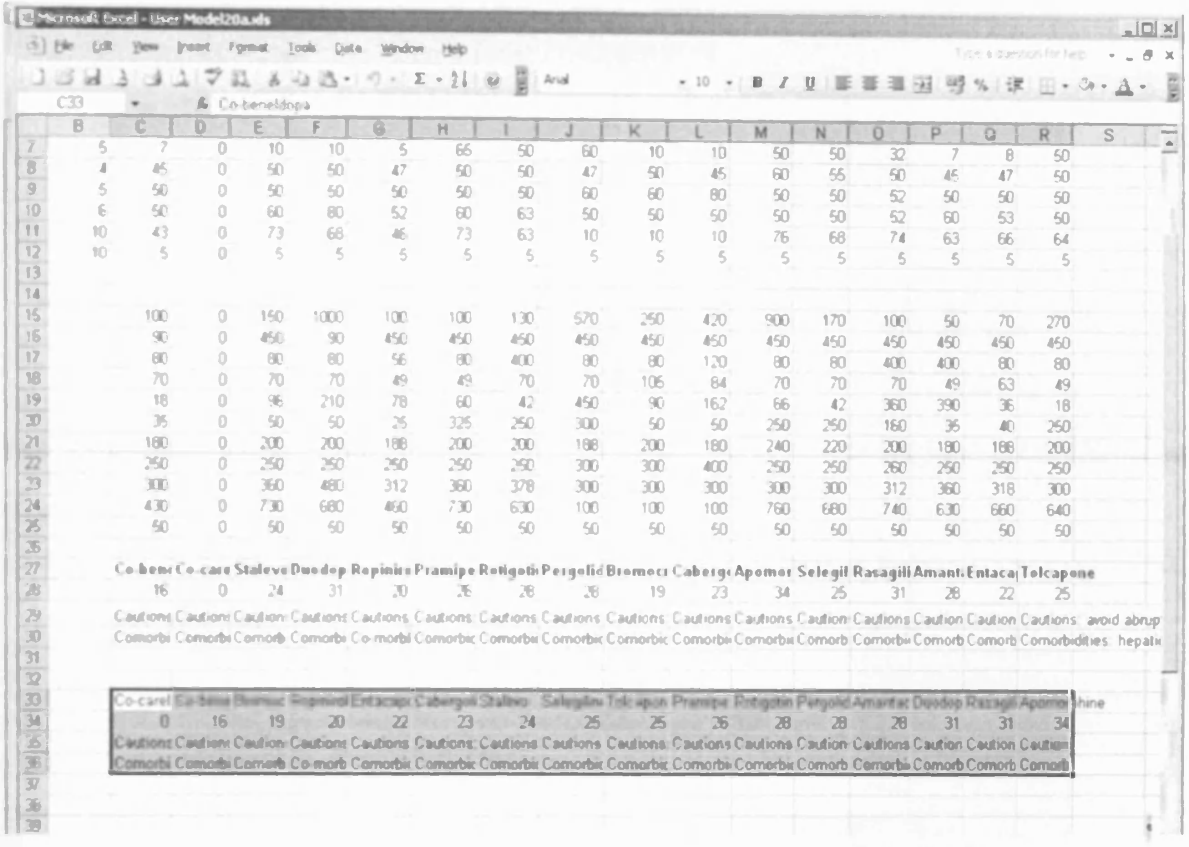
```
MsgBox "The results for all the drugs are as follows:" & vbCrLf & "1. " &
SortResult1 & " " & SortResult1Fig & vbCrLf & "2. " & SortResult4 & " " &
SortResult4Fig....."
```

Figure 5.14 shows the message box displayed on the user form.

'Reset' original values

Once the results have been displayed the original values of any drugs that were set to '0' for poor response need to have their original values reset. A list of all the drugs' values is stored at the bottom of the spreadsheet, in rows 41 to 51, and this was set to be copied and pasted back over the values in rows two to 12. This is shown in the following code:

Figure 5.12 Screenshot showing results sorted in ascending order, rows 33 to 36

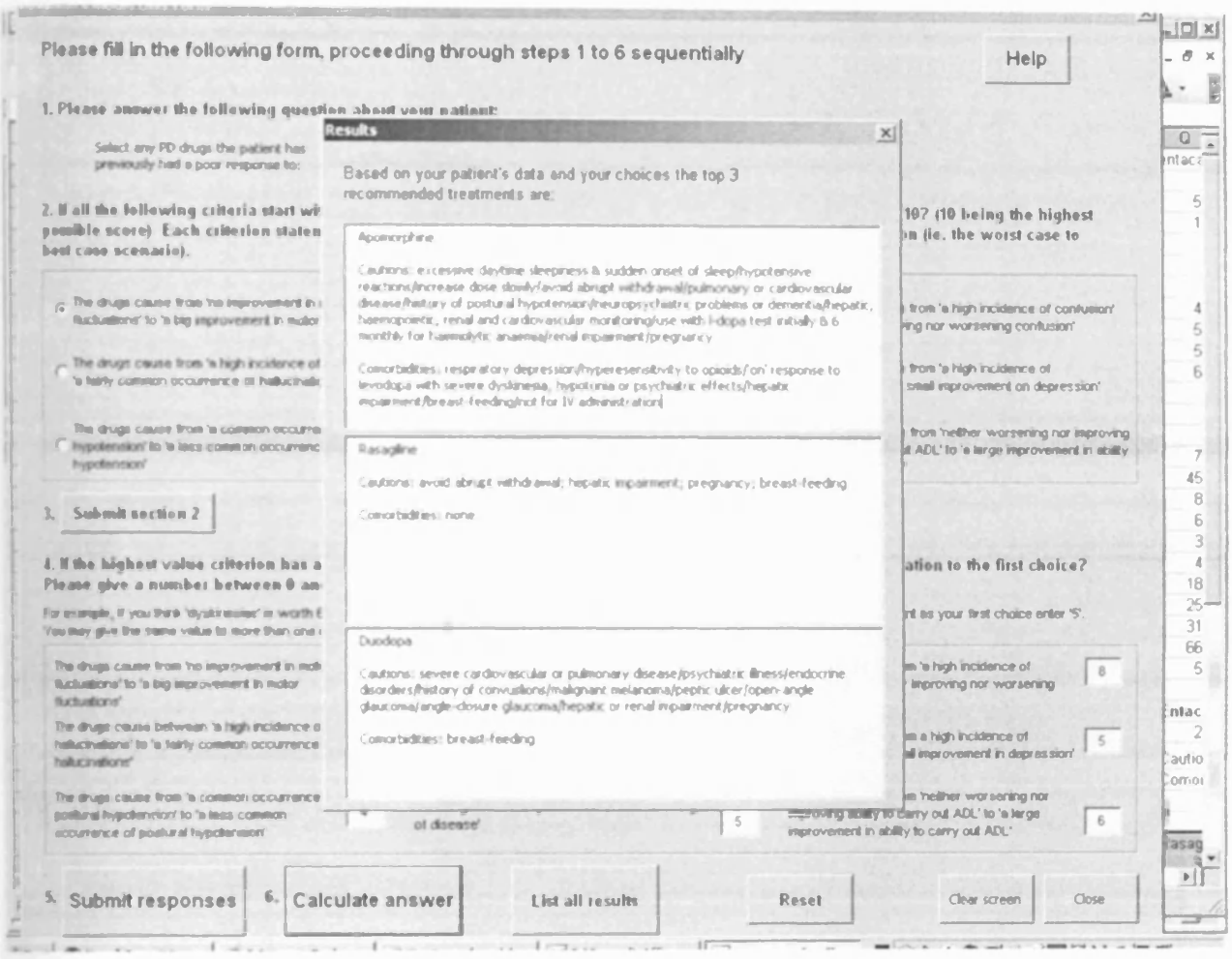


```
'Copy original scores from cells C41 to R51
Range ("C41:R51").Select
Selection.Copy
'Paste scores back into cells C2 to R12 after poor responses have been selected
Range ("C2:R12").Select
  Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
SkipBlanks:=False, Transpose:=False
```

'Help' facility

A basic help facility was added to explain to the user how to use the form and the order in which the sections should be completed. This was developed using a simple message box that is displayed when the user clicks on the 'Help' button. Figure 5.15 shows the screenshot.

Figure 5.13 Screenshot showing the top three results returned to the user in a user form

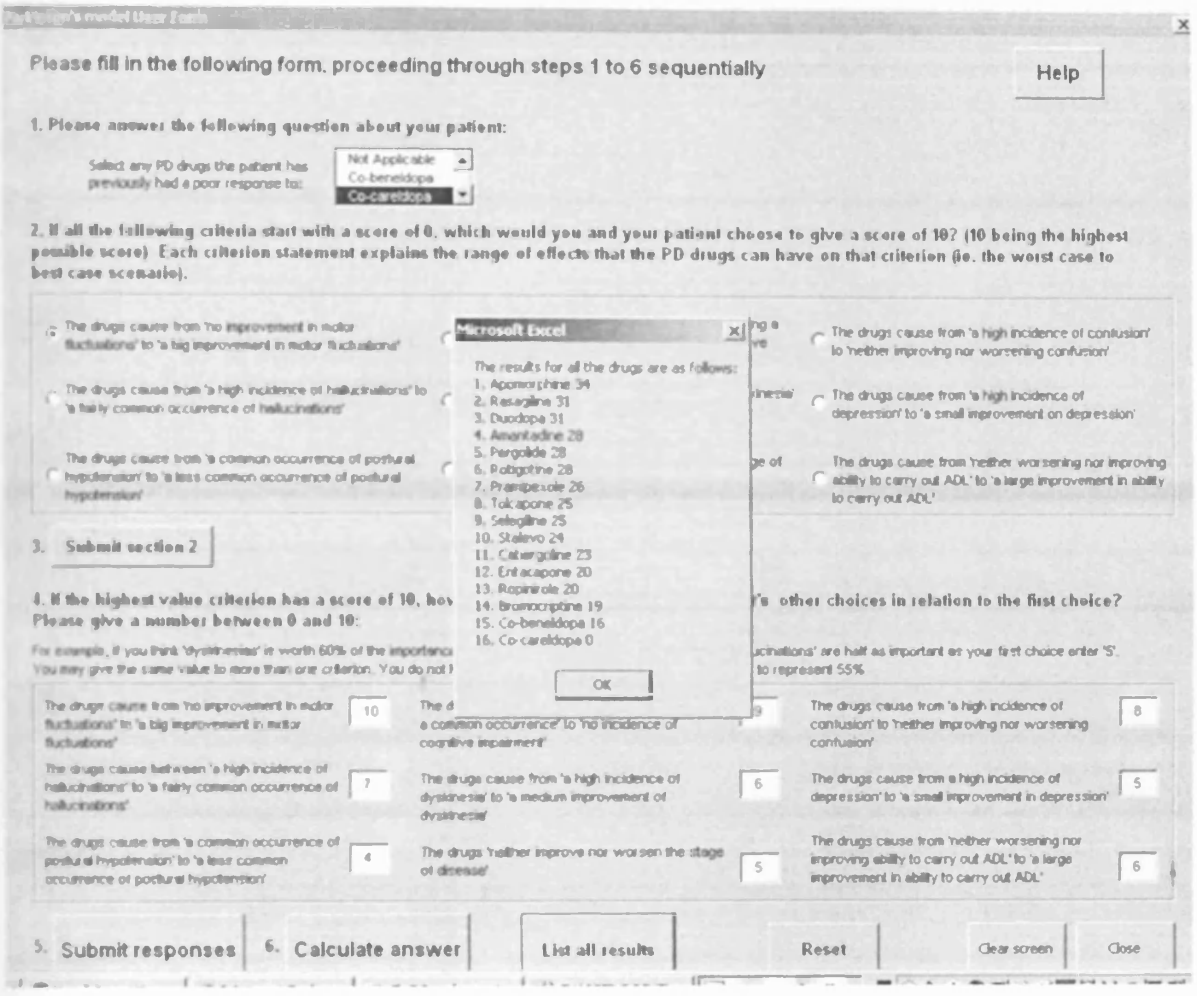


'Clear screen' button

A 'clear' button was added to the user form to enable the user to clear previous data entered if a mistake had been made or when the model was being run for a subsequent patient. This worked by setting the value of each option box and text box to 'null'. The values for each of the list box items were set to 'false'. This is illustrated in the following code for the 'motor fluctuations' option box and text box respectively and the first item in the list of drugs the patient has had a poor response to:

```
OptMotorFlucs.value = Null
TextBoxMotorFlucs.value = Null
ListBoxPoorResp.Selected(0) = False
```

Figure 5.14 Screenshot showing message box with all the results



'Close' button

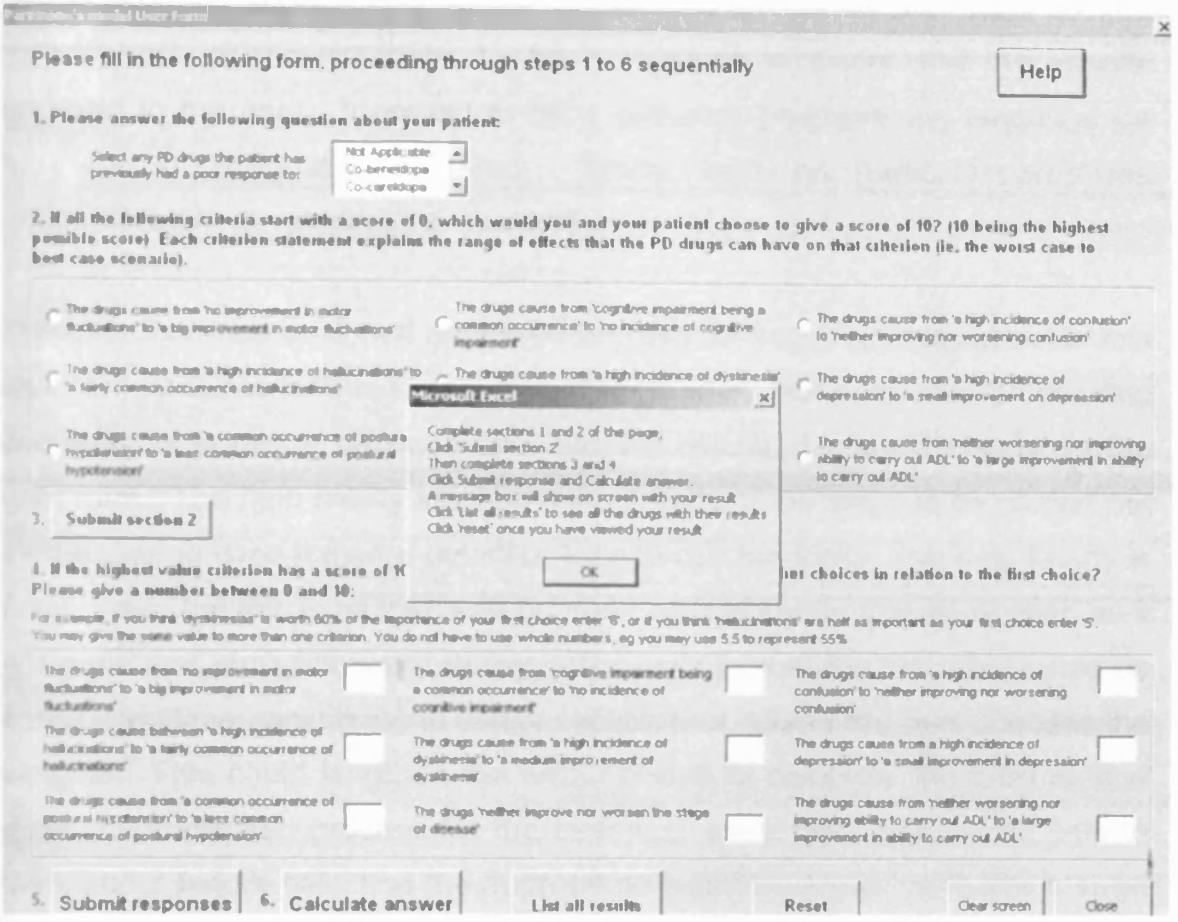
The final button was the 'close' button which enables the user to close the application. This was very simply coded with the following syntax:

```
Unload Me
```

DISCUSSION

In conclusion, a computerised prescribing decision support system was successfully developed using Excel and Visual Basic for Applications. The functional requirements, which were: the user being able to enter data; rate

Figure 5.15 Screenshot of the help facility



the criteria; receive the top results and receive a list of all the treatments with their results, were all met.

The CDSS was a relatively small application to develop. It was also relatively easy to fulfil the requirements of making the application quick and easy to use as it was possible to put all the data input requirements on a one page form. The amount of data required from the user was also quite small which helped to keep the application smaller.

VBA as a programming language is quite simple to use. The coding was successfully developed with no previous experience of this programming language. There are many books published on VBA and also many websites with tips, suggestions, coding ideas and user forums. One of these in particular, (www.ozgrid.com, 2008) proved to be very useful for tips and ideas.

In all, VBA performed the functions required of it, enabling a user interface to be developed, sub-routines to be developed to submit the data to the spreadsheet, the calculations to be performed in Excel and the results returned to the user. It proved to be a sufficient programming language for the type of application required. There were no particular problems encountered in developing the application.

The user interface designed appeared to meet the requirements set out in this chapter. The interface is simple and easy to use, with each step proceeding sequentially from the previous one and the results displayed clearly on the user form. The help facility also provides details of the steps to be carried out by the user in case they are not clear how to use the form. The help facility is fairly basic, but this is all that was deemed necessary for this application as it is simple and straightforward to use. The only part of the form that could be considered time-consuming to use is section four, where the user chooses the weights. This could lengthen the time needed to complete the form as it is quite a complicated process for the user and could take quite some time to think about before selecting the appropriate weights. However, if this is to be considered a limitation then it is more a limitation of the modelling methodology than of the CDSS. There is no way to make the user form quicker to complete without changing the methodology used for the weights section. This would of course mean the methodology was not being adequately or properly applied and this is therefore impractical. If the user is able to decide on the weights fairly quickly then the user form is still quick to use, but it is not the form or CDSS itself which makes it slower to use.

This stage of development of the CDSS did not include any validation of the data the user inputs, error handling or testing of the CDSS. These will all be discussed in chapter six. The CDSS should also be evaluated by external users, such as an expert panel, and this will be discussed in chapter seven when the model is validated.

Although the CDSS is adequate for the model developed, if the model were to be developed further a more sophisticated application would need to be

developed. There may be limitations to the functionality that VBA could incorporate. Both Excel and, therefore, VBA are widely available and most users would already have Excel installed on their machine as part of the Windows operating system. However, for the CDSS to be used in a live clinic situation it would mean having to send the application to each user individually. There could also potentially be problems for the user if they are using a different Windows operating system. The CDSS was developed using Excel 2003 as part of the Microsoft Office package. If a user had Excel 2007 installed on their machine or an older version of Windows the CDSS may not install or run correctly.

Another important facet of the CDSS which has not been able to be developed is explaining the result to the user. Therefore, the user has no way of knowing why particular drugs have been chosen for their patient. To incorporate this sort of facility in the CDSS would mean developing a far more sophisticated system, which was beyond the scope of this PhD. An expert system would be able to explain the reasoning behind the decision made to the user. Expert systems, an application of artificial intelligence, consist of a database, knowledge base and a rule interpreter. The knowledge base holds the rules of inference that are used for reasoning, with such systems typically containing hundreds or thousands of rules. The database contains the rules about the problem and the rule interpreter makes the inferences. This type of system would be able to deal with the complexity of the algorithm that would be necessary to make the decision on the best treatment for a particular patient and explain why that decision had been made. Therefore, for the CDSS to be used in clinical practice it would be necessary to develop an expert system.

SUMMARY

- Software development methods were explained and the prototyping method used discussed
- Unified modelling language was explained and the different kinds of UML diagrams explained

- The functional requirements of the system were elaborated and demonstrated diagrammatically by use of a Use Case Diagram
- The system requirements were elaborated and demonstrated in diagram form by means of an Activity Diagram
- The choice of software was explained
- The interface design was explained
- The implementation of how the form was set up was shown and demonstrated with sections of the coding used
- The process for the coding and submission of the user's data was elaborated on, including how the data was submitted, how the results were calculated and how the results were returned to the user
- The development of the help facility along with the 'clear' and 'close' buttons were examined.

CHAPTER 6

Validation of Data Entry and Testing of the Computer Decision Support System

INTRODUCTION

Once a software application has been developed it is necessary to fully test the application to ensure it meets its requirements and that everything functions the way that it is expected to. In the context of the software developed for the electronic prescribing support system described in chapter five, it was necessary to incorporate validation of the data that could be entered by the user and to test the prescribing support system overall. Therefore, the application developed in chapter five underwent a thorough testing process, which will be described in detail in this chapter.

METHODS

Software testing involves executing an implementation of the software and examining the outputs and its operational behaviour to check whether it performs as required. Testing is a dynamic technique, which works with an executable representation of the system. It can only be used when a prototype or an executable program has been developed (Sommerville, 2001).

Verification And Validation

Verification and validation (V&V) is the checking and analysis process which ensures that software conforms to its specification and meets the needs of the end users. It is a whole life-cycle process. It starts with requirements reviews, continues through design reviews and code inspections and finishes with testing of the product. V&V activities should be incorporated at each stage of the software process. These activities check whether the results of process activities are the same as were specified in the requirements (Sommerville, 2001).

Verification and validation do not specify the same thing. Validation can be summarised as 'are we building the right product?' and verification as 'are we building the product right?' Verification checks whether the software meets both its functional and non-functional specification. Validation, on the other hand, is a more generalised process which demonstrates that the software

fulfils the end user's expectations. This may be distinct from what has been specified, in that the end product may not match the user's original specifications even if it meets their specification at the end of the process.

Program testing is still the predominant verification and validation technique used. The existence of program defects or inadequacies is detected by examining the program's outputs and looking for anomalies. Testing may be carried out during the implementation phase, which verifies that the software behaves as its designer intended, and also after the implementation is complete (Sommerville, 2001).

The ultimate goal of verification and validation is to establish confidence that the software system is 'fit for purpose'. This does not mean that the program is completely free of defects, but that the system is good enough for its intended use. The level that is considered adequate depends on the system's purpose and the expectations of the users (Sommerville, 2001). Therefore, a series of tests were carried out to ensure the software system functioned the way it was intended to.

Testing Methods Used

Validating the user's data entry

Before any testing could be carried out a series of data validation techniques were incorporated into the coding to check the data that the user entered. These were added to ensure that the user only entered the correct form of data, such as figures not letters, for each section and also that each section had been completed so that the application would work as intended. These will now be outlined in turn.

Selecting a weight: section 2

The first stage of the validation was section two, where the user had to allocate the top weight to their criterion of choice. This was to check that a criterion had been selected when the 'Submit section 2' button was clicked.

Choosing all the weights: section 4

The next stage was to check that all the weights in section four had been filled in by the user once they clicked on 'Submit responses'. This would ensure none of the criteria weights had been inadvertently omitted.

Completing the weights with figures only

This stage was to check that the weights had been completed with figures and not with letters or other non-numeric characters.

Completing the weights with numbers between 0 and 10

A check was added here to ensure that the user had only used figures between 0 and 10, as requested, to complete the weights and had not entered a negative number or a figure over 10.

Completing each section before clicking 'Calculate answers'

This stage checked that the user had entered data for sections two and four and clicked both the 'Submit section 2' and 'Submit responses' buttons in order for the result to be returned to them.

Completing each section before clicking 'List all results'

Another check was added to ensure that the user had completed all the sections and clicked both the submit buttons before they tried to view the results.

Resetting scores before closing the application

This ensured that the user had clicked the 'Reset' button before they closed the application so that any drug scores that had been set to 0 when the drug was selected for poor response would be reset to their original values so that the model could be run again.

Closing the application

The final check was to ensure that the user closed the application by clicking on the 'Close' button, rather than using the automatically generated 'X' on the

top right-hand corner of the form. This thus ensured also that the scores would be reset, as in the check above.

Testing the application sections

Once all the data validation had been added it was necessary to test the whole application to ensure that the validation checks all worked as they were supposed to and that the application worked as expected overall. The first step in the process of testing the application was to develop the methodology to be carried out. The functionality of the application was broken down into a series of sections or steps that the user would have to work through when using the software. The options available to the user for each section were then outlined. Each section included options that the user was not supposed to use, such as inputting the wrong type of data for example, as well as the option that was expected of the user. The next step was to then run the application performing all the different options the user might carry out to see how the application would respond and to establish whether the data validation techniques detailed above performed as expected. The sections and available options are shown in the flowchart in Figure 6.1. A table was constructed (Table 6.1) with a list of possible inputs for each section and the result that would be expected from each input. Two further columns showed the actual result of each test and comments about the result.

RESULTS

Data Validation

Selecting a weight: section 2

To validate that a weight had been selected in section two when the 'Submit section 2' button was clicked an error message was included in the section of code that submitted the value '10' into the chosen weight in section four. The validation formed part of the 'If...Then...Else' structure submitting the value '10' to section four. This is demonstrated in the code below:

```
If OptMotorFlues.Value = True Then
ActiveCell.Value = 10
TextBoxMotorFlues.Value = 10
```

Figure 6.1 Flowchart to show testing procedure

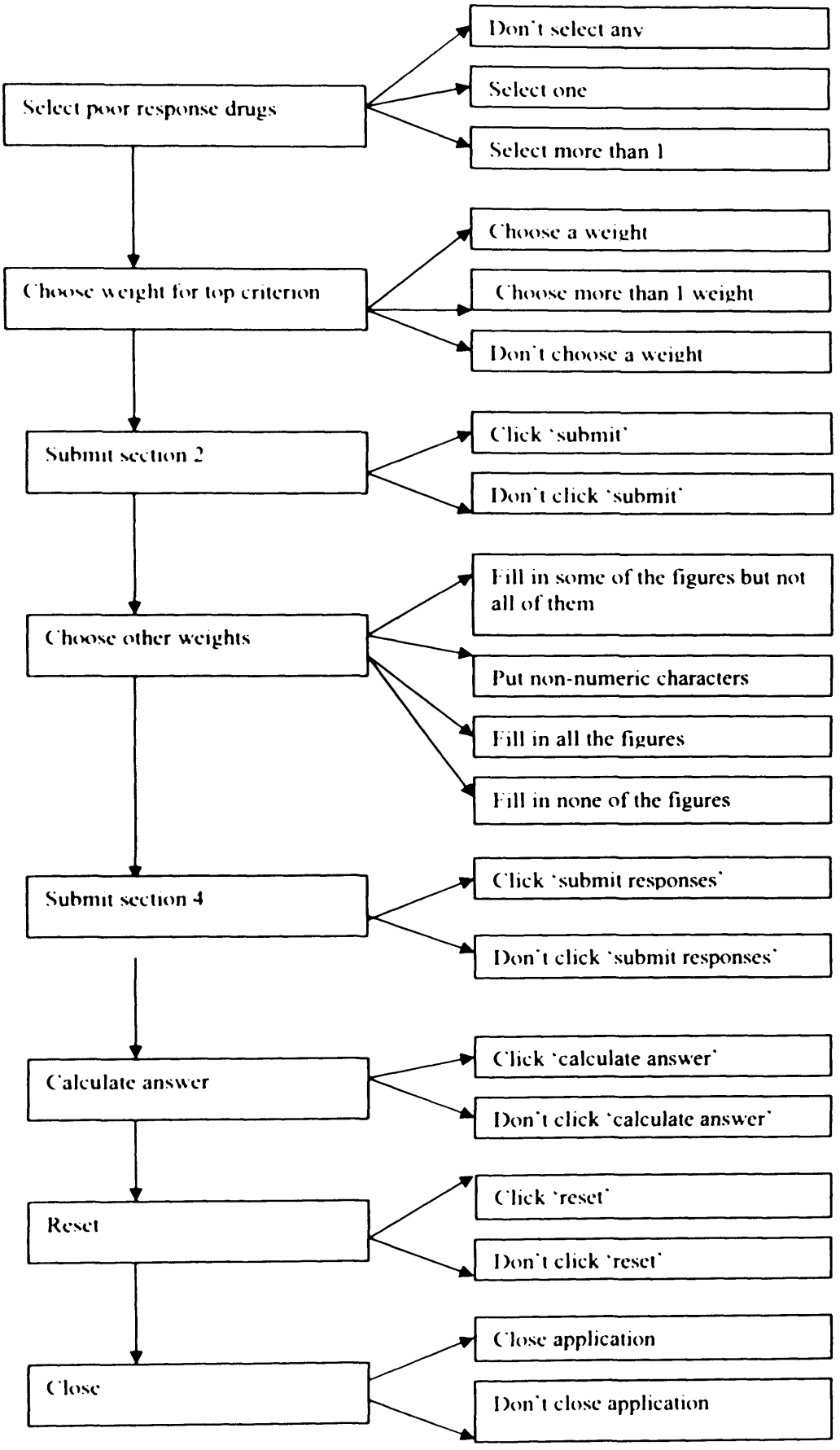


Table 6.1 Testing process documentation

Section	Input to be entered	Expected result	Actual Result	Comments
Select poor response select top weight	One drug No weights	Should be prompted by error message for weight when click 'submit section 2'		
	No drugs One weight	Should submit data to spreadsheet		
	One drug One weight	Should submit data to spreadsheet		
	Two drugs One weight	Should submit data to spreadsheet		
	Two drugs No weights	Should be prompted by error message for weight when click 'submit section 2'		
	Three drugs One weight	Should submit data to spreadsheet		
	Four drugs One weight	Should submit data to spreadsheet		
	Five drugs One weight	Should submit data to spreadsheet		
Choose other weights	No weights	Should get error message 'you must complete a value for ...' for each criterion in turn when click 'submit responses'		
	One weight	Should get error messages as above for all the other criteria		
	Two weights	Should get error messages as above for all the other criteria		
	Three weights	Should get error messages as above for all the other criteria		
	Four weights	Should get error messages as above for all the other criteria		
	All the weights	Should submit all the weights into spreadsheet when click 'submit responses'		

Table 6.1 Testing process documentation (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
	Letters not numbers for one weight	Should get error message for that criterion 'enter numerals and not any other characters for (criterion name)'		
	Letters not numbers for two weights	Should get error message for each criterion 'enter numerals and not any other characters for (criterion name)'		
	Number above 10 for one weight	Should get error message 'You must choose a number between 0 and 10 for (criterion name)' for that criterion		
	Number above 10 for two weights	Should get error message 'You must choose a number between 0 and 10 for (criterion name)' for each criterion		
	Number below 0 for one weight	Should get error message 'Number must be 0 or more for (criterion name)' for that criterion		
	Number below 0 for three weights	Should get error message 'Number must be 0 or more for (criterion name)' for each criterion		
Calculate answer	Click calculate answer	Should return user form with top 3 results displayed along with cautions and contraindications for each drug		
	Don't click calculate answer	Should receive no results – nothing will appear to have happened to user		
List all results	All results are listed	Should receive list of all results in order of overall score with their total score if all sections have been completed and submitted		

Table 6.1 Testing process documentation (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
	No results are listed	Should receive error message "You must enter data for all the sections, click 'submit section 2' and 'submit responses' before you can view the results" if have not entered and submitted data		
Reset	Click 'reset'	Should copy and paste original values of scores of all drugs into relevant cells		
	Don't click 'reset'	Should get error message 'You must click 'reset' before you can close the form' when click 'close'		
Close application	Click 'close'	Application should close		
	Click cross on top right of form instead of 'close' button	Should get error message 'You must use the 'Close' button to close the form'		

```
ElseIf OptADL.Value = True Then
  ActiveCell.Value = 10
        TextBoxADL.Value = 10
Else
MsgBox "You must select an option for section 2 before you click
'submit section 2'
```

Therefore, any time the user clicked 'Submit section 2' without having selected a weight in section two they would receive the above error message.

Choosing all the weights: section 4

For each of the criteria in section four a validation technique was added, so that the user was prompted with an error message if any of the criteria were omitted. This is demonstrated with the code below for the criterion 'motor fluctuations':

```
If IsNull(TextBoxMotorFlucs) Or Me.TextBoxMotorFlucs = "" Then
        MsgBox "You must complete a value for motor fluctuations"
```

The user would receive the error message for that criterion and if any other criteria text boxes were also empty once they had clicked 'Ok' on the first error message box they would receive the error message for all the subsequent missing criteria.

Completing the weights with figures only

To check that the user only entered figures and not letters or any other non-numeric characters, another error message was added to prompt them if they had entered incorrect data. This was also coded as an 'If..Then..Else' statement, as the code below demonstrates:

```
ElseIf Not IsNumeric(TextBoxMotorFlucs.Value) Then
MsgBox "Enter numerals and not any other characters for motor
fluctuations".
```

Completing the weights with numbers between 0 and 10

Two 'If...Then...Else' statements were used to ensure that the user had

submitted a number that was between 0 and 10. The first statement checked that the number was not negative and the second that the number was not greater than ten. These two statements are shown in the following code:

```
ElseIf IsNumeric(TextBoxMotorFlues.Value)And
Val(TextBoxMotorFlues.Value) < 0 Then
  MsgBox "Number must be 0 or more for motor fluctuations"
    ElseIf Val(TextBoxMotorFlues.Value) > 10 Then
    MsgBox "You must choose a number between 0 and 10 for motor
    fluctuations".
```

Completing each section before clicking 'Calculate answer'

In order to check that the user had completed each of the sections when they clicked 'Calculate answer' a flag was set in the spreadsheet in cell A56 which was set to 'False' in section two. This was done with the following code:

```
Range("A56").Value = "FALSE"
```

This flag was then to be set to 'True', once section four had been completed, under the following section:

```
Private Sub cmdSubmitWeights_Click()
```

using the following code:

```
Range("A56").Value = "True".
```

When the user clicked on 'Calculate answer' the code would first check that the flag had been set to 'True' in the 'SubmitWeights' section, implying that each section had been completed, and the calculations would be carried out and the results returned to the user. If the previous sections had not been completed an error message would be returned to the user telling them to complete the previous sections first. This is demonstrated by the following code:

```
If Range("A56").Value = "True"
  ....'perform calculations and return results....
Else
  MsgBox "You must select figures for section 4 and click 'submit
  responses' before you can receive the recommended treatments".
```

Completing each section before clicking 'List all results'

Similarly to the validation check for 'Calculate answers', a flag was created in the spreadsheet in cell A60. This flag was set to 'False' in section two and then set to 'True' once the user had completed all the sections and clicked 'Submit responses'. A check was then made under the section

```
Private Sub CmdListResult_Click()
```

to see if the flag had been set to 'True'. If it had the list of results was returned to the user, otherwise they received an error message telling them to complete all the sections, as demonstrated by the following code:

```
If Range("A60").Value = True Then
...'return list of results to user...
Else
  MsgBox "You must enter data for all the sections, click 'submit section2'
  and 'submit responses' before you can view the results".
```

Resetting scores before closing the application

Another flag was used to check that the user had clicked the 'Reset' button before they closed the application. This was set to 'False' in section two and set to 'True' in the section

```
Public Sub CmdReset_Click().
```

This demonstrated that the user had clicked 'Reset' if the flag had been changed to 'True'. An 'If...Then...Else' statement was again used in the close

application section, giving the user an error message telling them to click 'Reset' if they had not already done so. This is shown in the following code:

```
If Range("A54").Value = "True" Then
  Unload Me
Else
  MsgBox "You must click 'reset' before you can close the form"
```

Closing the application

To ensure the user only closed the application by means of the 'Close' button an error message was added if they tried to use the cross in the top right-hand corner of the form to close the application. This used an 'If...Then' statement which prevented them from closing the application with the cross, as demonstrated below:

```
If CloseMode = vbFormControlMenu Then
Cancel = True
MsgBox "You must use the 'close' button to close the form".
```

Testing Process

The tests described in the methods section of this chapter are demonstrated n Table 6.2 with the actual result and comments about each test. The test results are then described individually in more detail.

Poor response / selection of weight

One drug, no weight

The first test examined what happened if an option was selected for the 'poor response' drugs but no option was selected in section two for the weights. An error message had been expected if no weight was selected telling the user they must select an option and this was what was returned (Figure 6.2).

No drugs, one weight

The second test examined what happened when no option was selected for the poor response drugs but a weight was selected in section two. The

Table 6.2 Testing process documentation completed

Section	Input to be entered	Expected result	Actual Result	Comments
Select poor response select top weight	One drug No weights	Should be prompted by error message for weight when click 'submit section 2'	Received error message saying 'You must select an option from section 2 before you click 'submit section 2''	Result as expected
	No drugs One weight	Should submit data to spreadsheet	Submitted data to spreadsheet	Result as expected
	One drug One weight	Should submit data to spreadsheet	Set poor response drug scores to 0 in spreadsheet and submitted weight into section 4 and spreadsheet	Result as expected
	Two drugs One weight	Should submit data to spreadsheet	Set two poor response drugs' scores to 0 in spreadsheet and submitted weight into section and spreadsheet	Result as expected
	Two drugs No weights	Should be prompted by error message for weight when click 'submit section 2'	Set two poor response drugs' scores to 0 in spreadsheet and got error message 'you must submit a value in section 2'	Result as expected
	Three drugs / One weight	Should submit data to spreadsheet	Set three poor response drugs' scores to 0 in spreadsheet and submitted weight into section and spreadsheet	Result as expected

Table 6.2 Testing process documentation completed (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
	Four drugs One weight	Should submit data to spreadsheet	Set four poor response drugs' scores to 0 in spreadsheet and submitted weight into section and spreadsheet	Result as expected
	Five drugs One weight	Should submit data to spreadsheet	Set five poor response drugs' scores to 0 in spreadsheet and submitted weight into section and spreadsheet	Results as expected
Choose other weights	No weights	Should get error message 'you must complete a value for ...' for each criterion in turn when click 'submit responses'	Got error message 'You must complete a value for motor fluctuations', clicked ok, got error message for 'cognitive impairment', clicked ok, got error message for 'confusion' and so on through all the criteria except the one submitted in section 2	Results as expected

Table 6.2 Testing process documentation completed (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
	One weight	Should get error messages as above for all the other criteria	Got error message 'You must submit a value for cognitive impairment', clicked ok then got error messages for all subsequent criteria except the one entered and the one submitted from section 2	Result as expected
	Two weights	Should get error messages as above for all the other criteria	Got error message 'You must submit a value for confusion', clicked ok then got error messages for all subsequent criteria except the ones entered and the one submitted from section 2	Results as expected
	Three weights	Should get error messages as above for all the other criteria	Got error message 'You must submit a value for dyskinesia', clicked ok then got error messages for all subsequent criteria except the ones entered and the one submitted from section 2	Result as expected

Table 6.2 Testing process documentation completed (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
	Four weights	Should get error messages as above for all the other criteria	Got error message 'You must submit a value for depression', clicked ok then got error messages for all subsequent criteria except the ones entered and the one submitted from section 2	Result as expected
	All the weights	Should submit all the weights into spreadsheet when click 'submit responses'	All the weights submitted into the spreadsheet	Result as expected
	Letters not numbers for one weight	Should get error message for that criterion 'enter numerals and not any other characters for (criterion name)'	All the weights were submitted into the spreadsheet including the letter, got error message 'Enter numerals and not any other characters for motor fluctuations', once the letter was changed to a number the letter was over-written with the number in the spreadsheet	Result as expected

Table 6.2 Testing process documentation completed (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
	Letters not numbers for two weights	Should get error message for each criterion 'enter numerals and not any other characters for (criterion name)'	All the weights were submitted into the spreadsheet including the letters, got error message 'Enter numerals and not any other characters for confusion' and the same for 'hallucinations', once the letters were changed to numbers the letters were over-written with the numbers in the spreadsheet	Result as expected
	Number above 10 for one weight	Should get error message 'You must choose a number between 0 and 10 for (criterion name)' for that criterion	Got error message 'you must choose a number between 0 and 10 for 'depression'	Result as expected
	Number above 10 for two weights	Should get error message 'You must choose a number between 0 and 10 for (criterion name)' for each criterion	Got error message 'you must choose a number between 0 and 10 for confusion' and same message for 'depression'	Result as expected
	Number below 0 for one weight	Should get error message 'Number must be 0 or more for (criterion name)' for that criterion	Got error message 'Number must be 0 or more for dyskinesias'	Result as expected

Table 6.2 Testing process documentation completed (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
	Number below 0 for three weights	Should get error message 'Number must be 0 or more for (criterion name)' for each criterion	Got error message 'Number must be 0 or more for motor fluctuations', click ok and get same message for 'cognitive impairment', click ok and get same message for 'stage of disease'	Result as expected
Calculate answer	Click calculate answer	Should return user form with top 3 results displayed along with cautions and contraindications for each drug	Got unexpected error message "You must select figures for section 4 and click 'submit responses' before you can receive the recommended treatments", even though all sections had been completed and submitted	Re-checked code, discovered inconsistency in way true flag was recorded in code, sometimes written as "TRUE" and sometimes as "True", therefore VBA wasn't recognising that sections had been completed. All flags were written as "True" and the test re-run with the results then being as expected
	Don't click calculate answer	Should receive no results – nothing will appear to have happened to user	Received no results, nothing happens that user can see	As expected

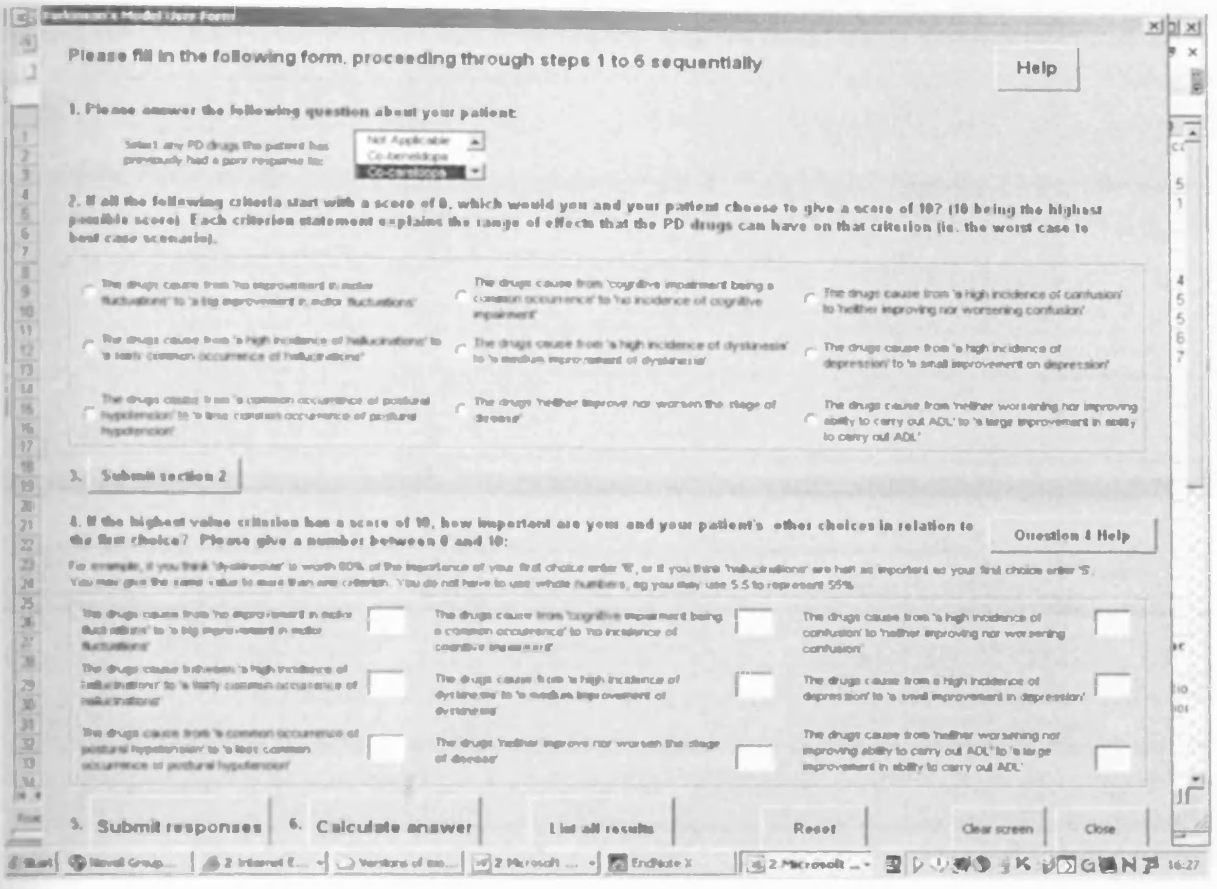
Table 6.2 Testing process documentation completed (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
List all results	All results are listed	Should receive list of all results in order of overall score with their total score if all sections have been completed and submitted	Got error message "You must enter data for all the sections, click 'submit section2' and 'submit responses' before you can view the results", even though all sections had been completed and submitted	Re-checked code, discovered inconsistency in way true flag was recorded in code, sometimes written as "TRUE" and sometimes as "True", therefore VBA wasn't recognising that sections had been completed. All flags were written as "True" and the test re-run with the results then being as expected
	No results are listed	Should receive error message "You must enter data for all the sections, click 'submit section 2' and 'submit responses' before you can view the results" if have not entered and submitted data	Got error message "You must enter data for all the sections, click 'submit section 2' and 'submit responses' before you can view the results"	Result as expected
Reset	Click 'reset'	Should copy and paste original values of scores of all drugs into relevant cells	Copied and pasted original values of scores of all drugs into relevant cells	Result as expected

Table 6.2 Testing process documentation completed (continued)

Section	Input to be entered	Expected result	Actual Result	Comments
	Don't click 'reset'	Should get error message 'You must click 'reset' before you can close the form' when click 'close'	Got error message "You must click 'reset' before you can close the application"	Result as expected
Close application	Click 'close'	Application should close	Application closed	Result as expected
	Click cross on top right of form instead of 'close' button	Should get error message 'You must use the 'Close' button to close the form'	Got error message 'You must use the 'Close' button to close the form'	Result as expected

Figure 6.2 Test to see if user can submit one drug but no weight

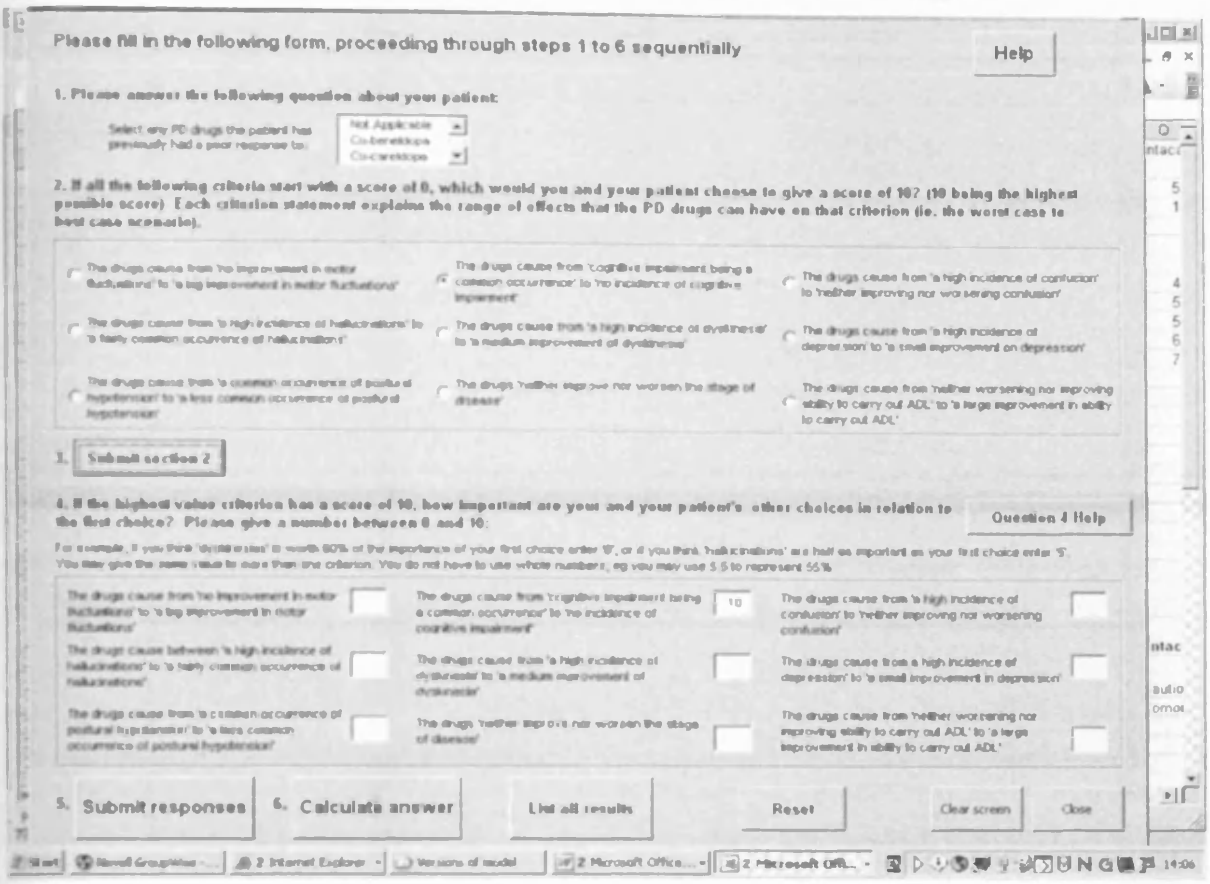


expected result was that the figure '10' would be inserted in the relevant criterion text box in section four for the chosen weight and that there would be no error message as the user had done what was required of them. An error message was not expected for the lack of selection of poor response drugs, as it did not matter if the user did not select any of the options. An option 'Not applicable' had been included if the patient had not had a poor response to any of the drugs, but it was decided that it did not matter if this was not selected. The results received were the same as the expected result, as shown in Figure 6.3.

One drug, one weight

A test was next run to see the result if one drug was selected for the poor response drugs and one weight for the weights in section two. It was expected that no error message would be produced as the user was doing what was required of them and that the figure '10' for the selected weight would be

Figure 6.3 Test to see if user can submit no drugs but one weight



selected. The results received were the same as the expected result, as shown in Figure 6.4.

Two drugs, one weight

Having tested the selection of one drug for the 'poor response' options the next step was to test what happened if more than one drug was selected. Two drugs were therefore selected, along with a weight in section two, with the result being expected that there would be no error messages and the relevant weight in section four would receive the figure '10'. The result was indeed as expected (Figure 6.5).

Two drugs, no weight

After testing the selection of two drugs with one weight the next stage was to test two drugs with no weight in section two, to see if the result would be the same as for selecting one drug with no weight. That is to say, there would be

Figure 6.4 Test to see if user can input one drug and one weight

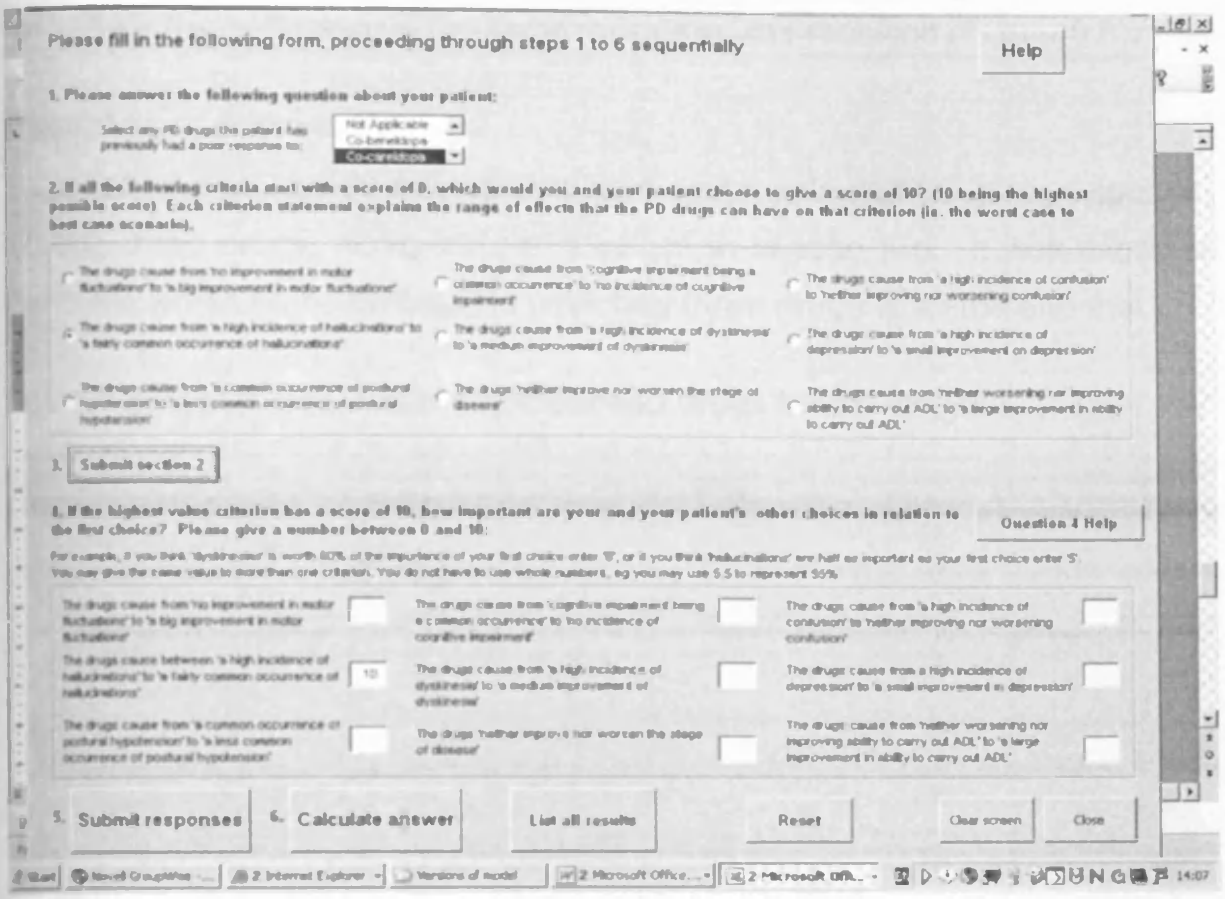
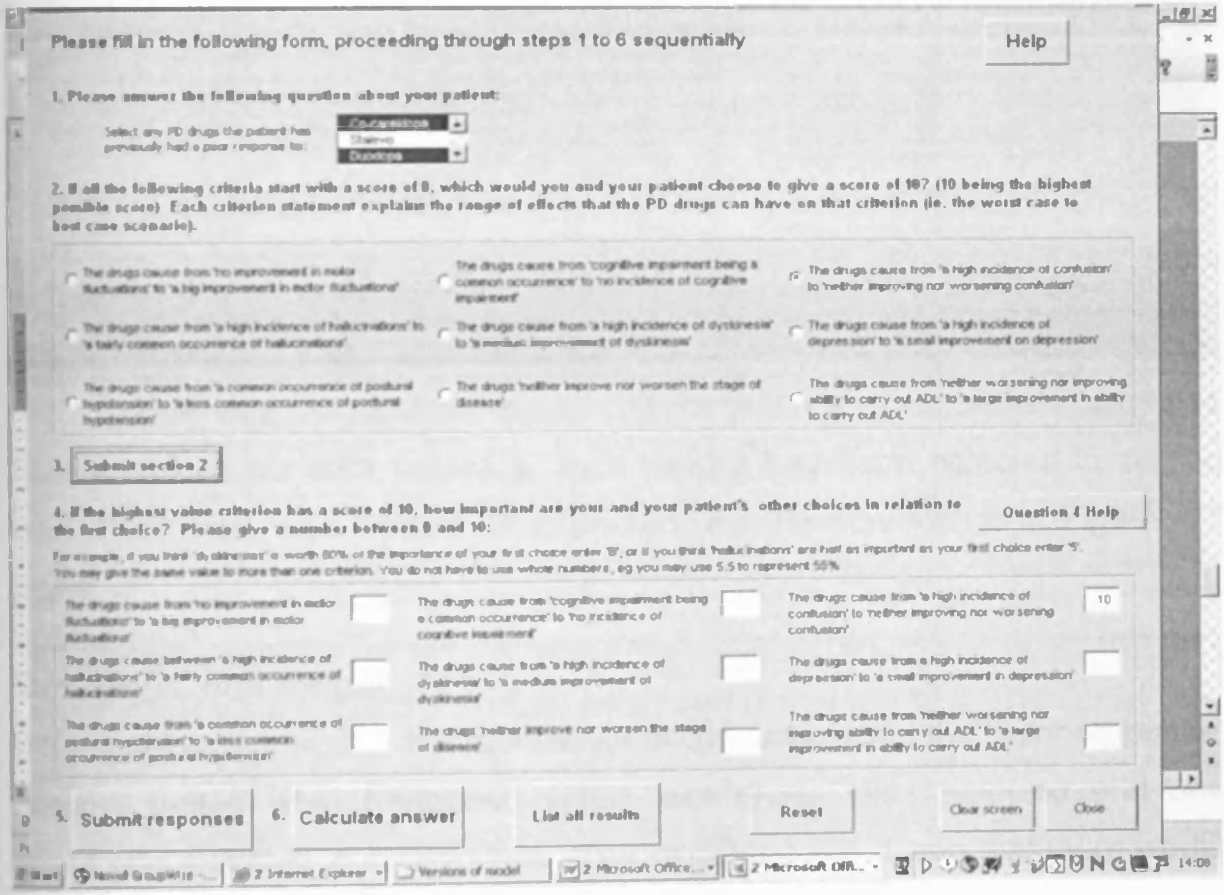


Figure 6.5 Test to see if user can input two drugs and one weight

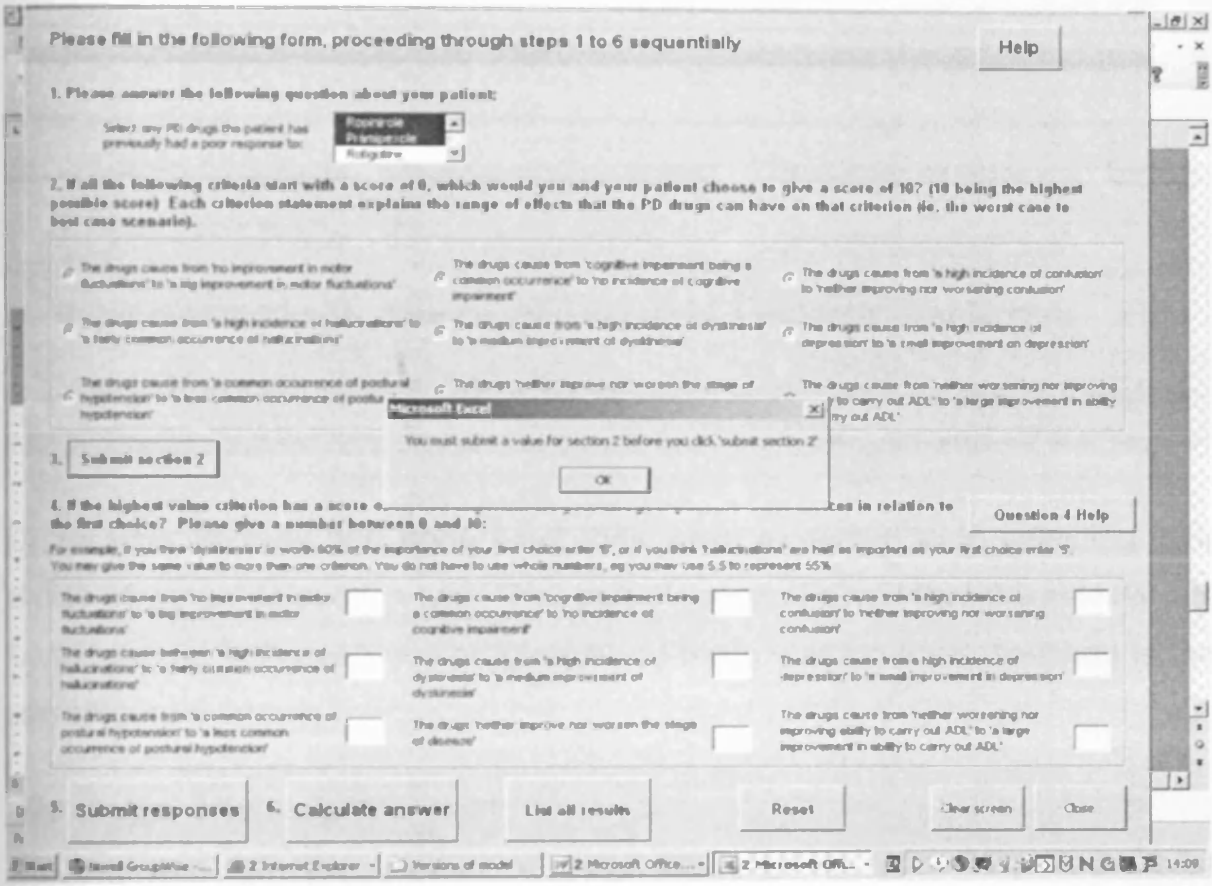


an error message telling the user they needed to select a weight in section two. Once the test was run the error message was received (Figure 6.6).

Three drugs, one weight

Another test was carried out with multiple drugs selected for 'poor response', totalling three drugs, along with one weight in section two. It was expected that there would be no problem in selecting three drugs at a time and that

Figure 6.6 Test to see if user can input two drugs but no weight

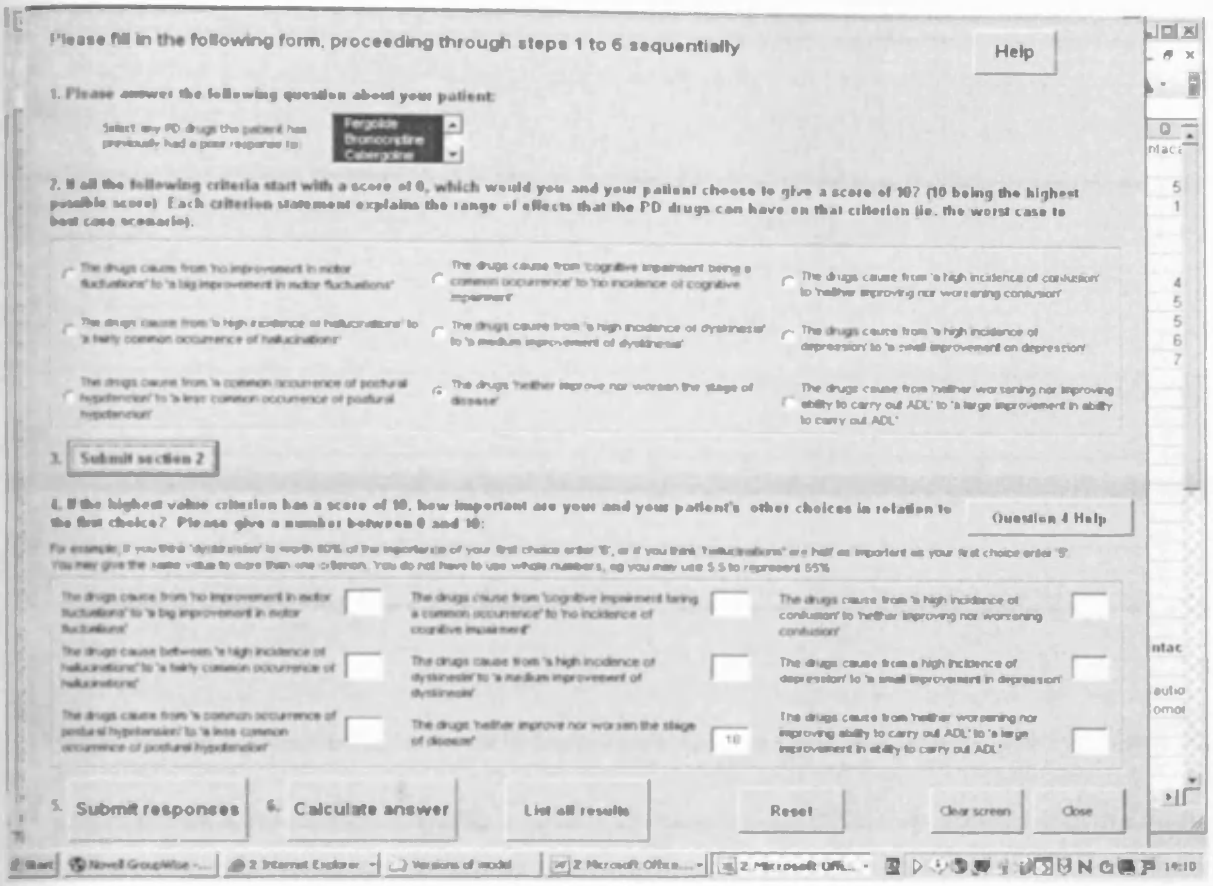


there would be no error message as a weight had been selected in section two. The result was indeed as expected, as the screenshot in Figure 6.7 shows.

Four drugs, one weight

The penultimate test with the number of drugs selected in the 'poor response' category tested what happened when four drugs were selected and one weight was selected in section two. The expected result was that there would be no problem selecting four drugs and that there would be no error message

Figure 6.7 Test to see if user can input 3 drugs with one weight



for the user as they had done what they were expected to in selecting their choice of weight in section two. The actual result showed that the selection of four drugs did not cause any problems and there was no error message to the user (Figure 6.8).

Five drugs, one weight

The final test with the number of drugs selected for 'poor response' whilst selecting one weight in section two was expected to cause no problems in the number of drugs selected (five) and to insert the figure '10' in the relevant weight text box in section four. The result was as expected (Figure 6.9).

Choosing other weights

No weights

A test was carried out to see what would happen if none of the weight text boxes was completed in section four, other than the one that had already been inserted from section two. It was expected that when 'submit responses'

Figure 6.8 Test to see if user can input four drugs and one weight

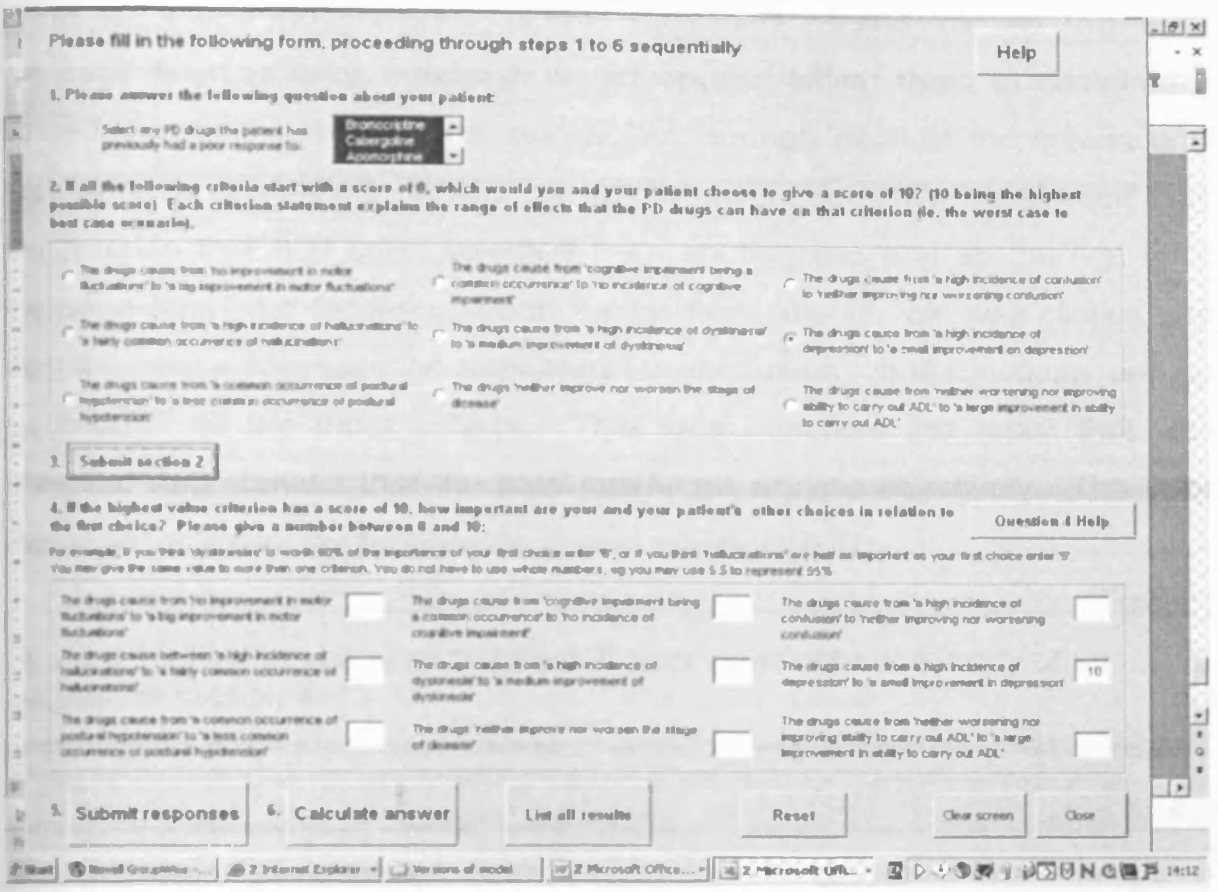
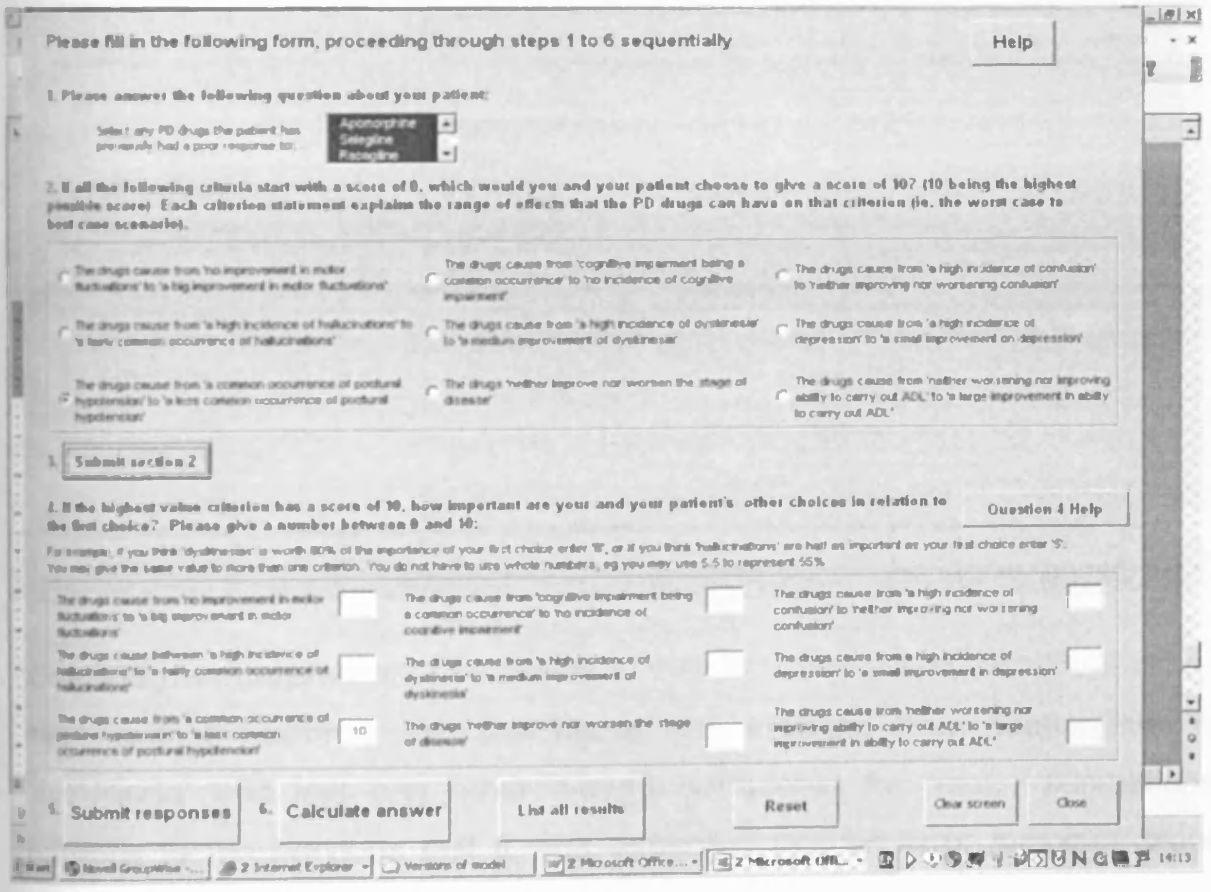
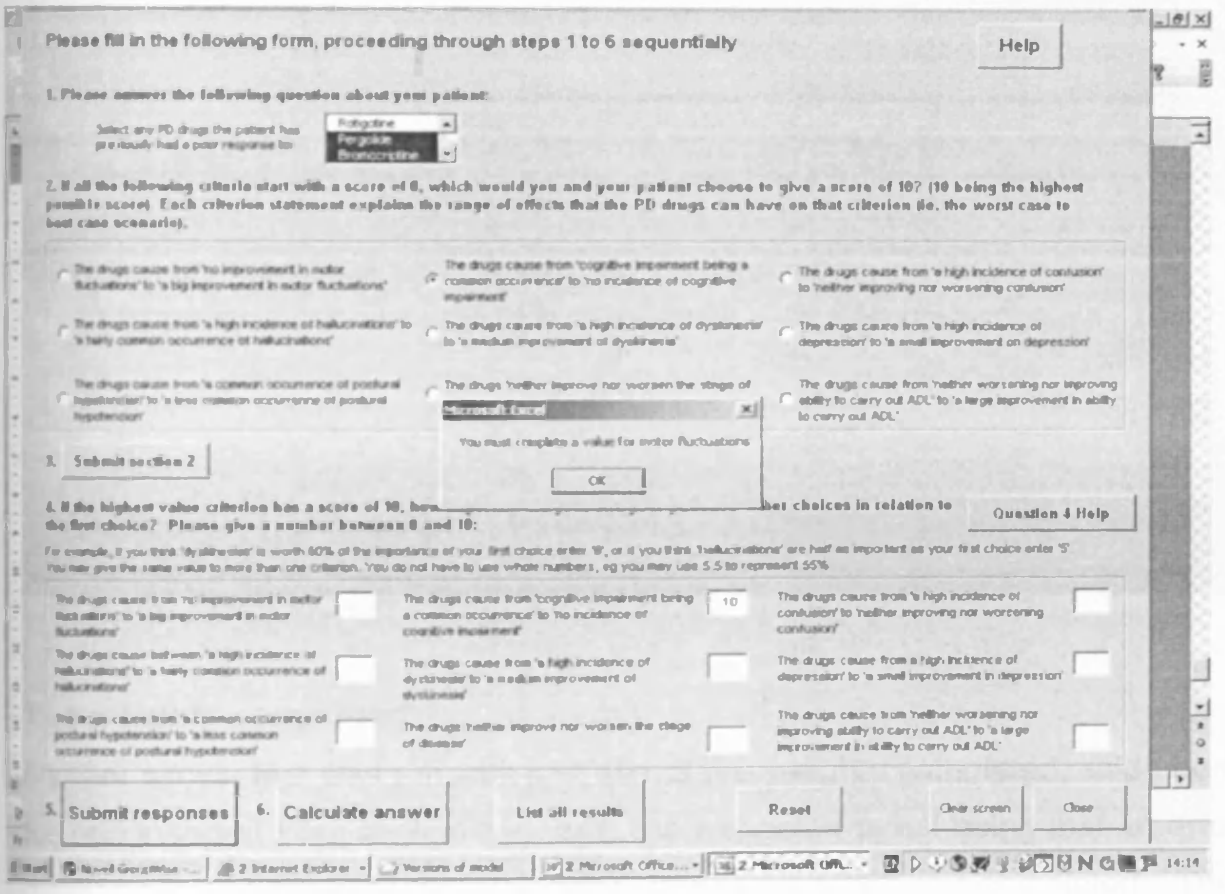


Figure 6.9 Test to see if user can input five drugs and one weight



was clicked an error message would be shown telling the user to complete a value for 'motor fluctuations'. Once they had clicked 'ok' on this error message another error message would appear telling them to complete a value for 'cognitive impairment' and so on through each of the criteria until they were all completed. When the test was run 'cognitive impairment' was the criterion that had been selected from section two and so the first error message appeared for the criterion 'motor fluctuations', 'ok' was clicked and then the next error message appeared for 'confusion', 'hallucinations' and so on through all the other criteria. This was therefore the result that was expected and showed that the data validation worked effectively. The error message for 'motor fluctuations' is shown in Figure 6.10.

Figure 6.10 Test to see what happens if user does not submit any other weights for section 4

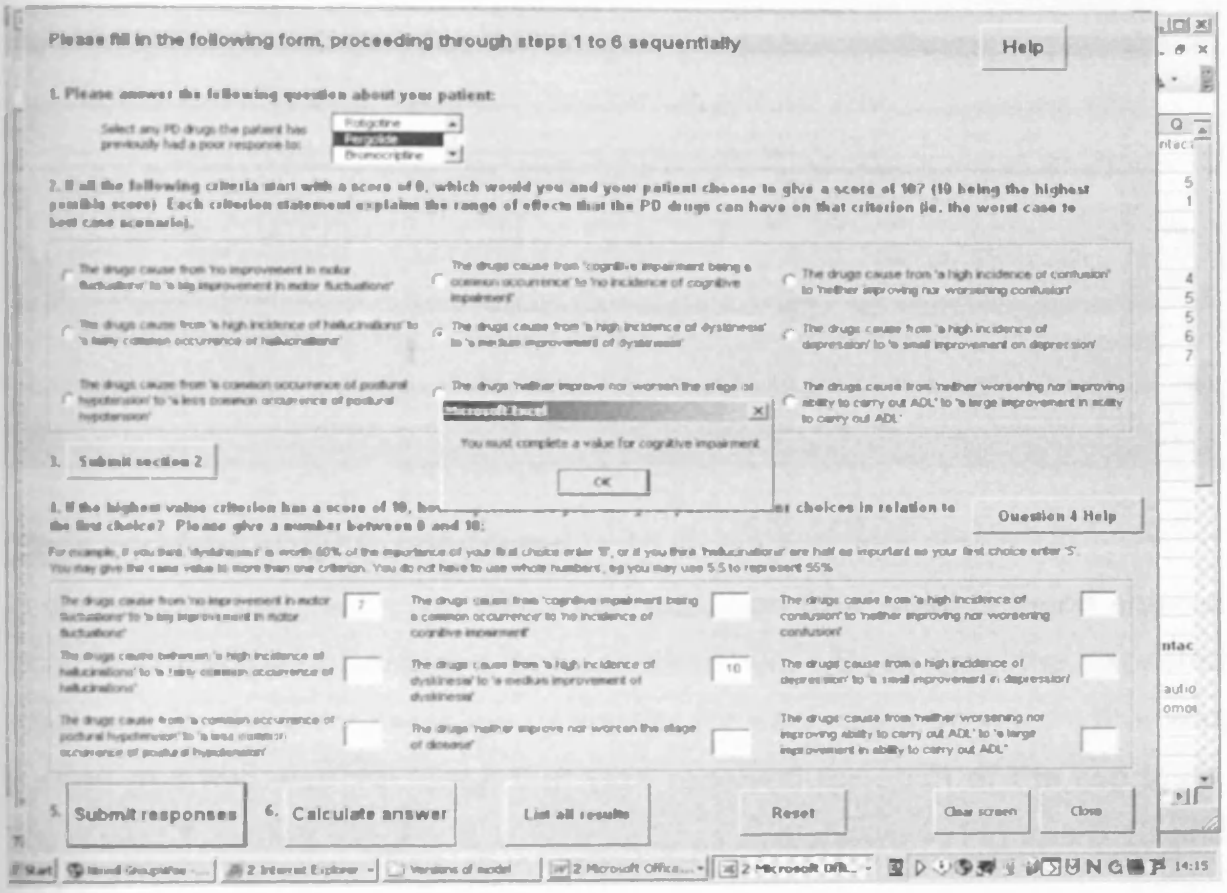


One weight completed

Next, a test was run with the figure '10' inserted from section two for 'dyskinesia' and just one other weight completed for 'motor fluctuations'. Similarly to the previous test it was expected that an error message would

appear for 'cognitive impairment' as it had not been completed and then once 'ok' was clicked for that message a message would appear for 'hallucinations' and so on through all the criteria which had not had a weight inserted. The actual results of the test showed that an error message appeared for each missing criterion weight, as expected. This is demonstrated with the error message for one of the criteria in Figure 6.11.

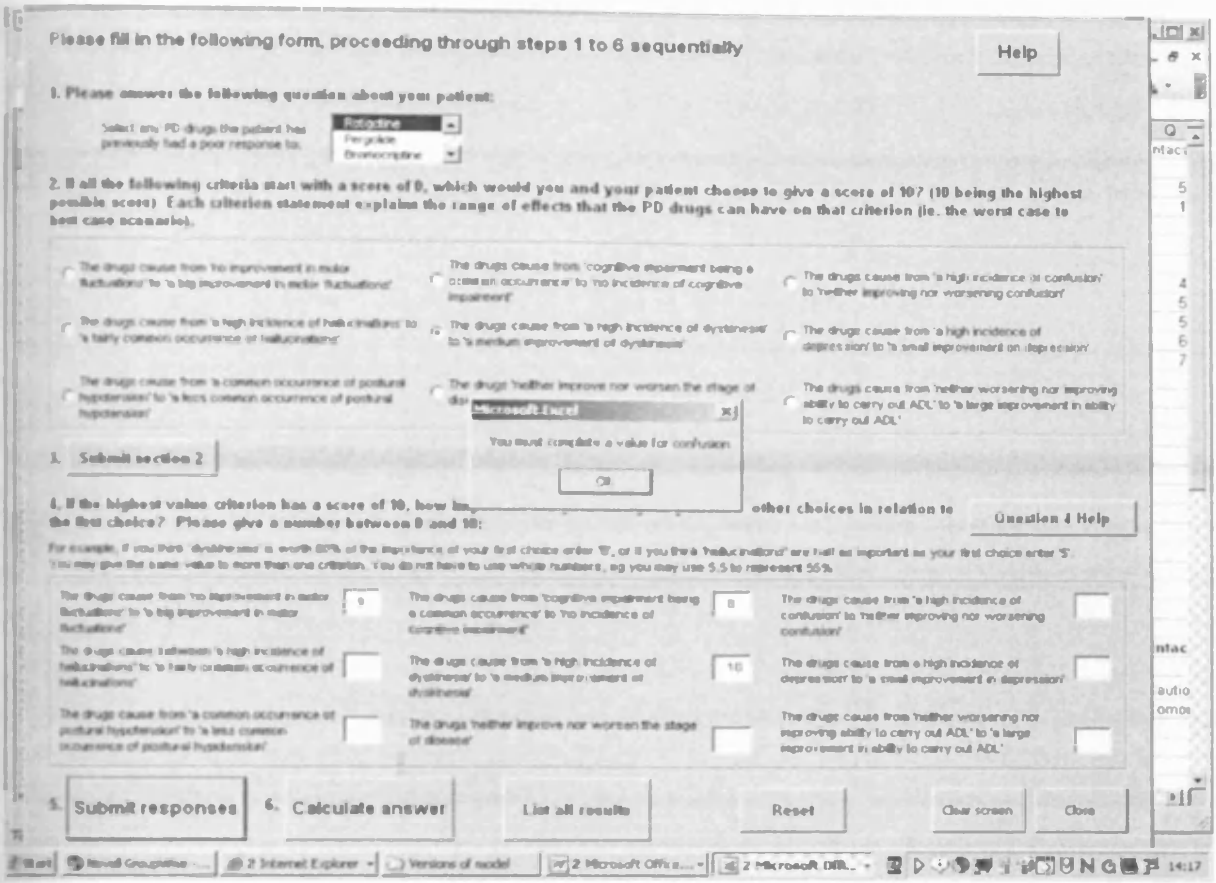
Figure 6.11 Test to see what happens if user only inputs 1 extra weight for section 4 and clicks 'Submit responses'



Two weights completed

Another similar test was run with just two of the weights completed, aside from the one inserted from section two, with the expected result being that an error message would appear for each of the criterion weights not completed. This was in fact what happened, showing the actual result was the same as the expected result (Figure 6.12).

Figure 6.12 Test to see what happens if user only inputs two weights for section 4 then clicks 'Submit responses'



Three and four weights completed

Further similar tests were run with three and then four weights being entered along with the weight inserted from section two. Each time the expected result was for the error message to appear for each criterion weight that was missing and this was the result that was received for each of the two tests. The results for three weights and four weights are shown in Figures 6.13 and 6.14 respectively.

All weights completed

In the next test all the weights were entered for the criteria in section four and the 'submit responses' button clicked. This time it was expected that there would be no error message, as everything had been completed as it should be, and that the figures for all the weights would be inserted into column B in the spreadsheet. The results were as expected and the weights were inserted into column B. The screenshot in Figure 6.15 shows part of the spreadsheet

Figure 6.13 Test to see what happens if user only inputs weights for 3 criteria then clicks 'Submit responses'

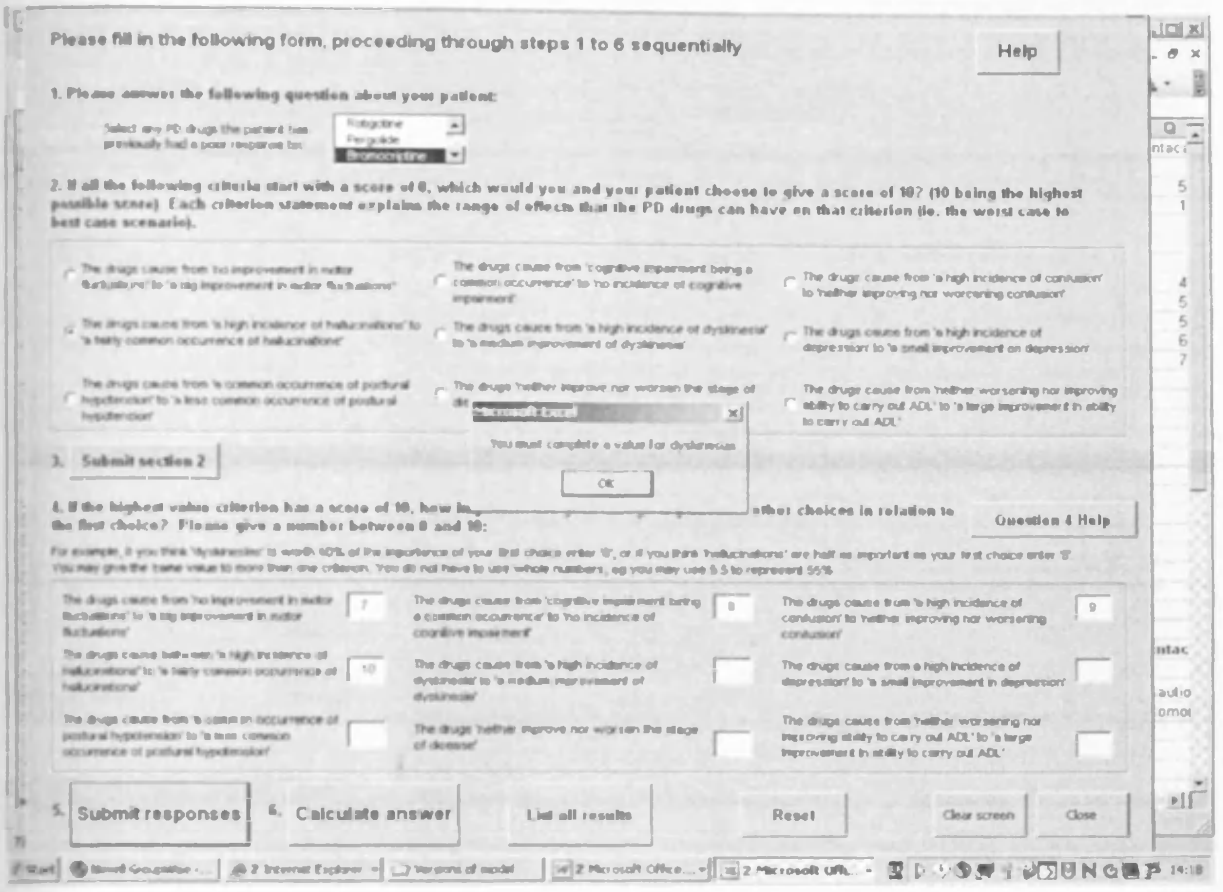


Figure 6.14 Test to see what happens if user only inputs 4 weights in section 4 then clicks 'Submit responses'

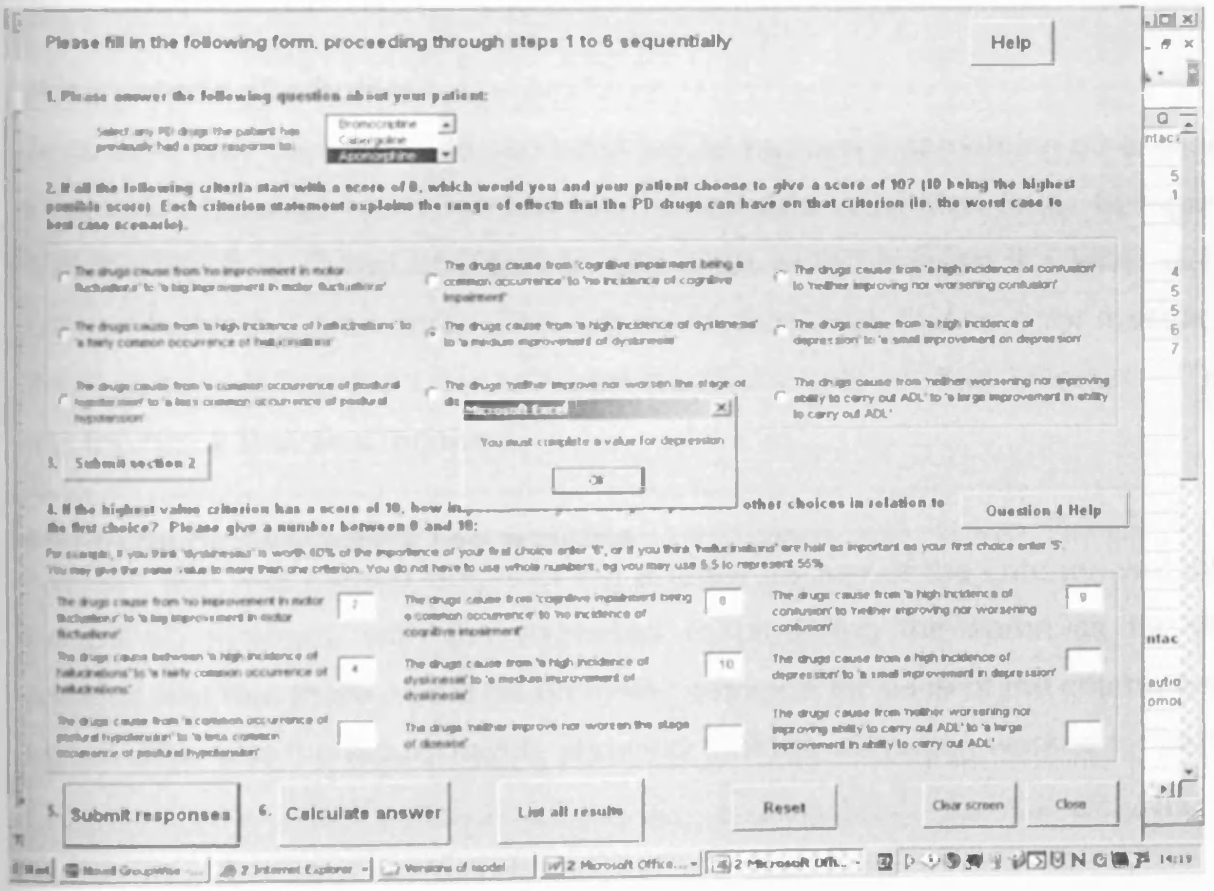
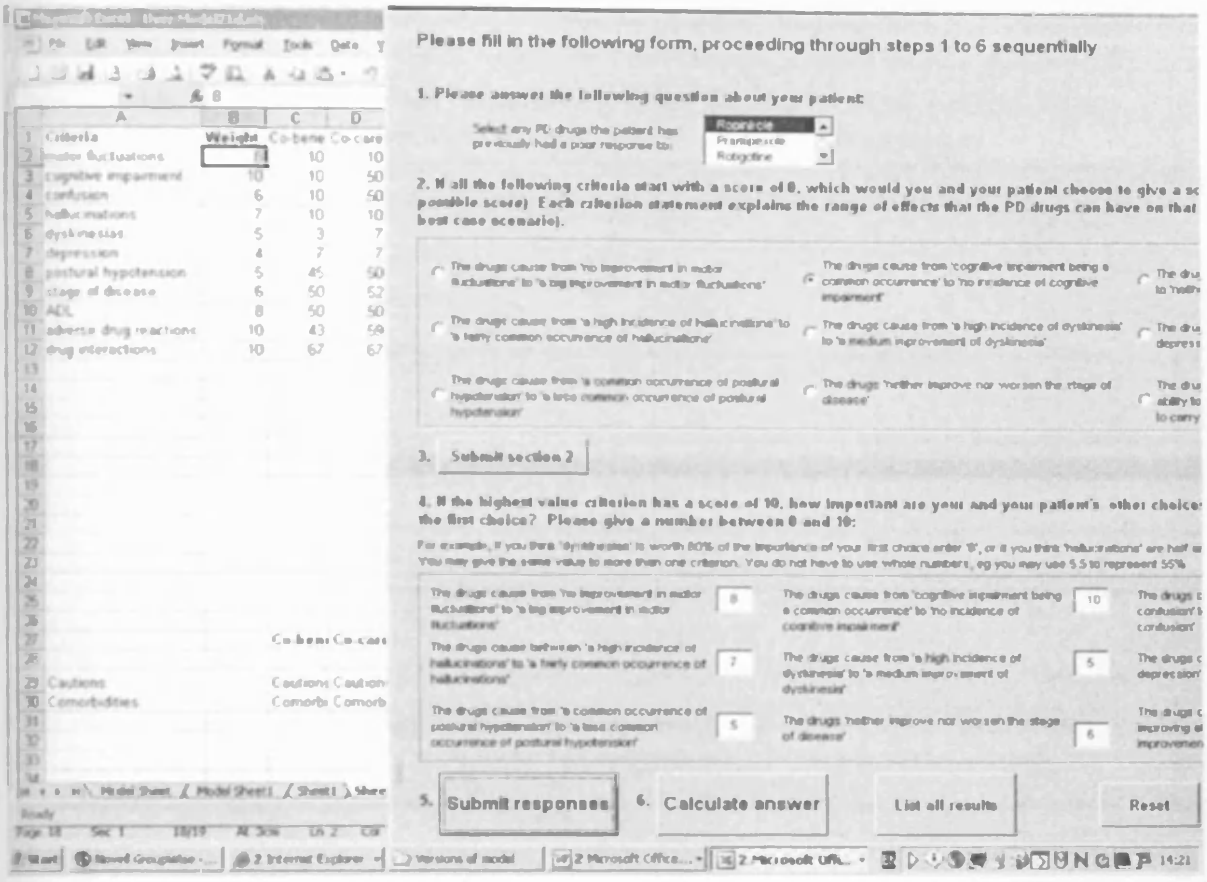


Figure 6.15 Test to see what happens when user inputs values for all the weights in section 4 and clicks 'Submit responses'



showing column B as well as a partial shot of the user form with the weights completed.

Non-numeric characters

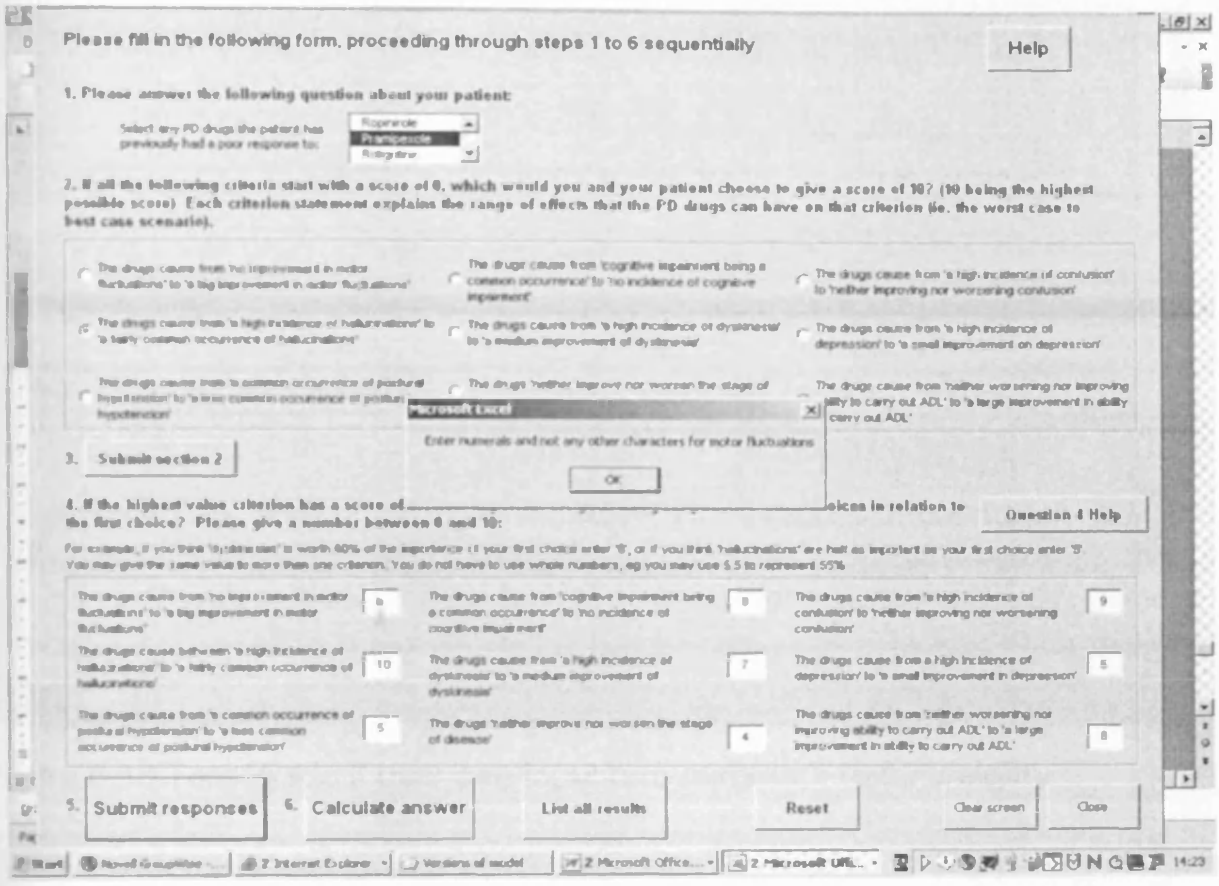
Tests were also carried out to see what would happen if something other than a numeric character were entered for the weights in section four. In Figure 6.16 the result is shown of a test to see what would happen if a letter were inserted instead of a numeral. The expected result was that an error message would appear telling the user to insert numbers only for that criterion. This was the result that was received.

Non-numeric characters two weights

A similar test was carried out inserting a letter for two of the criterion weights instead of numbers, with the expected result being the same as for the previous test that there would be an error message for each of the criteria with letters. This was the actual result, showing that the validation worked for both

criteria. The result for the second criterion with a letter ('hallucinations') is shown in the screenshot in Figure 6.17.

Figure 6.16 Test to see what happens if user inputs a letter instead of a number for a criterion in section 4 then clicks 'submit responses'



Number greater than 10: one weight

A test was next run to see what would happen if a number greater than ten was inserted for one weight. The expected result was that there would be an error message telling the user to choose a number between 0 and ten for that criterion. When the test was run the expected error message was received (Figure 6.18).

Number greater than 10: two weights

Another similar test was run inputting two weights with values greater than ten. The expected result here was that there would be an error message for the first criterion and once 'ok' was clicked there would be a similar error message for the second criterion. This was the result that occurred, with both error messages shown as expected. The result of the second criterion ('depression') is shown in Figure 6.19.

Figure 6.17 Test to see what happens when user enters letters for two criteria in section 4 then clicks 'submit responses'

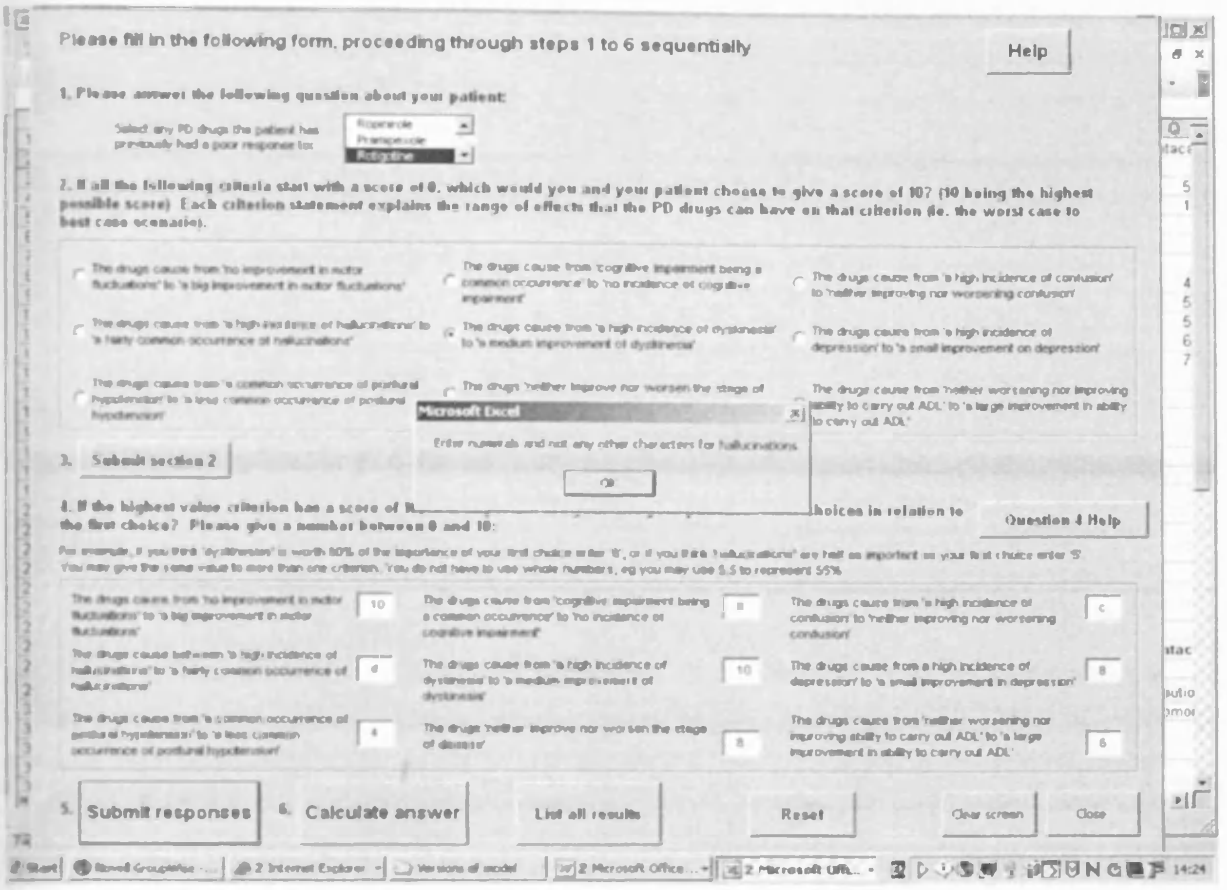


Figure 6.18 Test to see if user can input one number >10 for weight

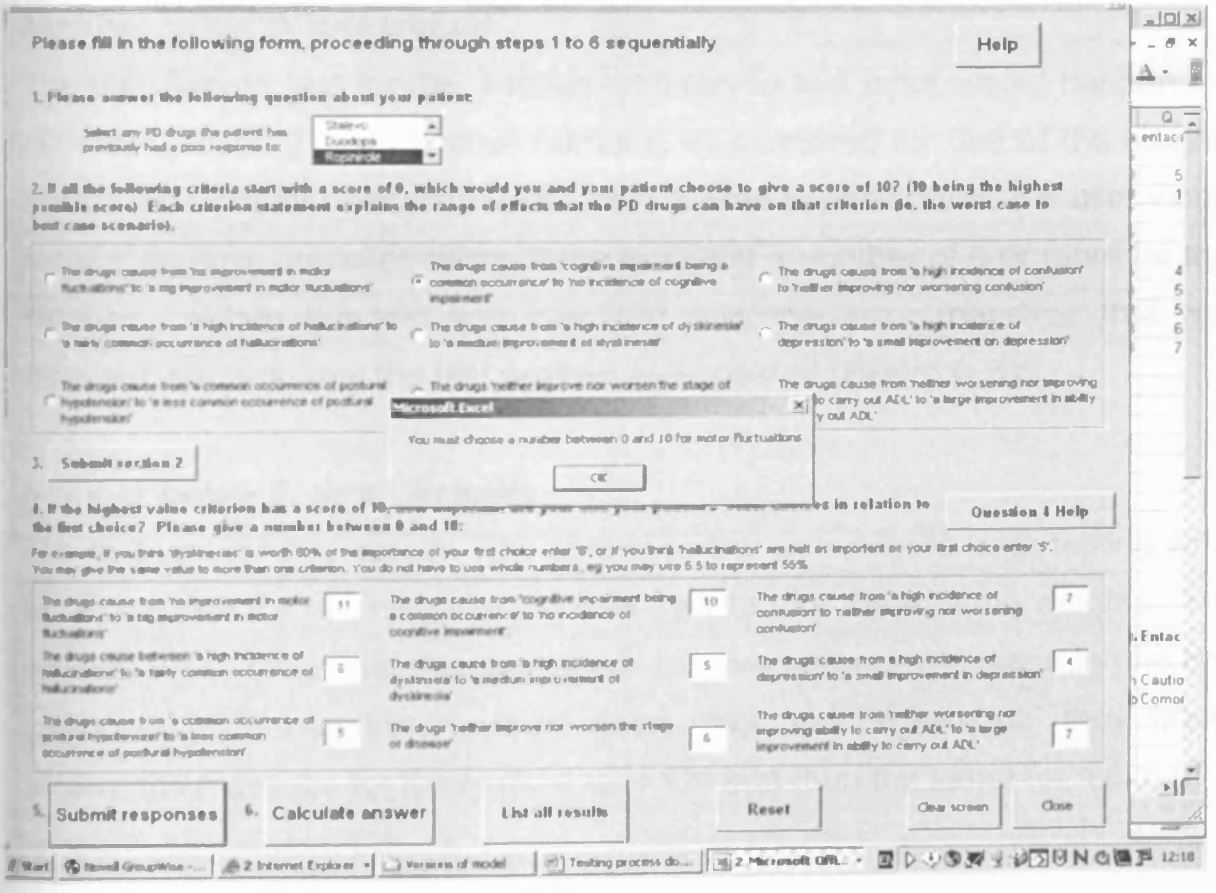
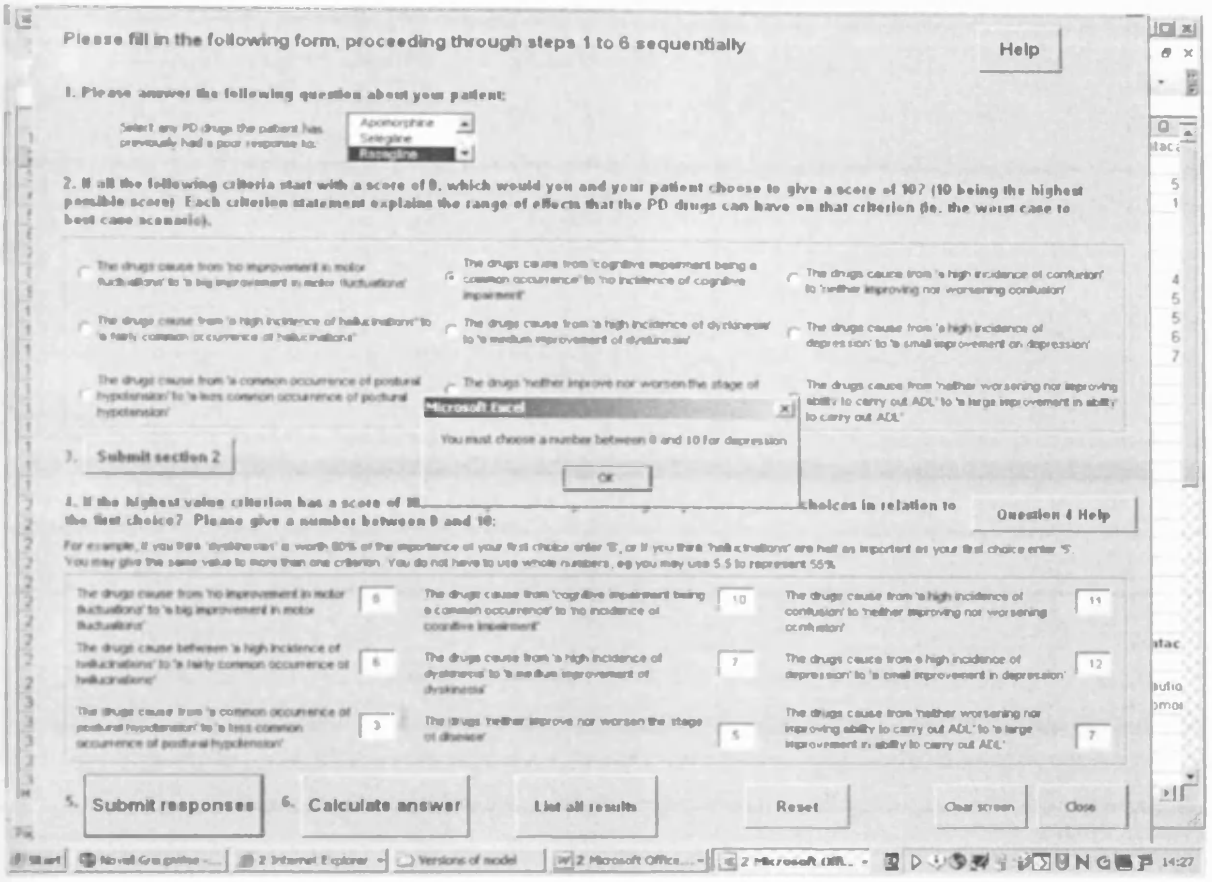


Figure 6.19 Test to see what happens if user enters number >10 for two weights



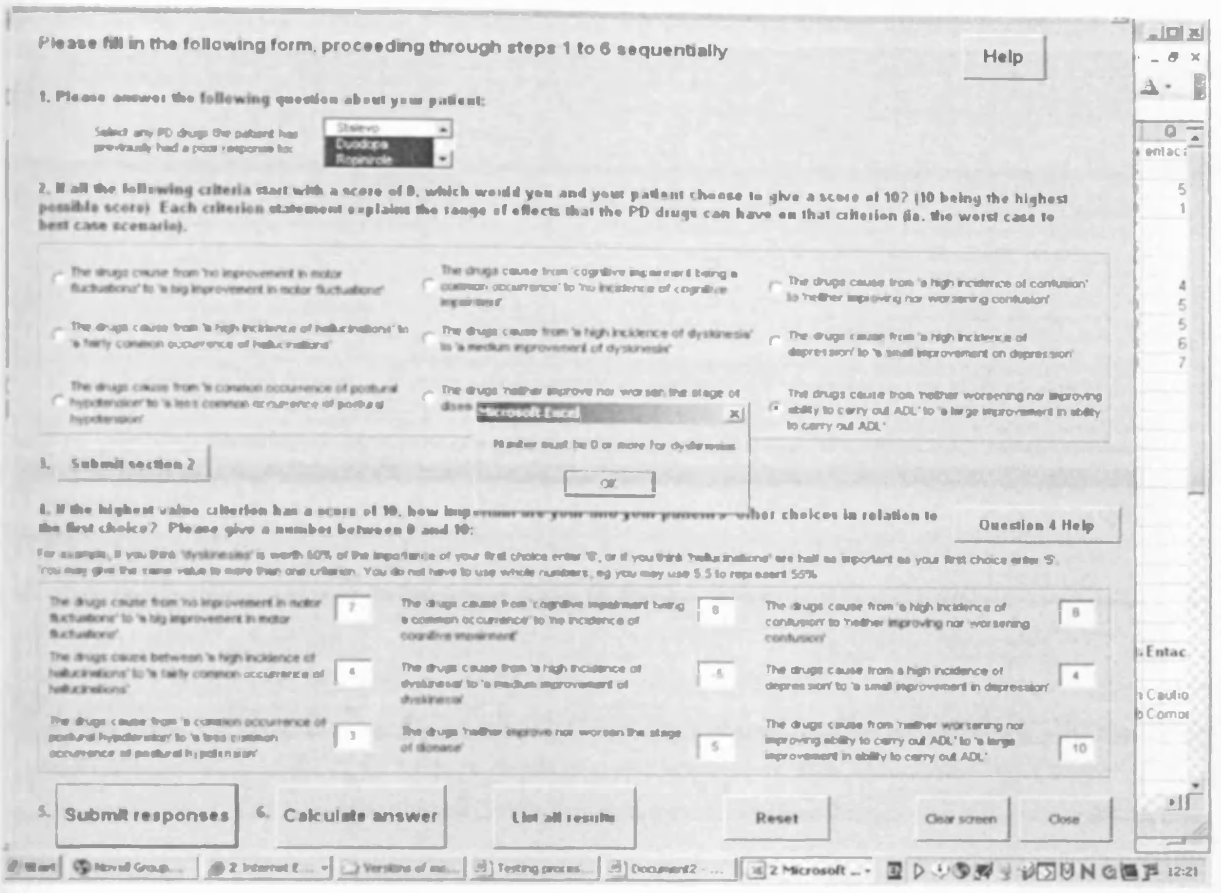
Number below 0: one weight

The penultimate test for this section was run to test what would happen if a number below 0 (i.e. a negative number) was entered for one of the weights instead of a number between 0 and ten. It was expected that the user would receive an error message telling them to select a number of 0 or more for that criterion. When the test was run that was the error message that was received, showing that the test worked as expected (Figure 6.20).

Number below 0: three weights

The last test for this section was similar to the penultimate one, testing what would happen if a negative number was inserted for three of the weights. The expected result was that the user would receive an error message for the first criterion with a negative number; once they had clicked 'ok' they would receive the message for the second criterion and then the same for the third

Figure 6.20 Test to see if user can input a negative number for weights in section 4



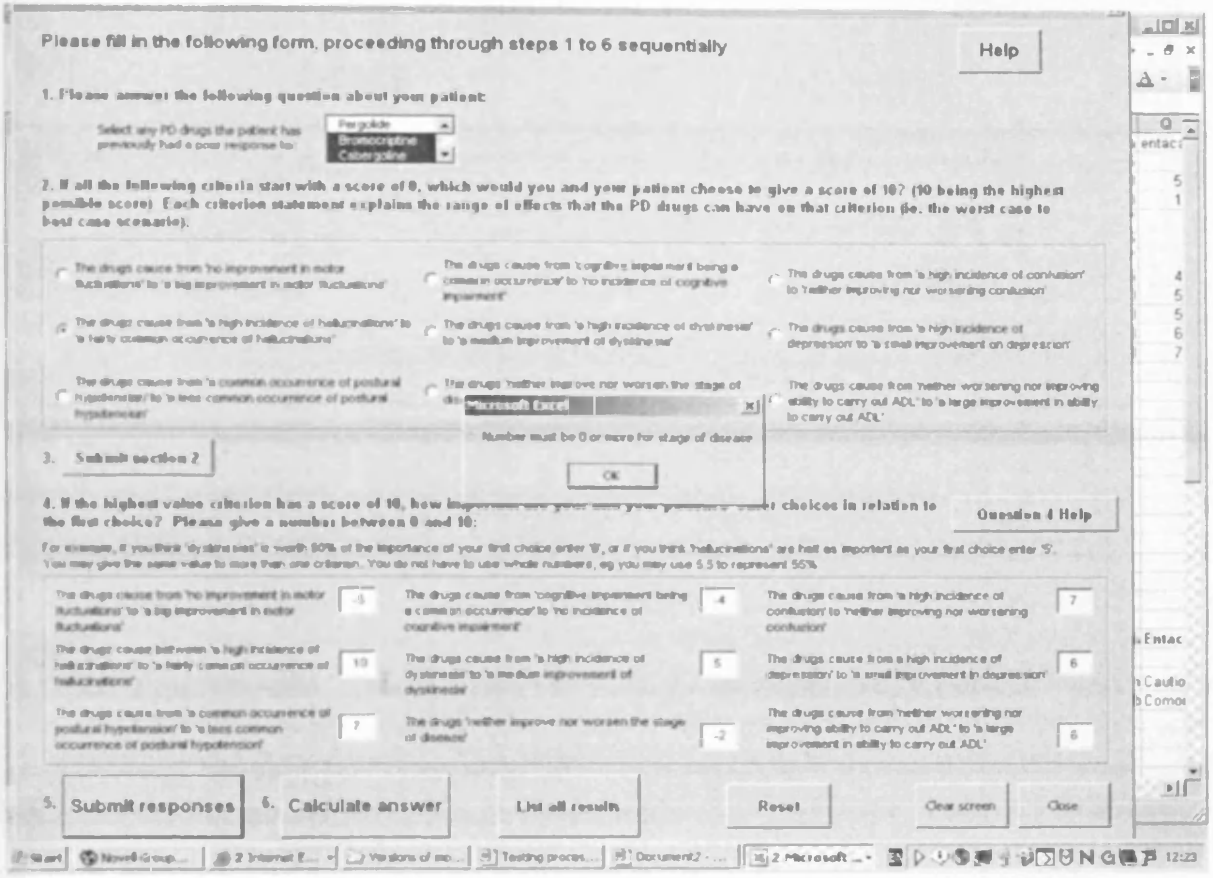
criterion. This was the actual result, showing that the test worked for all three criteria (Figure 6.21).

Calculate answer

Click 'Calculate answer'

The first test in this section looked at what should happen if the user clicked the 'Calculate answer' button. The expected result was for a user form to be returned to the user with the top three results displayed along with their respective cautions and contraindications. Unexpectedly, an error message was returned to the user telling them to complete all the sections before clicking 'calculate answer', even though they had already done so. It was discovered that there was an inconsistency in the code with the 'True' flag, as it was written as 'True' in one place, but as 'TRUE' in another. This was not expected to cause any problems with the execution of the code, but the test showed that it was in fact a problem. The word was changed to read 'True' in both places for consistency and the test was run again. The second run of the

Figure 6.21 Test to see if user can input three negative numbers for weights in section 4



test showed better results, returning the user form to the user as had been originally expected. The unexpected error message is shown in Figure 6.22 and the actual result of the second run of the test in Figure 6.23.

Don't click 'Calculate answer'

The other test in this section examined what would happen if the user did not click 'Calculate answer'. It was expected that there would be no results returned to the user and this was what happened when the test was run (Figure 6.24).

List all results

Click 'List all results'

When the button 'List all results' was clicked it was expected that a message box would be returned to the user with a list of all the drugs returned in the

Figure 6.22 Test to see what happens when user clicks 'Calculate answer' –

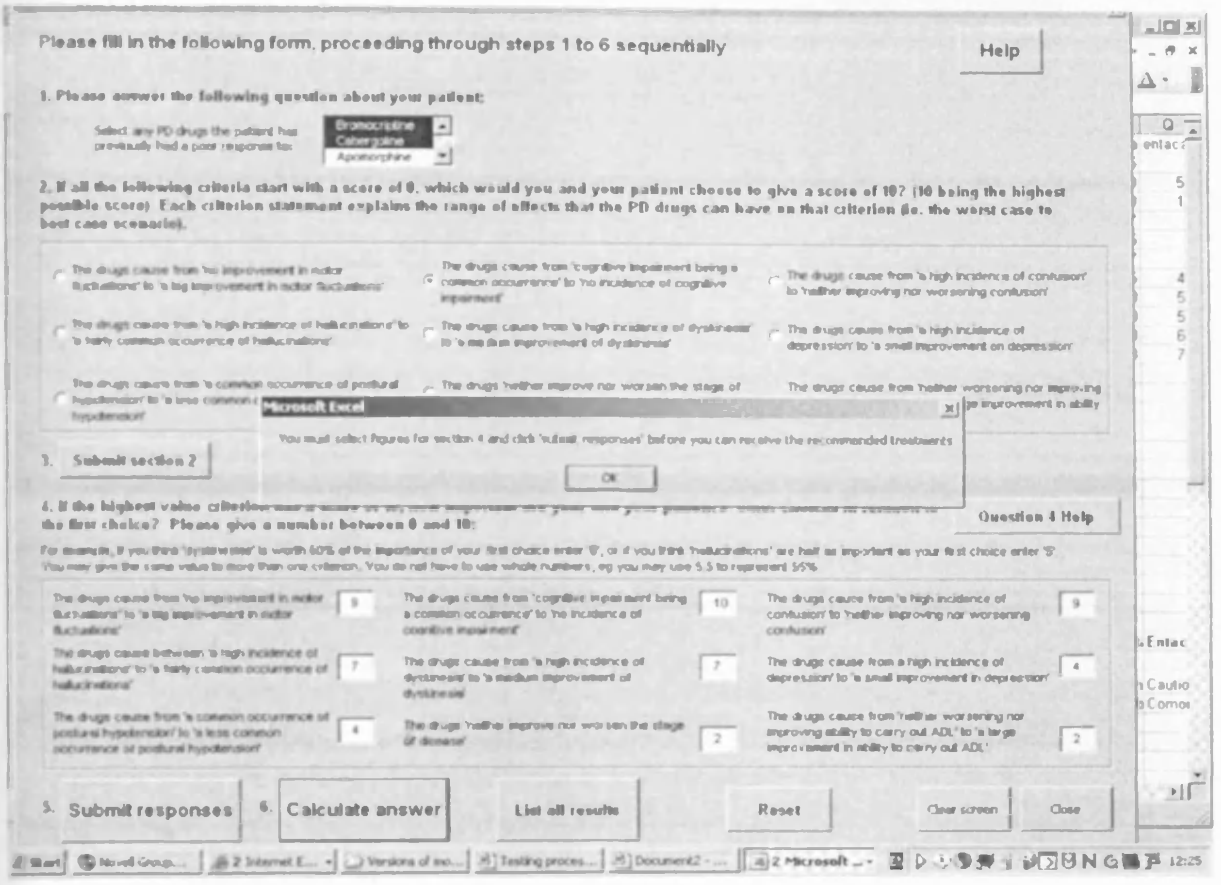


Figure 6.23 Corrected error from 6.22 with test re-run and correct results given

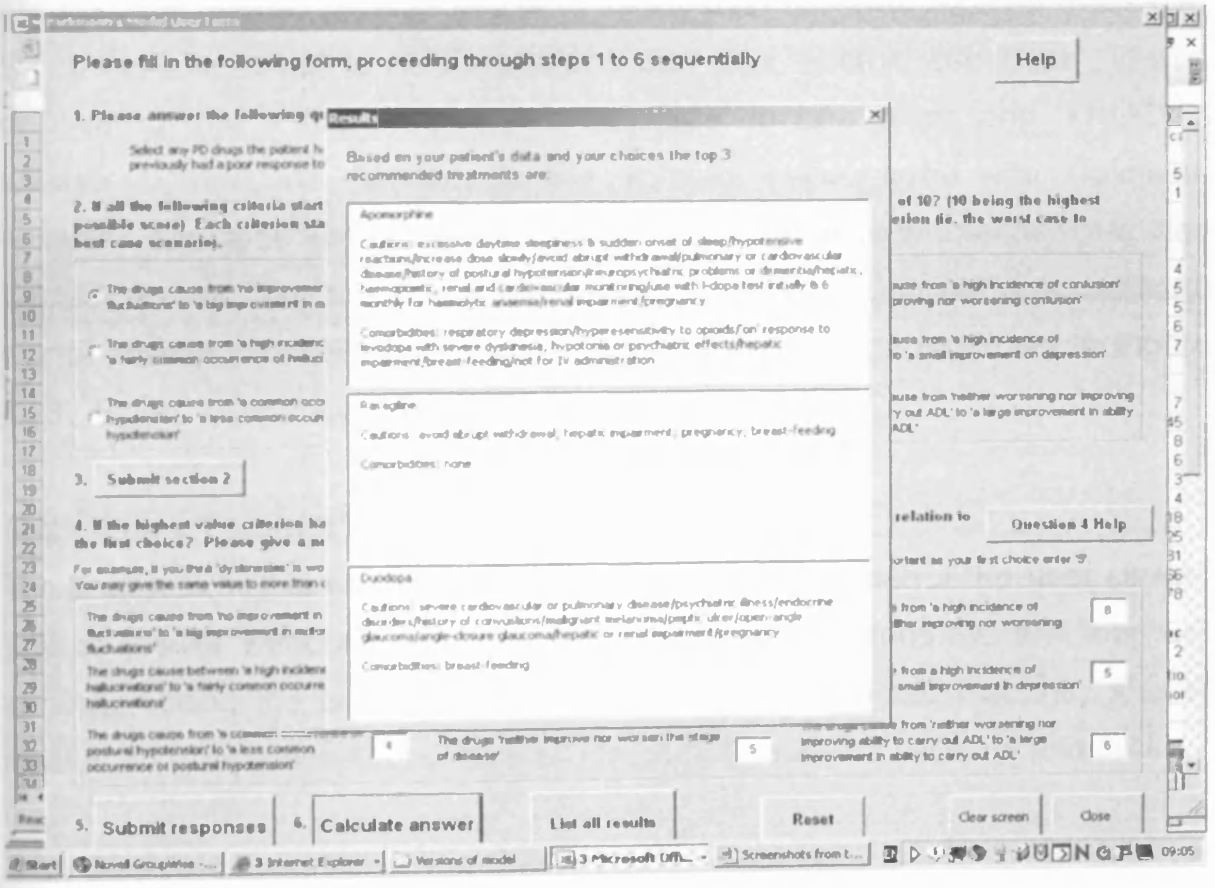
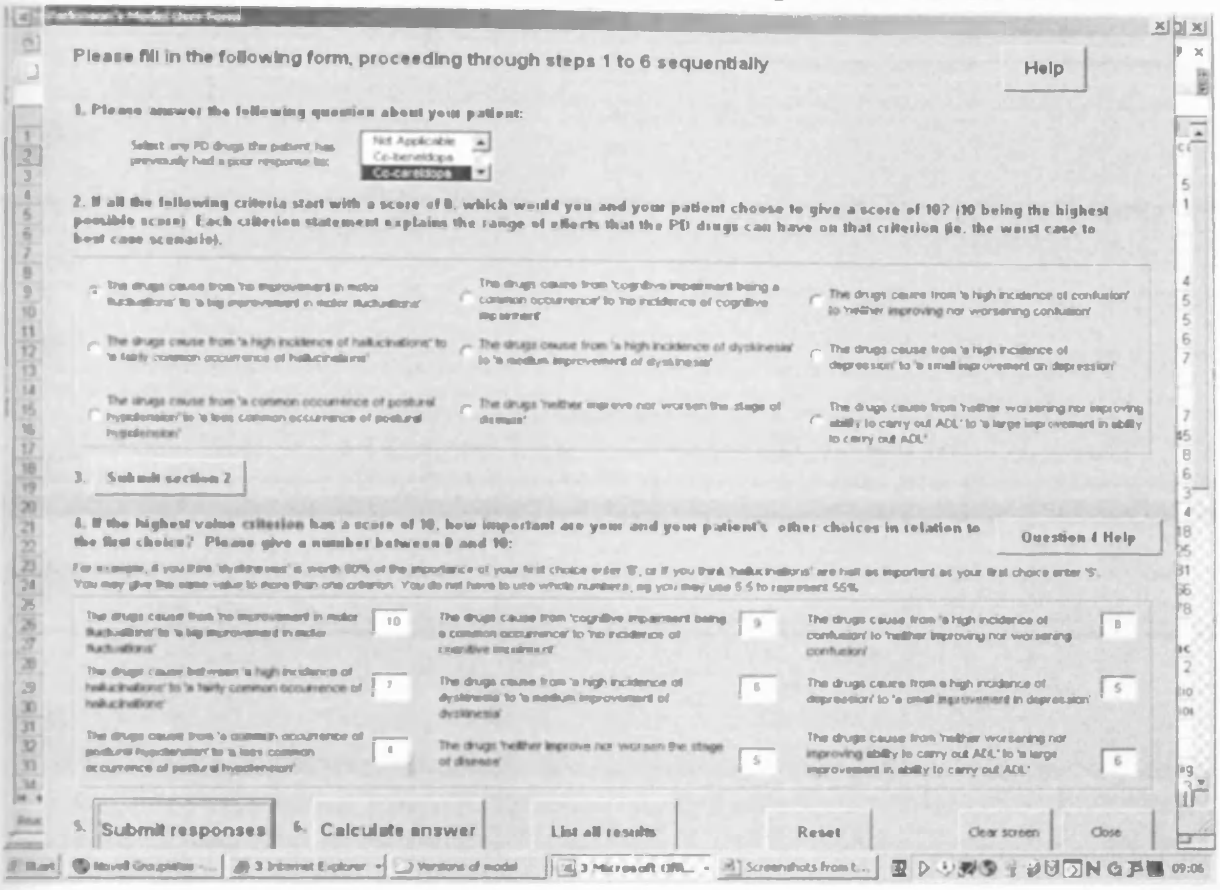


Figure 6.24 Test to show result of user not clicking 'Calculate answer'



order of highest to lowest scoring, alongside their actual result. The result of this test was another unexpected one, as the user received an error message telling them to complete all the sections and click 'submit responses'. It was discovered that a flag was written as 'True' in one place and 'TRUE' in another in the code, similarly to the problem encountered with 'Calculate answer'. The code was corrected so that both flags were written as 'True' and the test re-run. The result was then as originally expected with the message box of results returned to the user. The error message is shown in Figure 6.25. Figure 6.26 shows the corrected results.

Click 'List all results': no data entry

The final test in this section looked at what would happen if the user clicked 'List all results' without having entered any data in sections two and four and without clicking the two 'submit' buttons. It was expected that they should receive an error message telling them to complete all the sections and click

Figure 6.25 Test to show what happens when user clicks 'List all results'

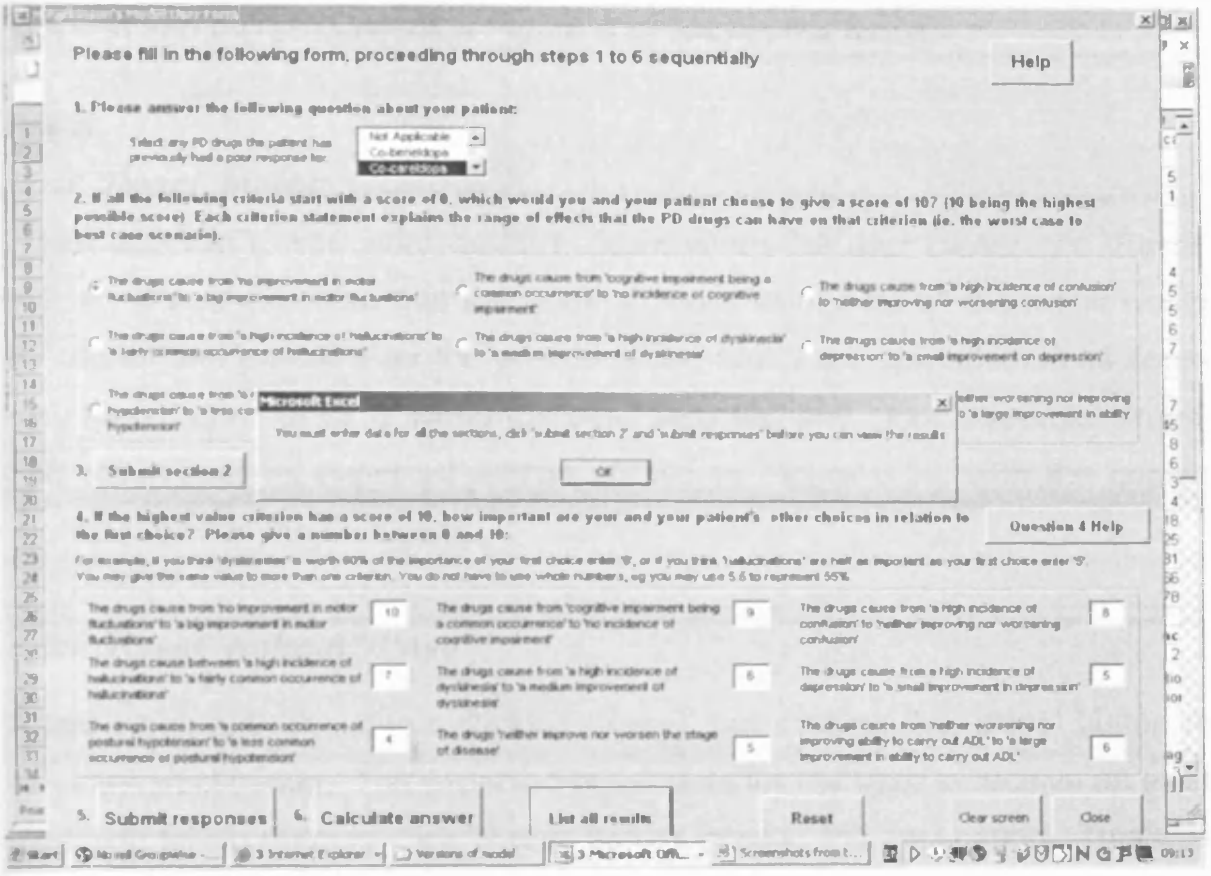
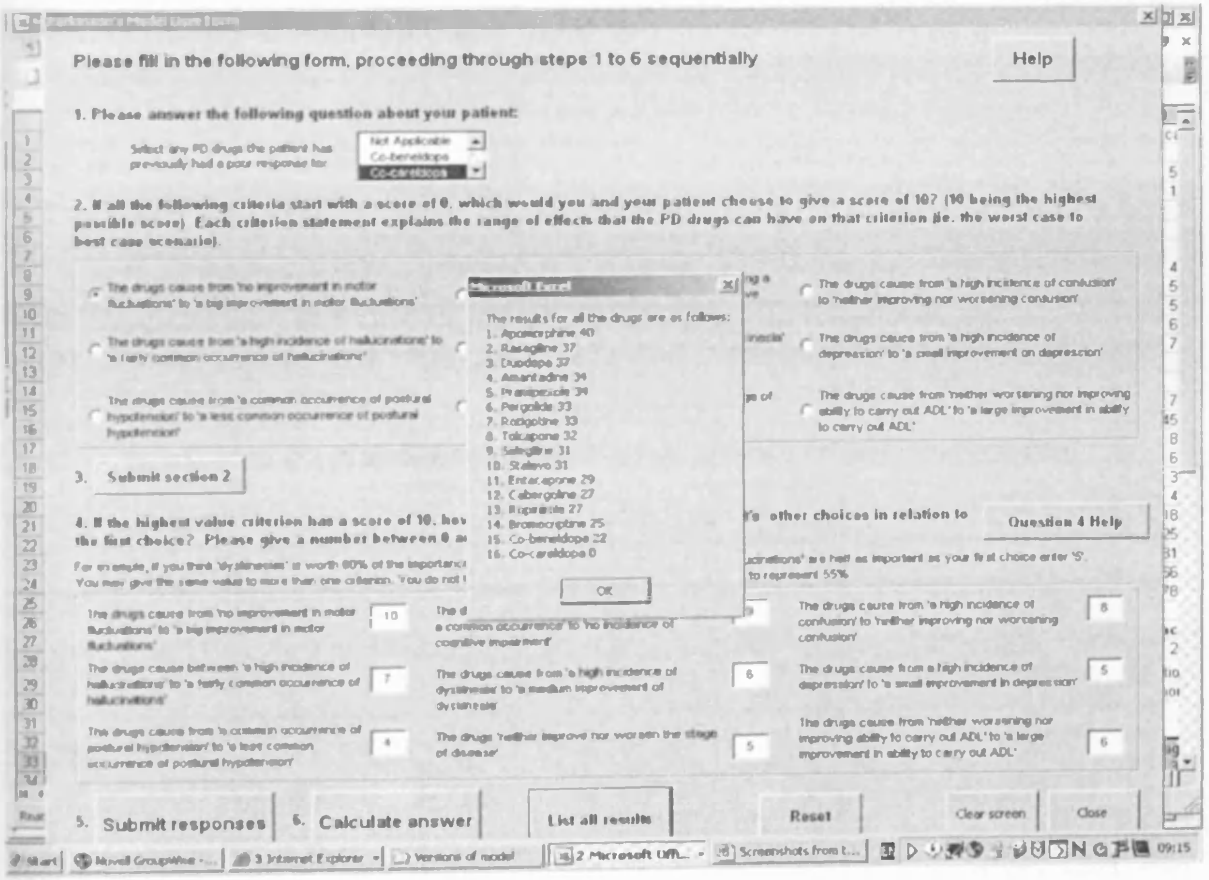


Figure 6.26 Test to show 'List all results' works ok once bug had been corrected



'submit section 2' and 'submit responses'. This was the result that was received and the screenshot in Figure 6.27 shows the result.

Reset

Click 'Reset' button

A test was run to see what would happen when the user clicked the 'Reset' button. It was expected that the original score values for all the drugs would be copied and pasted over the scores at the top of the spreadsheet as some may have been set to '0' when the user selected any 'poor response' drugs. The result was as expected and is shown in Figure 6.28, with the copied scores shown in the blue cells.

Click 'Reset' without 'Close'

A test was next run without clicking 'Reset' but clicking the 'close' button to close the application. The expected result was for the user to receive an error message telling them to click 'Reset' before closing the application. This was the result that was received (Figure 6.29).

Figure 6.27 Test to see what happens when user clicks 'List all results' when haven't entered or submitted any data

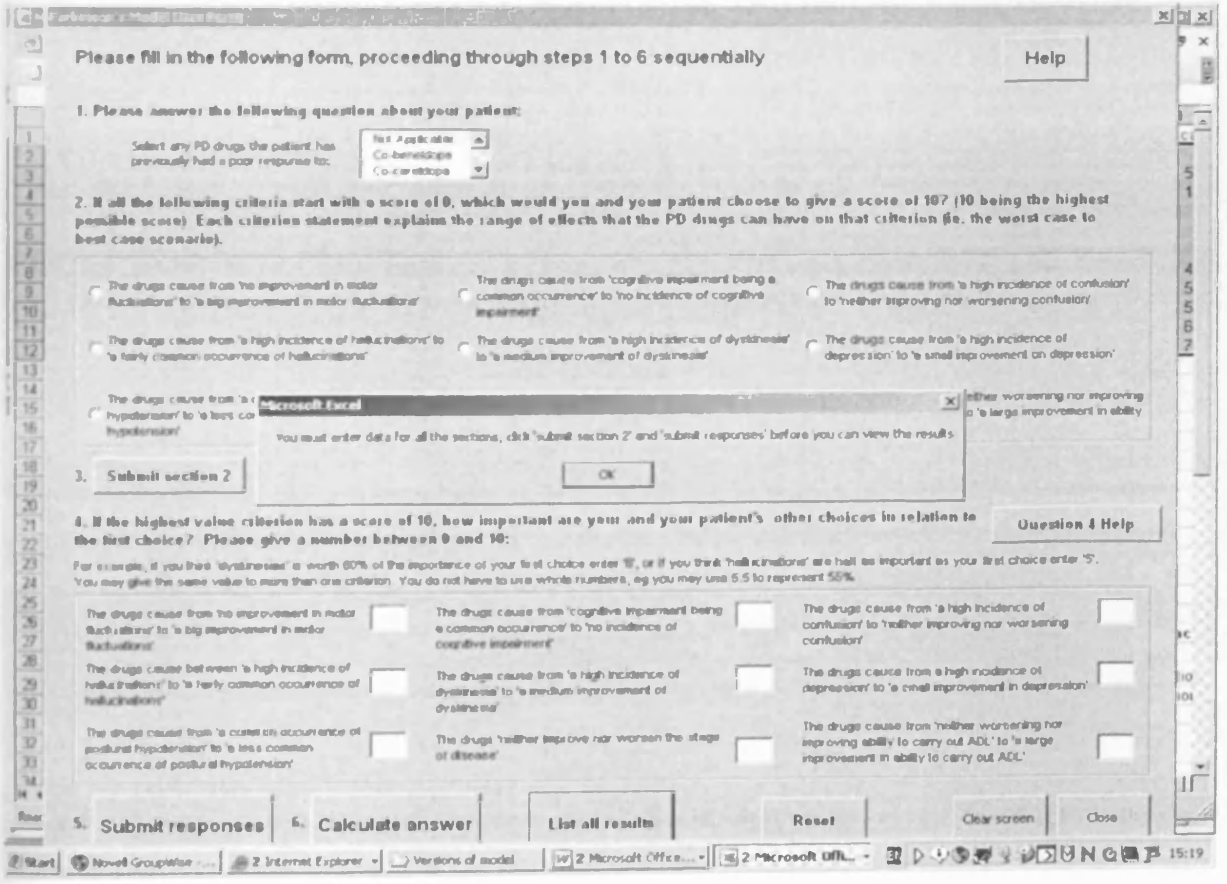


Figure 6.28 Test to see what happens when user clicks 'Reset'

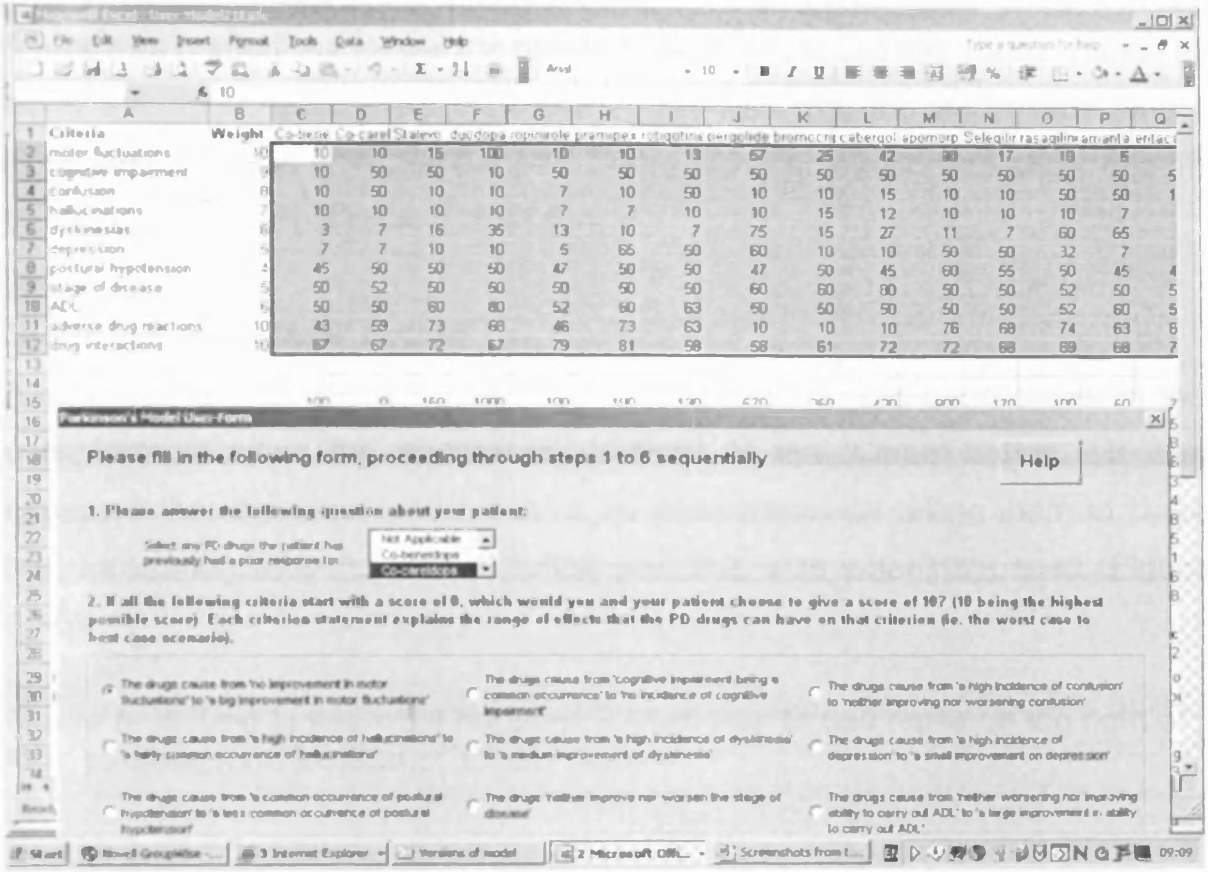
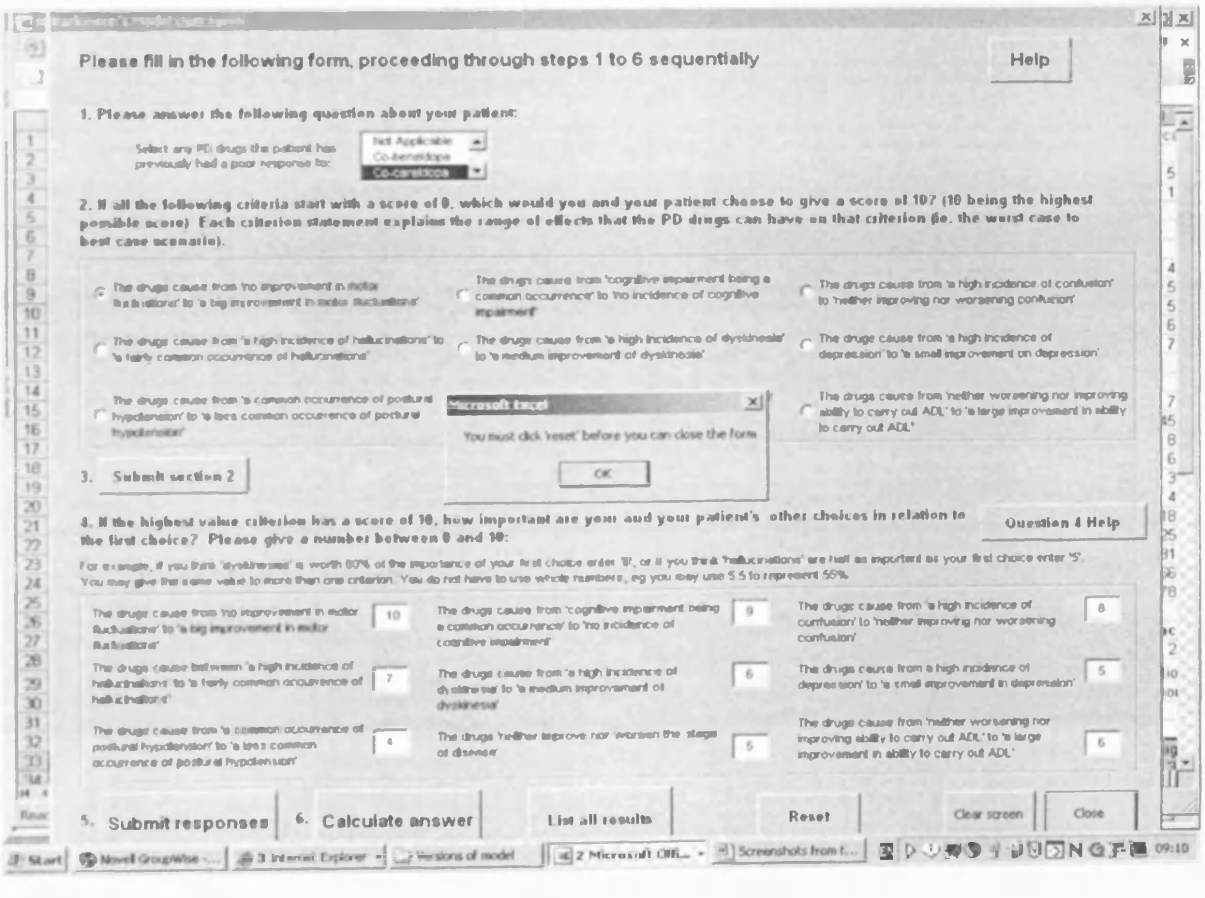


Figure 6.29 Test to show what happens when user clicks 'Close' without having clicked 'Reset'



Close application

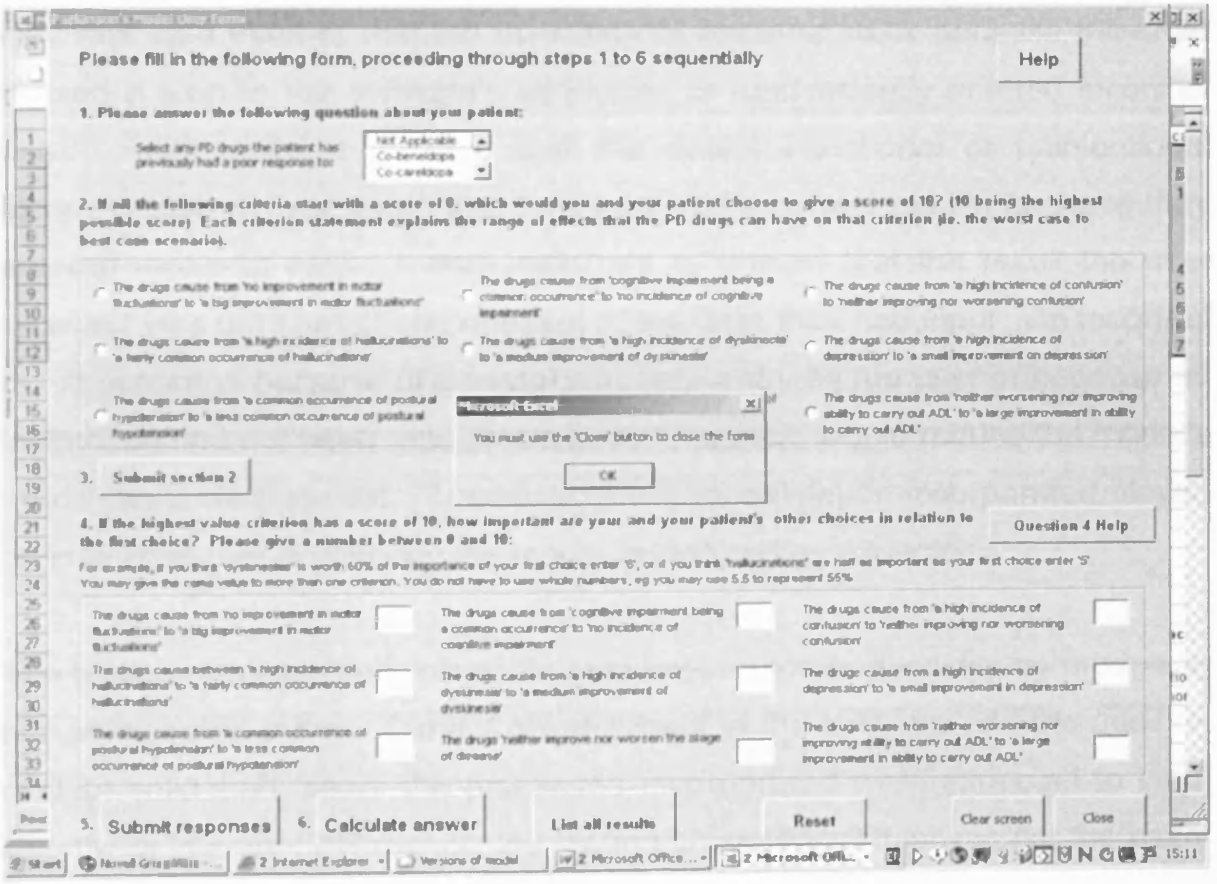
Click 'Close' button

A test was carried out to see the result if the user clicked the 'Close' button to close the application. The expected result was that the application would close and this was what happened. There is no screenshot to show this as the application was of course closed.

Close without 'close' button

A final test was carried out using the cross in the top right-hand corner of the user form to close the application, instead of the 'Close' button. It was expected that the user would receive an error message telling them to close the application with the 'close' button and this was what happened (Figure 6.30).

Figure 6.30 Test to see what happens if user tries to use cross on top right of form to close form instead of 'Close' button



DISCUSSION

In conclusion, a series of data validation techniques was added to the application and a number of tests carried out to validate how well the software performed. The tests on the whole proved successful and showed that all aspects of checking the user had inputted the correct types of data were covered and that the software performed as it should.

Incorporating methods of checking the user's data input proved that the data validation included was pertinent and comprehensive. Many types of data validation were included and were designed to be as thorough as possible so that the user would not be able to intentionally or unintentionally input the wrong data. Accounting for every possible step a user may take can be a difficult process, but as this application was fairly straightforward the user only had a small number of possible options available and it was therefore easier to anticipate what data they may input. It was important to include this step in the testing process to ensure that the program was not affected by the user's incorrect data input or that the user did not become stuck because they had missed a step in the software's sequence or inadvertently entered incorrect data. Additionally, it ensured that the user's intentional or unintentional incorrect data did not mean that they received incorrect results because they entered incorrect data. It was important to ensure that the result the user received was the correct one relevant to the data they had input. An incorrect result occurring because of a mistake in data entry by the user or because an instruction had not been read properly, for instance, would reduce the model's validity as a decision aid. Therefore, the data validation incorporated played an important role in ensuring the model performed as expected.

The testing process itself proved its own importance and validity by producing two unexpected errors. Careful development of the software and the addition of data validation meant the processes incorporated were expected to work exactly as intended. However, the testing showed that this was not the case. Importantly, it was two major parts of the application which did not function as expected and meant the user would not be able to view the results. Detecting

errors such as these was fundamental to ensuring that the model was not effectively made redundant by simple coding errors. The surprising factor was the type of error detected, as in both cases it was simply a problem with a mix of lower and upper case lettering. It had not been expected that this would cause problems with code syntax and in fact both functions had worked adequately during development. However, it was fortunately a simple error to correct and retesting showed that the correction meant the software then worked as expected. This showed that overall testing was a valuable and essential process. Detecting errors showed the necessity of the testing process and that value was gained from carrying out thorough and comprehensive testing. After the testing process the software could then be considered as being 'fit for purpose'.

The application having been thoroughly tested the next stage was to test the application with other users and for them to validate the ease and practicality of use of the whole application. This will be discussed in chapter seven.

SUMMARY

The software developed in chapter five was thoroughly tested to ensure the application worked as was intended.

- Functions were incorporated in the software to ensure the user could only input relevant data types
- Tests were carried out on all aspects of the application to ensure every section worked as was intended
- Two tests showed errors in coding which were easily corrected
- All other tests showed everything worked as expected

CHAPTER 7

Validation of the Model and Computer Decision Support System

INTRODUCTION

In chapter four the model for Parkinson's disease using MCDA was developed, in chapter five the software was developed and in chapter six the software was tested. These two products needed to both be validated. The process of validation shows whether something has met its requirements and is fit for purpose. Therefore, the purpose of the validation carried out in this chapter was to show whether the model and software had met their objectives and whether the model in particular would produce results that would make it suitable for use with Parkinson's patients.

A panel of experts in the field of Parkinson's disease would therefore need to be invited to take part in a validation exercise to test the model and associated software. These experts would need to be practitioners who were regularly in contact with Parkinson's disease patients and had substantial years of experience of treating this group of patients. This would give the panel the expertise to be able to assess a number of factors that would determine the suitability and usefulness of the model and software. For example, whether the model included all the necessary aspects and if the weighting methodology was apt.

This chapter will therefore report on the validation process that was carried out.

METHODS

Sensitivity Analysis Perspectives

Sensitivity analysis is carried out to investigate whether preliminary conclusions are robust or if they are sensitive to changes in certain aspects of the model. Changes can be made to investigate the significance of any information that may be missing, to explore any effect a decision maker's uncertainty about their values and priorities may have or to give a different perspective on the problem. Alternatively, there may be no practical or psychological motivation for changing values; the analysis may be led by a

wish to test the robustness of the results (Belton and Stewart, 2001). There are three different perspectives on sensitivity analysis:

Technical perspective:

From a technical perspective sensitivity analysis is the objective examination of the effect of changes in input parameters on the output of a model. The input parameters are the value functions, scores and weights that have been determined by the decision makers. The output is the synthesis of this information – the overall evaluation of alternatives, for example. The technical sensitivity analysis determines which, if any, of the input parameters have a critical influence on the evaluation overall. For example, a small change in a criterion weight or an alternative's score may affect the overall preference order (Belton and Stewart, 2001).

Individual perspective:

The function of a sensitivity analysis from an individual's perspective is to allow them to test their intuition and understanding of the problem. For example, whether they feel comfortable with the results of the model and if not, why not? They can also use the analysis to look at whether important criteria have been overlooked (Belton and Stewart, 2001).

Group perspective:

The function of a sensitivity analysis in a group context is to allow the exploration of alternative perspectives on the problem, which are often captured by using different sets of criteria weights (Belton and Stewart, 2001).

Sensitivity Analysis Perspectives Used

Both the individual perspective and the group perspective were used for this validation. The individual to give panellists a chance to express their own views and opinions on the model and its results, and the group perspective to try the use of different weights to see how this affected the results the model produced, for example if panellists received different recommendations from having entered different weights to each other.

The Expert Panel

A group of expert practitioners in the field of Parkinson's disease was selected from the Cardiff and Vale, Bridgend, Swansea, Newport and Powys areas to take part in the validation exercise. A preliminary panel of practitioners was invited to the initial validation: two consultant geriatricians and one Parkinson's disease nurse specialist, all from the Cardiff and Vale area. Two subsequent validation exercises were planned to take place at later dates, each with a further panel of three practitioners selected from consultant geriatricians, consultant neurologists and Parkinson's disease nurse specialists from the other areas of south and mid-Wales mentioned above. The second panel would comprise a geriatrician and PD nurse specialist from Bridgend and a neurologist from Swansea and the third panel two neurologists from Newport and a geriatrician from Powys.

Date And Location

The preliminary validation was held on Monday 29 September 2008 at Cardiff University, and took place over an afternoon. The validation exercise was held in a specialist training room, which was part of the Information Services department of Cardiff University, and which was chosen for its provision of IT facilities and layout. The panel members were seated next to one another near the front of the room, each in front of their own desktop PC. The panel members all faced the leader of the validation session. A projector screen at the front of the room showed the details of the validation leader's screen. Also present were Professor Sam Salek of the Welsh School of Pharmacy, who followed the details of the session and Dr Andy Skyrme of the Information Services Department, who provided IT support.

Points Covered By The Expert Panel

- whether or not the model included all the aspects, i.e. criteria, they would need to consider in treating a PD patient
- if the scoring effectively reflected the way they considered each drug would perform against the given criteria

- if the weighting involved, i.e. swing weighting, was a practical methodology to be used for choosing drug treatments for Parkinson's patients
- if the results produced reflected their own choice of treatments for each patient
- their thoughts and opinions on why different results were produced by the model to those they had chosen, if that was the case
- whether the software was quick and easy to use

Validation Procedure

Aims and objectives of work

The aim and objectives of the PhD as a whole were outlined to the panel.

Aim:

- To develop an electronic decision aid to help practitioners choose the most effective drug treatments for Parkinson's disease

Objectives:

- To develop a model using multi-criteria decision analysis for Parkinson's disease
- To develop a computer system to implement the model's functions

Methodology used

An explanation of the methodology used, i.e. MCDA, was given to the panel, detailing each stage of the work that had been carried out. This was delivered through a PowerPoint presentation.

Patient scenarios

The panel were given details of three different patient scenarios. These were taken from the Welsh Movement Disorder *e*Network, a database of movement disorder patients in South Wales, using details of three patients on the database. All data presented to the panel were completely anonymised.

Patient Scenario 1:

Patient 1 Symptoms:

- Slight dizziness: BP 142/91 sitting, 158/82 standing
- Occasional hallucinations
- Minimal PD symptoms – rigidity, bradykinesia
- Quite active – rides a bike
- Constipation and dreams since on pramipexole

Current medication:

- Madopar 125mg 1x QDS
- Madopar CR 125 1x nocte
- Pramipexole 1mg 1x TDS
- Voltarol 50mg 1x PRN

Previous medication not tolerated:

- Stalevo – bloated, loose stools, wind, nauseous
- Cabergoline – dizziness, SOB

Patient Scenario 2:

Patient 2 Symptoms:

- Slow in mornings and freezes
- Oro-facial dyskinesias. Sinemet 110 reduced by one tablet to improve dyskinesias but mobility deteriorated
- Voice softer and quieter, unable to hold long conversations
- Drags left leg

Current medication:

- Co-careldopa 125mg x1 nocte
- Co-careldopa 110mg x2 TDS
- Pergolide 1mg x1 TDS
- Domperidone 10mg x1 TDS
- Oxybutynin 5mg x1 OD

Previous medication not tolerated:

- None

Patient Scenario 3:

Patient 3 Symptoms:

- Increasing "offs", 4 bad days per week
- Huge loss of energy
- Sleep is variable: no dreams or nightmares but occasional transient hallucinations
- Mood is ok
- Increased sweating during "offs"

Current medication:

- Madopar 62.5mg dispersible x1 PRN
- Stalevo 150mg 1x 6 times per day
- Pramipexole 0.7mg 1x 5 times per day
- Rasagiline 1mg 1x OD

Previous medication not tolerated:

- Sinemet 110 – motor control worse
- Zelapar 1.25mg – lack of effect
- Selegiline 1.25mg – dyskinesia
- Ropinirole 2mg TDS – nausea and vomiting
- Entacapone 200mg – nightmares/sleep disturbance

Panel's choice of treatments

The panel were given the three scenarios in turn and asked to make their choice of treatment(s) for each scenario. Each panellist made their own recommendation initially, which was handed to the facilitator and the results read out anonymously. The panel then had to try to reach a consensus on the treatment(s) they would recommend. If a consensus could not be reached the

panel's individual choices were recorded. All the recommendations were recorded on a white board in the room for each patient scenario.

Model's recommended treatments

Having chosen their own treatments, the panel were then taken through the user form designed in VBA, referred to in the validation exercise as an 'electronic prescribing support system (EPSS)'. Each section of the form was explained to them. They completed the first section of the form individually for patient scenario one, selecting any drugs the patient had had a poor response to. The methodology for choosing the weights, swing weighting, was then explained to them and the panel each selected their own weights for patient one. They then submitted their responses by clicking on the 'Submit section 2' button and the 'Submit responses' button and clicked 'Calculate answer' to receive their three recommended treatments. The results each panellist had received were entered on the white board and discussed. The procedure was then repeated for the subsequent two patient scenarios.

Comparison of results

The results from the panellists' choices and the results the model had recommended were compared and discussed for each patient scenario. The panel members were asked to comment on whether they thought the results the model had produced were unexpected, and if so why they thought the model may have produced such results. They were also asked to discuss any changes or improvements they thought could be made to the model to produce different results, if this was deemed necessary.

Evaluation questionnaire

As a final part of the validation exercise the panel members were given a short questionnaire to complete eliciting their views on both the model and EPSS. The first section of the questionnaire, section A, evaluated their opinions on the criteria and scores used in the model, the ease of the methodology used to ascertain the weights and their opinions of the model overall. Section B questioned them on their opinions of the EPSS, as to how easy and practical they found it to use and whether its speed of use was

acceptable. They were also asked whether they would recommend it to colleagues or use it themselves in a clinic situation. Panellists were given space in appropriate questions to add their own comments. The questionnaire is shown in Figure 7.1.

RESULTS

The results of the validation exercise will be presented in three different parts. Part one will address the validity of the model and EPSS, part two the panel's general comments and suggestions and part three the applicability and practicality of the model and EPSS.

Part I – Validity Of The Model And EPSS

Panel's choice of treatments

Patient scenario one

The recommendations the panellists made individually for patient one followed two options: to make no drug changes or to discontinue the pramipexole. On discussion the group agreed as a consensus that both these options should be considered.

Patient scenario two

The panellists were in agreement on only one aspect of treatment for the second patient, which was to discontinue pergolide. No consensus could be reached on any other options for this patient, so all the possible options were considered. These included adding a non-ergot dopamine agonist, adding Stalevo, increasing the co-careldopa and to consider adding amantadine.

Patient scenario three

The panellists all thought that patient three was the most complicated scenario of the three. Each panellist described different options for treatment. These were: defer to other PD experts, consider increasing pramipexole if the patient was depressed; increase stalevo and consider an apomorphine trial; increase the dose of dispersible Madopar in the early part of the day, consider

Figure 7.1 Questionnaire used to measure applicability and practicability of the model and EPSS

Evaluation of Parkinson's disease model and Electronic Prescribing Support System (EPSS)

Please complete both sections of the questionnaire selecting the response which you feel is most appropriate for each question:

A. Parkinson's disease Model

1. How do you rate the criteria chosen? Please choose one option

Very good	Good	Fair	Poor	Very poor
❑	❑	❑	❑	❑

2. Do you think any important criteria have been missed out?

Yes	No	Not sure
❑	❑	❑

3. How do you rate the way the drugs have been scored against the criteria?

Very good	Good	Fair	Poor	Very poor
❑	❑	❑	❑	❑

4. How do you rate the ease or difficulty of weighting the criteria?

Very easy	Easy	Fair	Difficult	Very difficult
❑	❑	❑	❑	❑

5. Do the weights need rewording to improve their clarity?

Yes	No	Not sure
❑	❑	❑

If yes, please give any suggestions here:

6. What is your opinion of the model overall?

Very good	Good	Fair	Poor	Very poor
❑	❑	❑	❑	❑

7. Are there any amendments you think could be made to improve the model?

Yes	No	Not sure
❑	❑	❑

8. Do you think this is a suitable methodology for use in PD?

Yes	No	Not sure
❑	❑	❑

Please give details:

9. Would you use this model in clinic yourself or recommend it to colleagues to use?

Yes ❑ No ❑ Not sure ❑

Please give details, for example, would you use it yourself for difficult cases only, would you recommend it for colleagues:

B. Software (EPSS)

10. How easy did you find the EPSS to use? Please tick one option

Very easy ❑ Easy ❑ Fair ❑ Difficult ❑ Very difficult ❑

11. Are there any amendments you think could be made to the EPSS to make it easier to use?

Yes ❑ No ❑ Not sure ❑

Please give any suggestions here:

12. How well do you think the questions are explained on the EPSS?

Very well ❑ Well ❑ Fair ❑ Poorly ❑ Very poorly ❑

13. How quick was the EPSS to use?

Very quick ❑ Quick ❑ Fair ❑ Slow ❑ Very slow ❑

14. How would you rate your own knowledge and experience of computers?

Very good ❑ Good ❑ Fair ❑ Poor ❑ Very poor ❑

15. Would you be happy to use the EPSS in your clinic or to recommend it to colleagues to use?

Yes ❑ No ❑ Not sure ❑

Please give any details:

the timing of tablets and take them before rather than after meals. Much discussion of these options ensued, with consensus being difficult to reach. Eventually the panellists agreed to increase the levodopa, in whatever format, and to consider a trial of apomorphine.

The panel's overall decisions for the three patient scenarios were:

- Patient 1: discontinue pramipexole, no change of treatment
- Patient 2: discontinue pergolide, add a non-ergot dopamine agonist, add stalevo, increase co-careldopa, consider adding amantadine
- Patient 3: increase the levodopa, consider a trial of apomorphine

Model's recommendations

Patient scenario one

All the panellists opted to give the highest weight of ten to the criterion 'Activities of daily living', one of the nine criteria defined in chapter three which needed to be weighted. The remaining two criteria defined in chapter three, 'drug interactions' and 'adverse drug reactions' were pre-weighted, as defined in chapter four. The other weights the panel chose varied from panellist to panellist, with some degree of agreement between them on some of the criteria, such as similar choices for 'hallucinations' and 'postural hypotension' but no consensus for any of the criteria. The results of the weights the panel chose are shown in Table 7.1.

Table 7.1 Panellists' weights for patient scenario one

Criterion	Panellist one	Panellist two	Panellist three
Hallucinations	7	8	9
Postural hypotension	7	9	8
Stage of disease	5	1	1
Confusion	5	6	2
Dyskinesia	4	2	3
Depression	3	3	4
Cognitive impairment	2	5	6
Motor fluctuations	0	4	5
Activities of daily living	10	10	10

Despite the differences in the weights chosen by the panellists the results that the model produced were very similar for each of the panellists. None of the panellists had identical top three recommended treatments to any of the other panellists, but the same drugs were recommended overall, with only amantadine being recommended for one panellist and not the others. The model's recommended treatments for patient one are shown in Table 7.2.

Table 7.2 Model's recommended treatments for patient scenario one

	Panellist one	**Panellist two**	**Panellist three**
Drug 1	Rasagiline	Apomorphine	Apomorphine
Drug 2	Amantadine	Rasagiline	Duodopa
Drug 3	Pramipexole	Duodopa	Pramipexole

Patient scenario two

Again, the weights chosen by the panellists were quite different, although there were similarities between panellist two and panellist three and all three panellists gave the same criterion, 'Activities of daily living' the highest weighting (Table 7.3).

Table 7.3 Panellists' weights for patient scenario two

Criterion	**Panellist one**	**Panellist two**	**Panellist three**
Hallucinations	2	7	8
Postural hypotension	5	8	8
Stage of disease	5	2	3
Confusion	6	6	5
Dyskinesia	9	4	3
Depression	2	3	4
Cognitive impairment	4	5	4
Motor fluctuations	6	5	6
Activities of daily living	10	10	10

The results provided by the model were perhaps quite surprising, as panellists two and three had exactly the same results, although their weights were slightly different. Panellist one had chosen very different weights to the other

two, but two of the top three recommended treatments were the same for panellist one as for the other two panellists. The third recommendation, amantadine, was however different to the other drugs recommended. However, there was little difference overall, despite the difference in weights chosen. The model's recommended treatments for patient scenario two are shown in Table 7.4.

Table 7.4 Model's recommended treatments for patient scenario two

	Panellist one	**Panellist two**	**Panellist three**
Drug 1	Duodopa	Apomorphine	Apomorphine
Drug 2	Rasagiline	Duodopa	Duodopa
Drug 3	Amantadine	Rasagiline	Rasagiline

Patient scenario three

The weights chosen by the panellists for patient scenario three were quite distinct from each other. All panellists again gave their top weight to the same criterion, 'Activities of daily living' and all the panellists gave the same weight, '9' to 'hallucinations', but the similarities ended there. One panellist, panellist three, gave the same weight to all the criteria bar 'Activities of daily living'. There were similarities between panellists one and two on some of the criteria, namely 'postural hypotension', 'stage of disease' and 'motor fluctuations', whilst other criteria such as 'dyskinesia' and 'depression' were close in the weights chosen although the figures were different. Two criteria, 'confusion' and 'cognitive impairment' were scored very differently between panellists one and two, with an even larger difference between the weights chosen by panellists one and three. The panellists' weights are shown in Table 7.5.

Despite the differences in weights chosen by the panellists the model still recommended the same top treatment for all three panellists, namely 'apomorphine' (Table 7.6). The second and third recommended treatments for all three panellists were 'Duodopa' and 'rasagiline', although 'rasagiline' was the second drug and 'Duodopa' the third drug for panellists two and three

Table 7.5 Panellists' weights for patient scenario three

Criterion	Panellist one	Panellist two	Panellist three
Hallucinations	9	9	9
Postural hypotension	5	5	9
Stage of disease	5	5	9
Confusion	2	8	9
Dyskinesia	4	5	9
Depression	4	5	9
Cognitive impairment	2	7	9
Motor fluctuations	5	5	9
Activities of daily living	10	10	10

whilst the order of 'rasagiline' and 'Duodopa' was reversed for panellist one. Considering the differences in the weights chosen by the panellists one may have expected different results to have been recommended by the model.

Table 7.6 Model's recommended treatments for patient scenario three

	Panellist one	Panellist two	Panellist three
Drug 1	Apomorphine	Apomorphine	Apomorphine
Drug 2	Duodopa	Rasagiline	Rasagiline
Drug 3	Rasagiline	Duodopa	Duodopa

Comparison of the panel's treatment decisions and the model's recommendations

Patient scenario one

The choices the panel had agreed on, no drug changes or to discontinue pramipexole, were very different to the results the model recommended. For instance, despite the fact that the panel had agreed that 'pramipexole' should be discontinued two of the panellists had 'pramipexole' as one of their top three recommended treatments (Table 7.7). There was similarity between the results the model produced for each of the panellists, but no similarity at all with the choices the panel had made prior to using the model. The panel were surprised that the model had recommended 'apomorphine' for patient one, as the patient's condition was not that advanced and 'apomorphine' is

usually a drug that is reserved for more advanced patients, as is 'Duodopa'. The panel felt the recommendations the model had produced were unsuitable for patient scenario one.

Table 7.7 Comparison of the panel's decision and the model's recommendations for patient scenario one

	Panellists' choice(s)	Model's results: panellist one	Model's results: panellist two	Model's results: panellist three
Patient 1	No drug changes / discontinue pramipexole	Rasagiline / amantadine / pramipexole	Apomorphine / rasagiline / Duodopa	Apomorphine / Duodopa / pramipexole

Patient scenario two

The panel made various recommendations for the treatment of patient scenario two as consensus could not be reached on choice of treatment. As with patient scenario one there was little similarity between the choices the panel had made and the recommendations the model made (Table 7.8). The only similarity shown was with 'amantadine' which the panel had agreed could be considered as a drug for patient two and which was recommended by the model for panellist one. Once again, the panel felt the choice of 'Duodopa' was inappropriate for patient two as their condition was not advanced enough for this medication. The model did not recommend discontinuing 'pergolide' or increasing 'co-careldopa' as the panel had suggested, as the model had only been designed to recommend new treatments and did not take account of medication that needed discontinuing or amending. However, this was all that a MCDA model would normally be expected to do, as its purpose is to choose a treatment, that is to say it makes the decision about the most effective new treatment for each patient. This was the objective of the model, as described previously in chapter one. This type of model would therefore not be expected to recommend amending or discontinuing a drug.

Patient scenario three

There was more similarity between the treatments chosen by the panel and the model's recommendations for patient scenario three (Table 7.9). The

Table 7.8 Comparison of the panel's decision and the model's recommendations for patient scenario two

	Panellists' choice(s)	Model's results: panellist one	Model's results: panellist two	Model's results: panellist three
Patient 2	Discontinue pergolide / add non-ergot dopamine agonist / add Stalevo / increase co-careldopa / consider amantadine	Duodopa / rasagiline / amantadine	Apomorphine / Duodopa / rasagiline	Apomorphine / Duodopa / rasagiline

panel had suggested considering 'apomorphine' as a treatment for this patient and the model recommended 'apomorphine' for all three panellists. The panel had recommended increasing levodopa in whichever form and the model recommended adding 'Duodopa', which is a form of levodopa, although of course it could not recommend increasing any levodopa-based drugs the patient may already be taking due to the fact that it could only recommend adding new treatments, as described under patient scenario two. Although the model had recommended a levodopa-based drug the panel were not entirely happy about 'Duodopa' being recommended as it is such an expensive drug to prescribe and is generally only prescribed in a minority of cases where other drugs have failed. Therefore, it may have been unnecessary for this particular patient.

Table 7.9 Comparison of the panel's decision and the model's recommendations for patient scenario three

	Panellists' choice(s)	Model's results: panellist one	Model's results: panellist two	Model's results: panellist three
Patient 3	Increase levodopa / consider apomorphine	Apomorphine / Duodopa / rasagiline	Apomorphine / rasagiline / Duodopa	Apomorphine / rasagiline / Duodopa

Part II - Panel's General Comments And Suggestions

Frequency of recommendation of 'Duodopa'

The panel commented on the frequency with which 'Duodopa' was recommended for each patient, despite any differences in the weights they may have selected. As 'Duodopa' is recommended for very advanced patients suffering from complications arising from severe motor fluctuations it would not be a suitable drug for all patients, although the model had recommended it for less advanced patients, such as patient scenarios one and two. The panel therefore felt it was unsuitable for many patients and were surprised that it was recommended for all the patients without their severity of symptoms being taken into account. They felt the model should be taking more account of the level of advancement of the patient's disease.

Treatments for non-symptomatic relief

The panel felt that some drugs, such as 'rasagiline', 'selegiline' and 'entacapone', which do not provide symptomatic relief, should not be recommended as treatments in the same way as drugs which do provide symptomatic relief, such as 'co-beneldopa' or 'ropinirole'. They suggested that the model should recommend only drugs that provided symptomatic relief where the user was expecting a treatment to be recommended for particular Parkinson's disease symptoms. The other non-symptomatic relief drugs should be treated differently as these are generally prescribed as adjuncts to other treatments such as the levodopa-based drugs. The model would therefore need to be able to distinguish between symptomatic relief drugs and adjunct drugs and make recommendations accordingly.

Inclusion of more patient variables

The panel suggested that not enough patient variables were taken into account in the model. They felt that the criteria included in the model did not encompass all the possible criteria that they would need to consider when choosing a patient's treatments. For example, not all the characteristics of the patients' symptoms described in scenarios one, two and three, such as freezing, bradykinesia or mobility problems, could be entered into the model, which meant the model was not looking at all the aspects of the patient's

condition that needed to be considered in order to choose the best treatment for that patient. Having the ability to enter more data about each patient would ensure that all aspects of the patient's care were considered which would help ensure the most effective treatment was chosen.

Use of clinical trial data

The panel queried whether the trial data used for scoring the drug options had led to any bias in the treatments being recommended by the model. For instance, where more recent clinical trials may have encompassed all, or the majority, of the different criteria assessed in the model perhaps leading to better scores, some of the older trials would not have encompassed so many criteria or not have been able to assess them in the same way. For instance, a rating scale such as the mini-mental state examination (MMSE) would perhaps not have been developed when some of the earlier clinical trials were carried out. There could therefore have been some degree of unintentional bias in the scoring of the drugs because of lack of uniformity in the trial data.

Levels of disease progression

Suggestions were made by the panel regarding the consideration of the degree of advancement of the patient's disease. At the current time, the model did not take account of how advanced the patient's condition was, nor if the patient was newly diagnosed. The panel therefore suggested that it might be more useful to have perhaps three different versions of the model according to the patient's severity of disease. So, one version would choose treatments for newly diagnosed patients or those in the early stages of the disease, such as Hoehn and Yahr stages one or two. Another version would choose treatments for patients who were a little more advanced and a third version would recommend treatments for the most advanced patients who had reached the complicated or palliative stages of the disease, such as those at Hoehn and Yahr stages four or five. This would then help to ensure that the model chose the most appropriate treatment(s) for each patient and could help to avoid drugs such as Duodopa, which are generally for the most advanced stage patients, being recommended for patients in the early stages of the disease.

Unexpected scores for drug options

The panel felt some of the scores that had been derived for the drug options were unexpected. For instance, co-beneldopa scored poorly overall and much worse than co-careldopa, despite the similarities in the two drugs. Levodopa-based drugs are also considered to be the 'gold standard' of anti-Parkinson's treatments and one would therefore expect all of them to score highly. There were also comments about the overall scores and some of the individual scores for the non-ergot dopamine agonists 'ropinirole' and 'pramipexole'. The panel felt these were different to what they would have expected in that both drugs might be expected to score in a fairly similar vein, although the actual scores in the model showed that there was a difference between the two on a few of the criteria.

'Duodopa' as poor response drug

One panellist raised the issue of Duodopa still being included in the list of recommended treatments even when it had had been selected as a 'poor response' drug and therefore should have been excluded by having all its scores set to zero. However, when this was tested after the validation exercise it was found that it was excluded and the scores were in fact all set to zero. There appeared to be no explanation for this anomaly.

Patient risk alert

The panel suggested that the model could be amended to incorporate a 'risk box', where data of the criteria that patients were most at risk from, eg 'hallucinations', could be entered. This data would then be taken into account in the model and drugs that were most likely to cause this risk factor would be excluded. For example, if a drug was not known to cause a particularly high occurrence of hallucinations it would be excluded from the treatments that could be recommended.

Part III – Applicability And Practicality Of The Model And EPSS

The final stage of the validation exercise was the completion of the questionnaire by the panel members assessing the practicality and applicability of both the model and software (Appendix III).

Parkinson's disease model

The responses from the questionnaire overall were fairly consistent, with all the respondents feeling that amendments needed to be made to the model. The respondents all felt that the criteria in the model were deficient, rating the criteria from 'fair' to 'very poor', with all of them stating that important criteria had been missed out. There was also little satisfaction with the way the criteria were scored, with respondents rating the scores from 'poor' to 'very poor'. The weights too were poorly received, the respondents rating the ease or difficulty of weighting the criteria from 'fair' to 'very difficult' and all the respondents agreeing that the weights needed rewording to improve their clarity. Only respondent two made a suggestion as to how the wording could be improved, stating that the language needed simplifying. The respondents' views of the model overall were mixed, ranging from 'good' to 'poor', although all the respondents felt amendments would need to be made to improve the model. None of the respondents agreed that the methodology was suitable for use with PD, although only respondent three explicitly disagreed, the other two both being unsure. Respondent two commented that the weights should be more representative of real world experience and priorities and respondent three commented that the methodology was not suitable for PD in its current format but that it has potential if the recommendations were made. Similarly, none of the respondents felt they would definitely use the model themselves or recommend it to colleagues, although again only one respondent explicitly stated they would not use it, with the other two being unsure whether they would or not. Figure 7.2 shows a pie chart of the panel's ratings of both the model and EPSS. This pie chart only shows the responses for questions one, three, four, six, ten, twelve and thirteen. A second pie chart shows the breakdown of the panel's responses for questions on the model, which include questions one, three, four and six (Figure 7.3). The responses regarding the questions pertinent to the EPSS (questions 10, 12 and 13) are shown in a further pie chart (Figure 7.4). The panel's responses for all the questions together on both the model and EPSS are shown in Table 7.10.

Figure 7.2 Pie chart of the panel's ratings of the model and EPSS together

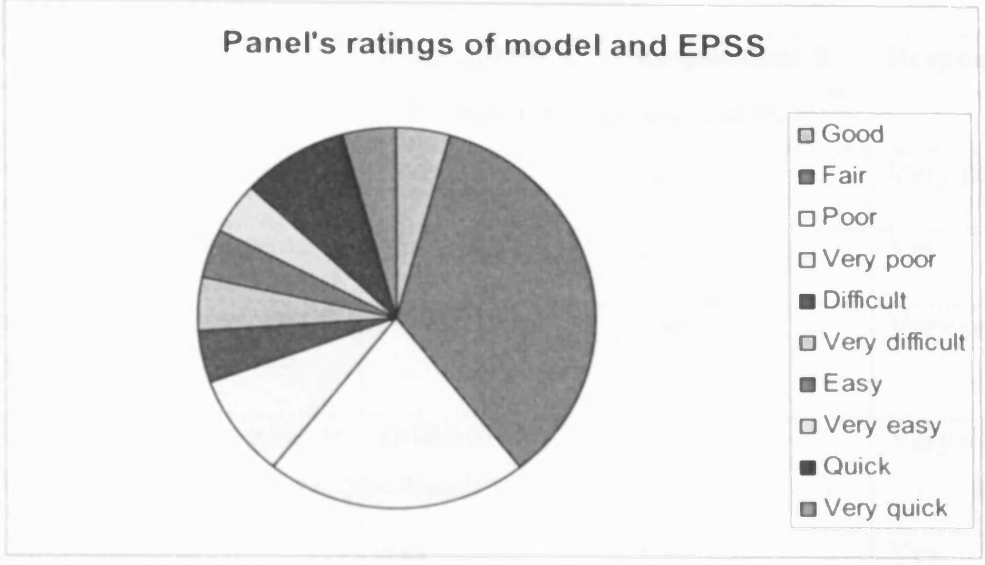


Figure 7.3 Pie chart of the panel's ratings of the model

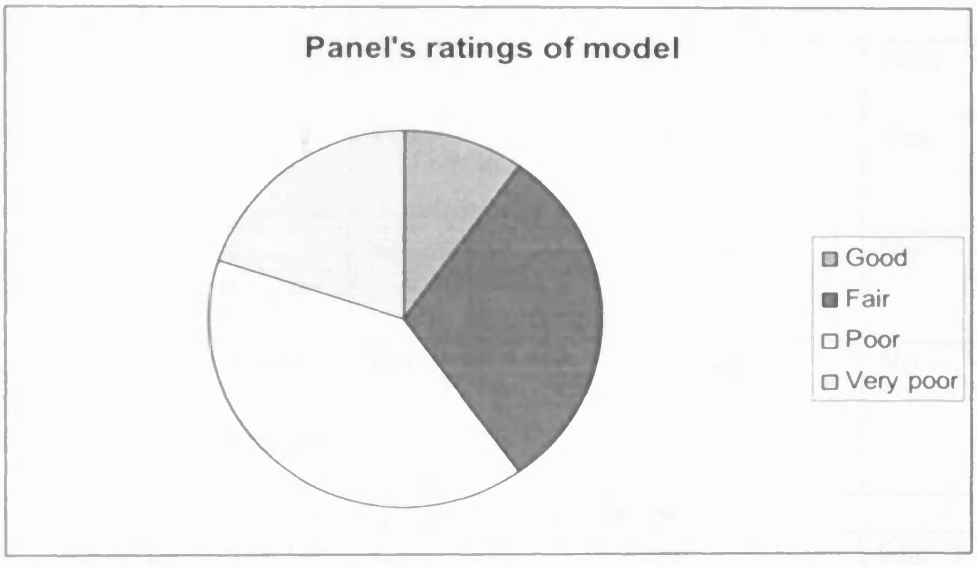


Figure 7.4 Pie chart of the panel's rating of the EPSS

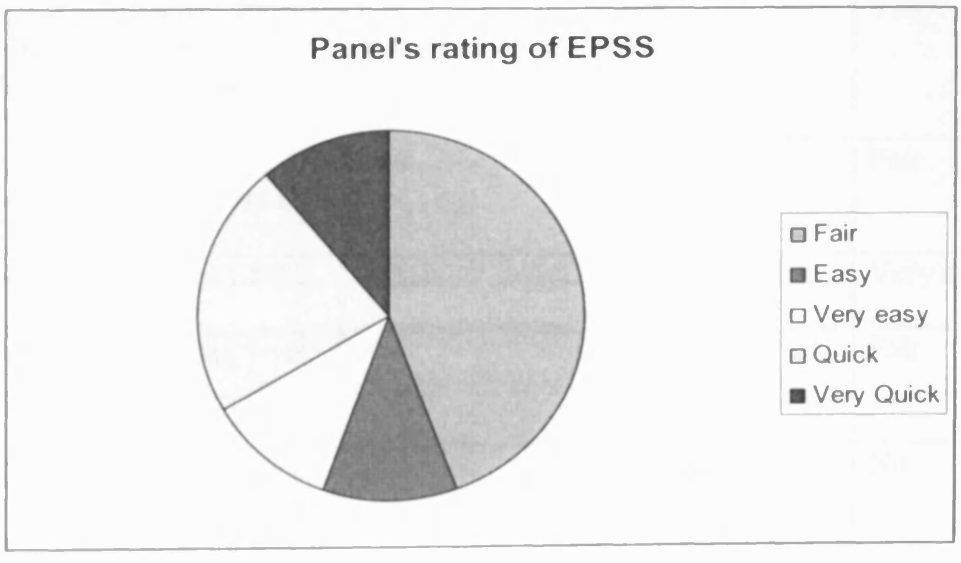


Table 7.10 Panel's ratings of the model and the EPSS's applicability and practicality

Question	Respondent 1	Respondent 2	Respondent 3
Section A: Parkinson's disease model			
1. How do you rate the criteria chosen?	Poor	Fair	Very poor
2. Do you think any important criteria have been missed out?	Yes	Yes	Yes
3. How do you rate the way the drugs have been scored against the criteria?	Poor	Poor	Very poor
4. How do you rate the ease or difficulty of weighting the criteria	Difficult	Fair	Very difficult
5. Do the weights need rewording to improve their clarity?	Yes	Yes	Yes
6. What is your opinion of the model overall?	Good	Fair	Poor
7. Are there any amendments you think could be made to improve the model?	Yes	Yes	Yes
8. Do you think this is a suitable methodology for use in PD?	Not sure	Not sure	No
9. Would you use this model in clinic yourself or recommend it to colleagues to use?	Not sure	Not sure	No
Section B: Software (EPSS)			
10. How easy did you find the EPSS to use?	Very easy	Easy	Fair
11. Are there any amendments you think could be made to the EPSS to make it easier to use?	Yes	Yes	Yes
12. How well do you think the questions are explained on the EPSS?	Fair	Fair	Fair
13. How quick was the EPSS to use?	Quick	Quick	Very quick
14. How would you rate your own knowledge and experience of computers?	Poor	Good	Fair
15. Would you be happy to use the EPSS in your clinic or to recommend it to colleagues to use?	Yes	Not sure	No

Software (EPSS)

The responses regarding the actual software (EPSS) were more positive. The respondents felt the ease of use of the EPSS was from 'fair' to 'very easy', although all the respondents felt amendments could be made to make it easier to use. Only respondent two made a suggestion as to how to make the EPSS easier to use, suggesting the ability to see all the PD drugs rather than having to scroll to see them. The respondents all agreed that the explanation of the questions on the EPSS was 'fair'. Likewise, all the respondents felt the EPSS was quick to use, the responses ranging from 'quick' to 'very quick'. The respondents' assessment of their own knowledge and experience of computers ranged from 'poor' to 'good'. Finally, the responses to the last question, asking whether they would use the EPSS themselves or recommend it to colleagues, were mixed, ranging from 'no' to 'yes', with all the respondents having a different response.

Subsequent validation exercises

Due to the results obtained from the preliminary validation exercise, which highlighted some major issues that needed addressing such as problems with the scores and criteria used in the model, it was decided not to carry out the subsequent validation exercises that had been planned. Further work would be needed to modify the model and therefore it was felt that nothing would be gained from further validation of the model and 'EPSS' at this stage.

DISCUSSION

The preliminary validation exercise carried out with the first expert panel was a valuable exercise which gave a good picture of the panel's views of where the model and EPSS are now as well as some interesting insights into ways of improving the model in particular and the direction the model could be taken into in the future in order to make it more robust for use in clinical practice.

The validation of the model and software described in part I of the results section provided some interesting and at times surprising results. Firstly, the panel's choice of drugs for the three patient scenarios showed that reaching consensus on choice of treatment was not a straightforward or easy matter, with consensus only being clearly reached for patient scenario one. Patient scenario three in particular showed the difficulty in choosing treatments for patients who are at the complex stage of disease progression. Although some degree of agreement was reached for this patient it was more as a result of general agreement on choice of treatment rather than an explicit consensus on precise drugs.

The model's recommendations showed some conflicting results. There seemed to be little parity between the weights chosen by the panel and the recommendations made by the model. For example, for patient scenario one there was a degree of similarity in the weights chosen by the panel, but only the top weight was the same for all panellists, yet the results chosen by the model were very similar. For patient scenario two the weights chosen by the panel were quite different, yet the results were again similar, with panellists two and three receiving the same results despite having chosen different weights. With patient scenario three there was again differences in the weights chosen but the recommendations made by the model were more or less the same. This would seem to suggest that the choice of weights was having little effect on the drugs recommended by the model.

Once the panel's treatment choices and the model's recommendations were compared it was easy to see that there was little similarity between the two. For patient scenario one the panel's choice was very different to the model's recommendations, with the panel feeling the drugs recommended were unsuitable for a patient who did not have advanced PD. Likewise, there was little similarity between the panel's choice and the model's recommendations for patient scenario two with the panel feeling that Duodopa was an inappropriate choice for this patient. The model was also limited in that it could not recommend stopping or amending a drug as the panel wished. There was more similarity between the panel's choice and the model's

recommendations for patient scenario three. This could perhaps have been because patient three was at a more advanced stage of disease which the model seemed more likely to recommend appropriate treatments for.

The panel had various comments and recommendations to make for the model, as were described in part II of the results. A major criticism from the entire panel was regarding the frequency of the recommendation of Duodopa by the model. This certainly showed a deficiency in the model in that it was not taking account of the progression of the disease appropriate to each patient. The stage of disease was incorporated as a criterion in the model and was therefore included in the scoring, but it was not included as an additional variable for the user to input data specific to the patient the model was being used for. This would be something to incorporate in revisions of the model in order to develop a model that was more specific to the patient's stage of disease.

Another general criticism was that the model did not incorporate enough of the variables that would be needed to properly assess a patient and choose the most appropriate treatment. Examples of this might include symptoms such as bradykinesia and tremor, two of the more common symptoms of PD. Additionally, the panel had suggested incorporating 'risks' that were pertinent to each individual patient and this too could form an additional variable of information needed about individual patients in order to choose the most appropriate drug treatment. Although the patient's response to previous drug treatments had been incorporated into the model the panel's suggestions showed that further information would be needed to be collected about each treatment to inform the model.

The panel also suggested that the model should distinguish between symptomatic and non-symptomatic treatments. Clearly it was not appropriate that the model could recommend a treatment that provided non-symptomatic relief, such as rasagiline, for treatment of particular symptoms when this is not its intended use. The model would therefore need to distinguish between symptomatic and non-symptomatic relief drugs and recommend treatments

that were appropriate for symptomatic relief and to recommend non-symptomatic relief drugs as adjuncts, for example.

One particularly interesting result that came out of the validation was the highlighting of the problem with the scores. The panellists had commented on unexpected scores for certain criteria on some of the drugs. The reasons for this were unclear although it would seem most likely that the problem was caused by the use of clinical trial data, something that the panellists had also commented on as a potential source of bias. The problem of using clinical trial data to calculate the scores on the drugs was partly the difficulty in comparing one clinical trial against another. For example, clinical trials may use different criteria as outcomes for their results and clinical trials conducted in different decades for example may have completely different assessment scales available to them and therefore by comparing the results from these clinical trials one may not actually be comparing like with like.

One of the suggestions the panel made as a way of improving the model's results was to redesign the model so that it took account of individual patients' stage of disease. Effectively this could mean developing three separate models or three modules of the same model, for example one for newly diagnosed patients, one for intermediate stage patients and one for advanced stage patients. This would mean that the user would enter the patient's stage of disease as part of the patient's background information and the model would be selected which was appropriate to the patient's stage. A different form of the model would then be developed for each of the three major stages following the format and methodology developed previously, with pre-set criteria, the drugs scored on their performance on each criterion and the user selecting weights for the criteria appropriate to each patient. This could help to make the model more appropriate for individual patients and potentially solve problems such as drugs like Duodopa being inappropriately prescribed for less advanced patients.

The questionnaire testing the applicability and practicality of the model and EPSS described in part III showed a mixed response to the decision aid

overall. The questionnaire, similarly to the panel's comments, highlighted many problems with the model but showed that the software developed was satisfactory and met its intended objectives, such as speed and ease of use. Although the panel had given various criticisms of the model their comments showed that the principle of the model and therefore decision aid was accepted and that it could become useful for clinical practice if the recommendations and suggestions listed above were put into practice. The model itself would need much further refinement and sophistication for it to be able to be used in clinical practice, which by definition would mean further refinement of the software too in order for it to implement the model.

The number of major issues that were raised through this preliminary validation exercise meant that further validation exercises with expert panels were deemed unnecessary at this stage. The model would need further refinement and development, as discussed above, at which point it could again be validated by expert panels and this would provide more value than carrying out multiple validation exercises when major issues had been identified at an early stage in the validation process.

Therefore, the validation of the model and software proved to be a valuable exercise. It was shown that a model could be developed for Parkinson's disease and software developed that practitioners would find quick and easy to use. The panel agreed that the principle of the model and decision aid were sound, and that it could be a useful tool in clinical practice. The validation exercise was also particularly useful in pinpointing areas that need further development and ways that this could be carried out. The panel were able to identify areas that needed further work and also make suggestions on ways to incorporate improvements so that the model would fulfil a role as an effective decision aid for all individual patients with PD. This meant that a future direction for the model and EPSS could start to be determined. Further development and refinement of both the model and software could lead to a more sophisticated decision aid being developed for Parkinson's disease that would have good potential for use in a clinical setting.

SUMMARY

The Parkinson's disease model and software were validated by a panel of experts to show whether they were applicable, practical and valid for use with Parkinson's disease patients.

- Consensus on choice of treatment by the panel was limited, consensus only being reached for one patient scenario
- The results of the model's recommendations for each patient scenario were conflicting
- There was little similarity between the panel's choices and the model's recommendations
- Issues were identified with the criteria in the model, with the panel suggesting several variables were missing
- The scores on the criteria were shown to have problems, producing what the panel considered to be unexpected results
- Several recommendations were made by the panel as to ways of improving the model
- The questionnaire showed a mixed response to the decision aid, but showed that the principle of the model was accepted and the software was satisfactory.
- The panel's choices were compared against the recommendations made by the model.
- The panel completed a questionnaire evaluating their use of the model and software.

CHAPTER 8

General Discussion

"I have yet to see any problem, however complicated, which when you looked at it the right way did not become still more complicated"

Poul Anderson

Medical decision-making is a complex affair, as indeed is any kind of decision-making. However, medical decision-making in particular has an additional level of complexity due to not only the expectations of the patient, but also the considerations the clinician must make in choosing a treatment that is not only effective, but also maximises benefits whilst minimising risks. Decision-making in medicine was historically based on intuition and the clinician's personal experience, rather than solely on solid clinical evidence and therefore often incorporated bias. However, the phenomenon of evidence-based medicine, which became popularised in the early 1990s, changed the way decision-making was viewed, with the emphasis since then being on implementation of sound evidence from the highest sources of clinical evidence such as randomised clinical trials. Decision-making has moved too from the traditional paternalistic model to a shared model with increasing emphasis on incorporation of the patient's views and wishes in the choice of treatment.

The development of new methods of medical decision-making led to the incorporation of decision analysis, both with patient decision aids and with the development of computer decision support systems. The development of such decision aids and CDSSs meant that the large volume of literature which clinicians would have to search for and critically appraise was automatically reduced, as the evidence was already incorporated through the use of decision analysis. Thus, one of the limitations or criticisms of evidence-based medicine, that it would be too time-consuming for clinicians to read and appraise all the available literature in their field, was naturally discredited. Indeed, the use of CDSSs, for example, meant that the highest level of evidence from randomised clinical trials or meta-analyses of trials was automatically incorporated.

The review of the literature on decision aids and CDSSs described in chapter one showed that they are a useful means of implementing evidence-based medicine and improving healthcare quality, although results from trials using CDSSs were somewhat mixed. However, the general view was that CDSSs had the potential to be useful and improve decision-making. Four features had been identified as critical for new CDSSs to be accepted in clinical practice (Kawamoto, 2005), namely the automatic provision of CDSSs as part of the clinician's workflow; provision of a CDSS at the time and place of decision-making; provision of a recommendation not an assessment and the system being computer based. Sittig et al (2006) also established that CDSSs were more likely to be used if patients were elderly, on multiple treatments and had a chronic condition. Not all areas of medicine have CDSSs in use or even developed for them and there was therefore a need for more CDSSs to be developed, with the features identified above incorporated. Thus, the development of a model and CDSS to implement it was deemed to be the aim of this thesis.

Parkinson's disease is a complicated disease exacerbated by the complications that may arise from the drug treatments used to reduce patients' symptoms. Difficulties in choosing the most effective treatments for the disease lie in the choice of drug treatment in the early stage to minimise the patient's symptoms through to dealing with complications in the advanced stages of the disease very often arising from the treatments themselves. Parkinson's disease is therefore a complicated disease to treat and to date there has been no algorithm or decision aid developed to help practitioners choose the most effective treatment for individual patients. Thus a need was exhibited for a CDSS that could be applied to Parkinson's disease which would incorporate evidence-based medicine and shared decision-making.

Among the many types of models used in decision analysis, such as Markov models, ANN and Bayesian networks, is multi-criteria decision analysis. This provides a means of breaking a complex problem down into more manageable pieces and allowing data and judgement to bear on them before the pieces are reassembled to give an overall picture of the decision problem.

MCDA has been widely used in certain areas such as environmental management, but has had little application in medicine. The few MCDA models that have been developed in medicine have tended to be small and for relatively less complex decision problems.

A model was therefore developed for Parkinson's disease using MCDA and was implemented in a CDSS. Developing the model using MCDA involved carrying out seven stages, as described below:

1. Establish the decision context
2. Identify the options to be appraised
3. Establish the criteria to be used
    a. Divide the criteria into 'risk' and 'benefit' categories
    b. Devise a value tree for the criteria
4. Develop the scores by assessing the performance of each option against the criteria
    a. Define measurement scales
    b. Develop scoring scales
    c. Calculate total score for each option
5. Assign a weight to each criterion according to its importance to the decision problem
6. Combine the scores and weights into an overall value
7. Carry out a sensitivity analysis

The early stages of developing the model were described in chapter three, where the decision context was ascertained, the options described and the criteria developed. The rest of the model, which involved developing the scores and weights, was described in chapter four, with the sensitivity analysis carried out in chapter seven.

The decision context and available options for the model were simple to establish. The process of establishing the criteria was more complex and produced some interesting results. The initial survey sent to geriatricians, neurologists and Parkinson's disease nurse specialists, which ascertained whether they used any kind of algorithm and whether they used personal

experience for their decision-making, showed that hardly any of the practitioners used any kind of established algorithm and a large majority were using personal experience as part of their decision-making process. This result could be considered somewhat surprising considering the emphasis in recent years on the use of evidence-based medicine. One would have expected the role of professional judgement to perhaps have diminished with the growth of evidence-based medicine. Although it could be suggested that some degree of personal experience is still to be expected in the use of evidence-based medicine, especially where evidence is lacking, it is the degree to which it appears to still be being used in Parkinson's disease, as shown by the results of this survey, that would lead one to question whether practitioners are really using evidence-based medicine in conjunction with their professional judgement.

The second survey that was sent to the same geriatricians, neurologists and Parkinson's disease nurse specialists, following on from the first, showed that some practitioners were considering a large number of criteria in their decision-making for PD, up to 68 criteria. The range of criteria considered varied greatly, from 10 to 68. This, together with the results from the first survey suggested a disparity between prescribing practices for practitioners and a lack of uniformity in decision-making between individual consultants and also, one could intimate, between hospitals. Therefore, patients could be unlikely to receive equality of treatment.

With the criteria established, the rest of the model was then developed, as described in chapter four. The process of developing the scoring of the drugs on the criteria provided some interesting results. Some drugs, such as pergolide, scored much better than expected, whilst others, such as co-beneldopa, scored much more poorly than one would have thought, bearing in mind that levodopa is considered to be the 'gold-standard' of PD treatments. The scores showed that for some criteria, such as 'depression' and 'postural hypotension', very few of the drugs had any positive effect. Overall, the drugs tended to have a fairly negative effect on the criteria, to a greater or

lesser degree. 'Activities of daily living' was the only criterion for which none of the drugs had a negative effect.

Developing the scores raised some interesting issues in terms of the clinical trial data used. Collecting the data to calculate the scores from highlighted an initial problem: the availability of the original clinical trial data from when the drugs were first developed. Difficulties in obtaining original clinical trial data meant data had to be used from subsequent trials. However, this was not the only problem. Many issues surround the data that clinical trials produce. For example, there is a lack of uniformity in the data that clinical trials collect. This was most evident when trying to establish the scoring scales for the criteria. Many of the trials did not examine all the criteria needed for the model, although there were also problems in the reporting of the data established, such as statistical significance not always being listed. Different clinical trials used different measurement and assessment tools for some criteria. For example, for measuring the effect of the drug treatments on 'depression' some trials used the Montgomery-Asberg Depression Rating Scale, whilst others used the Zung self-rating depression scale. Furthermore, some clinical trials used a rating scale such as the UPDRS to measure certain aspects of the effects of their drug treatments, but did not use all the sections, so effects of the drugs that could have been measured were lost. This could suggest a deficiency in clinical trials, where an effect of a drug is missed simply because in the trial design it has been decided not to look at all aspects of a measurement scale.

An additional problem with the clinical trials was that certain patient groups were often excluded. For example, many of the trials excluded patients under the age of 30 or over the age of 80. Therefore, there is often a lack of data available on the effect of PD drugs on these groups of patients. This is particularly important for young-onset PD patients, who, whilst forming a small minority of patients, may still have different needs to older patients and on whom the drugs may have different effects. Their exclusion from clinical trials means we have no or little knowledge of how the drugs will perform for them. For patients over the age of 80, there may be many who would have been

excluded from clinical trials anyway due to failing cognition, but for others who have sound cognition we again would be lacking data on how the drugs would perform for them in relieving their symptoms. This leads on to the issue of cognitive impairment and other neuro-psychiatric problems. These patients too were excluded from the clinical trials, and whilst there are ethical and other issues connected with the inclusion of such patients in clinical trials which are beyond the scope of this thesis to address, their exclusion does lead to a deficit in data on how to effectively treat this important group of symptoms.

The original criterion for collecting the data for the scores was to obtain all the data from pivotal clinical trials. Other data was obtained from searches for trials using the drugs in the model, although a literature review was not carried out at that stage due to the time limitations of the project. In retrospect, it would have been useful to have carried out a comprehensive literature review giving reference to the meta-analyses, systematic reviews and randomised clinical trials that were used as the evidence-base for the NICE guidelines (NICE, 2006). These were incorporated into the NICE guidelines as the best available evidence and should, therefore, have been used as the evidence-base for this model, perhaps eliminating some of the potential bias that was highlighted in the validation exercise, such as the unexpected scores pergolide and co-beneldopa received, for example. It is difficult to be certain whether or not these issues would have existed if a review of the literature had been carried out using the same sources as the NICE guidelines, but by carrying out such a review one can at least ensure that the best evidence has been assessed and incorporated into the model. This would also help to make the model more robust, an important issue if it were to be used in a clinical setting in the future. However, issues to do with evidence from clinical trials were highlighted in the NICE guidelines. For example, drugs evaluated from many of the early trials conducted in the 70s and 80s may have been found by NICE not to be efficacious. This does not though mean the drugs are necessarily ineffective, but the clinician would need to use their clinical experience as the only appropriate judgement of the drugs' safety and efficacy. The NICE guidelines found that trials used in the systematic reviews

incorporated into the NICE evidence-base often had methodological limitations. They suggest that such trials should be treated with caution because of this. They therefore did not give evidence statements based on data from individual trials. However, the purpose of this study was to develop an initial prototype that would assess whether a model could be developed for PD with MCDA. Having a more comprehensive review of the clinical evidence available on each drug would be part of future work carried out in developing the model further, with the issues identified above taken into account.

The process of trying to develop the weights showed that they would not be able to be pre-defined in the usual way for such a model, as allowing the user to develop their own weights was the only really feasible way of making the model unique to each patient. Two criteria were an exception to this, 'adverse drug reactions' and 'drug interactions', as both of these criteria needed to have their weight pre-defined as they were considered to need the maximum weight for all patients. However, the majority of the criteria weights not being pre-defined was in some ways an advantage, as not only would the model therefore be unique for each patient it was used for but it would also mean that the patient could be involved in the decision-making process, enabling the important aspect of shared decision-making to be naturally incorporated. This would provide a benefit for the patient, in that their view would be considered and incorporated, and also for the clinician who would not have to rely on their own value judgements to decide which criteria were most important for the patient. Generally, one would expect a MCDA model to have pre-defined weights and scores and for the model to produce one solution to one decision problem. Medicine, though, is not such a straightforward field, particularly in the case of choosing treatments for Parkinson's disease patients. However, MCDA was shown to be an adaptive methodology, in allowing in effect many models to be developed for many patients, by varying the weights to suit the individual. Thus, not just one model was developed, but the potential for as many variations of the model as would be needed, that is to say as many individual models as there are individual patients in terms of their symptoms and values.

The process for calculating the weights used in the model follows the methodology of MCDA, but brings issues of its own. For example, swing-weighting is quite time consuming and cumbersome for users. It is a complicated methodology to understand and apply correctly without guidance or someone knowledgeable present to explain how to calculate the weights. Although a 'help' mechanism was added to the software to explain how to carry out swing-weighting it is questionable whether that would be adequate in a clinical situation where time is limited and a lack of understanding of the methodology could lead to the weightings being developed without truly using swing-weighting. It requires time to think about the weightings, to discuss them with patients, to perhaps explain some of the criteria to the patient if they do not understand the symptoms that are being assessed and which may anyway in part be irrelevant for some of them. One would have to ask therefore whether swing-weighting is the best way of calculating weights for the purpose of this type of model which ultimately one would hope to see used in a clinical setting. It would be necessary to assess whether there is a way of improving the weighting wording for example so that it is quicker and easier for users to choose their weights. Swing-weighting is currently considered to be the most apt way of calculating the weights in a MCDA model, thus if MCDA is to be used for this type of disease model it needs to be improved to make it more practical and accessible.

The issues with the data used for the scores lead to an interesting point regarding the use of evidence-based medicine. EBM has been advocated by many as the best method of medical decision-making, but this project has shown problems with the evidence that has been used in developing the model. If this is the best evidence that practitioners can access in order to make their treatment decisions, with all the flaws that have been identified, can one truly advocate the use of EBM as the best means of decision-making? However, one could argue that the results of this study support the views of some, such as Sackett et al. (1996), Lacaine (2005) and Akobeng (2005), who have argued that the use of EBM is justified if it is used in the way it should be, with individual clinical expertise and personal experience being used alongside the best available evidence as well as patients' opinions and

values being incorporated. Although there may be insufficiencies in the evidence available, it is still the best available evidence, particularly as it is from randomised clinical trials, and therefore if used along with the clinician's expertise and the patient's own values provides the best basis for medical decision-making. Therefore, although problems have been identified in the scoring and weighting used in this model, if they are further refined they will still provide the means for the clinician to make the best informed decision they can which incorporates EBM, clinical judgement and shared decision-making.

The developed model lacked a means of implementation and a CDSS was thus developed to implement its functionalities. Although propriety software exists for MCDA models, the uniqueness of this model meant it was more suited to bespoke software which could cater for its variation in weights, for example. Choosing Microsoft Excel to carry out the mathematical functions of the model and Visual Basic for Applications (VBA) as the interface development language meant two compatible applications were used together. Developing a user interface in VBA also meant that the user would not have to be involved in, or even aware of, the calculations that the model needed to carry out, such as multiplying the scores and weights together. The user interface also provided the means of allowing the user to enter data specific to each patient so that the user's reaction to previous medication could be recorded and incorporated into the model.

The interface and overall design of the software kept the CDSS quick and easy to use. The interface design followed the design principles of Schneiderman (http://faculty.washington.edu, 2008) as closely as possible, which helped to make it simple and easy to use as well as accessible. In terms of the implementation of the software, Excel and VBA provided everything that was needed in respect of accepting the user's data input, submitting data to Excel for calculations to be carried out and providing a result for the user to see.

Methods were incorporated into the coding of the software application to ensure that all data the user entered was within the correct format, such as figures only or numbers between 0 and ten, as necessary for each section. This process of data validation was described in chapter six. Every possible type of data the user might enter which could be invalid was tested in a series of checks. A thorough evaluation of the user's data input was therefore incorporated and proved to be an effective means of ensuring that only valid data was entered. This necessary process ensured also that the model would function effectively with the correct form of data provided.

The rest of chapter six looked at the process of testing the software to ensure it worked effectively and without any problems. This was expected to be a fairly straightforward process as it was a small application. However, carrying out all the specified tests on the application showed that testing the software was a very valuable exercise. Two tests that were expected to be performed without any hitches highlighted bugs in the coding that might otherwise have been overlooked. All the other tests provided results as expected, showing that the original coding was sound and also that the user data validation techniques added had ensured everything would work smoothly and perform as expected. The end result was that a piece of software was produced which performed the way it was designed to do and that had been tested as thoroughly as possible to ensure that all its functionalities were complete and effective. The CDSS also met three out of four of the features identified by Kawamoto (2005) as necessary to make a CDSS successful for use in clinical practice. These were the provision of a recommendation rather than an assessment, the system being computer-based and the CDSS being provided at the time and place of decision-making, which it would be if it were used in clinic. The only feature which this CDSS did not comply with was the automatic provision of the CDSS as part of the clinician's workflow, which was beyond the scope of this study, but which could be considered as part of future development.

The final stage was carrying out the 'sensitivity analysis', which was covered by the validation exercise described in chapter seven. This tested whether

the model met its objectives and whether it could provide suitable recommendations on treatments for Parkinson's patients, as determined by a panel of experts. The validation exercise also looked at whether the panel considered the software to be quick and easy to use. The validation was a particularly interesting exercise in the results that it produced. A number of issues were identified by the panel but the basic principles of the model were also considered to be worthwhile and workable. The panel identified problems with both the criteria and the scores in the model. The criteria were not considered comprehensive enough and did not reflect all areas of the information about the patient that would be necessary to choose effectively the best treatment for each individual patient. For example, if the patient's main symptoms were problems with bradykinesia and tremor, two very common symptoms in PD patients, the model would not currently provide any means of incorporating these criteria. This is due to the fact that these two criteria were not listed in the surveys carried out ascertaining the criteria PD practitioners use. This could have been due to a comprehensive enough procedure not having been carried out when the criteria were developed. For example, if a panel of experts had been involved in assessing the criteria that arose from the two practitioner surveys carried out they may have identified that essential criteria which one would consider to be the cornerstone of PD symptoms, such as bradykinesia and tremor, had not been identified in the surveys. It could also be considered that the application of the eight considerations to the criteria from the surveys was to some extent arbitrary. Having an expert panel involved in the application of the considerations may help to make the process more robust and accountable. One option for ensuring the criteria chosen were more robust and the procedure more explicit could be to use a procedure such as the Delphi technique. This is a structured technique that is used for obtaining opinions with the aim of obtaining consensus among a group of experts (Campbell and Cantrill, 2001). With the modified Delphi methodology, for example, a literature review and survey development are carried out, an expert panel selected and data collection and analysis is then carried out (Hanlon et al, 2009). Using a technique such as this could help to ensure that there was consensus among experts on the criteria that were selected for the model and also reduce over-

reliance on an evidence-based approach. For example, the higher cognitive aspects used by clinicians in decision-making on choice of treatment for PD, such as pattern recognition and individualised care assessments for patients, were not taken into account in the process of developing the criteria. These are aspects which could be incorporated in refining the criteria and which could ensure that a more comprehensive methodology for developing the criteria was carried out.

Additional problems were identified with the scoring. The panel felt that the scores did not accurately reflect the way the drugs perform and this therefore unduly biased the performance on the scoring of individual drugs, such as co-beneldopa for instance. The panel also identified additional problems, such as the frequency of the model's recommendation of Duodopa, which they felt was inappropriate for less advanced patients. This is an issue that might perhaps have been addressed if evidence had been used from the same sources as the NICE guidelines, for example. As identified earlier, this may have eliminated some of the problems such as the unexpected scores for pergolide and co-beneldopa. It could also have been useful to perhaps have developed separate 'modules' for the different stages of the disease, such as early, middle, late, as suggested by the expert panel in the validation exercise. This may have overcome the problem of the model recommending inappropriately drugs for advanced patients, such as Duodopa, for patients who were less advanced. Further problems were identified with the weightings, which the panel firstly found difficult to understand. This was because of the methodology of swing-weighting for which the users had to consider a range of effects each drug might have on each criterion, which the panel felt was complicated to understand and carry out. Additionally, the weights were shown to have little impact on the results the model recommended, with the same or very similar results being provided by the model even when panel members had quite distinct choices of weights. As discussed previously, the weightings may need re-wording or a re-working of how the weights are calculated may be necessary. Overall, the sensitivity analysis showed its worth with the issues of the scores and weights that were highlighted, as variations in weightings should still produce a feasible result

and this was not always the case with this model. However, overall the software was considered to be quick and easy to use, which was its objective. The panel felt both the software and model were useful tools which, with further refinement, could be successfully used to choose treatments for PD patients. The panel also felt that in principle the methodology of MCDA could be used for PD, although with refinements taken into consideration.

The work carried out on developing the model and the results of the validation exercise could lead one to question whether MCDA is the most appropriate methodology for developing a model for Parkinson's disease. There are a number of issues to consider. Firstly, a model was successfully developed for Parkinson's disease using MCDA, which shows that it is possible to do so. Although this model was shown to have a number of issues, the expert panel involved in the validation exercise did agree that it was a methodology that could be used for Parkinson's disease, albeit with a number of modifications and refinements. A question that one might ask is whether in fact Parkinson's disease is too complicated a disease to model effectively. The issues and problems raised through this project, such as with the criteria and scores, show that Parkinson's disease was perhaps too complicated a disease to model effectively solely through carrying out the work covered in this thesis. It would perhaps have been better to have modelled just one aspect of the disease, such as early stage patients only to begin with. If that had been successful then other stages could have been modelled subsequently as further work. It should be remembered also, that at this stage this model is a prototype and "a proof of principle" consistent with the objectives of the thesis, it did not however meet the more rigorous aims of providing a validated clinical decision aid which was fit for purpose and satisfied "proof of concept" (PoC). It will be the effect of the further refinement and sophistication of the model that will determine how effective a model can be at treating this complex disease. However, the fact that PD is such a complicated disease emphasises the fact that a methodology such as MCDA is the right choice for this disease as it is specifically designed to deal with complicated decision problems and to incorporate both quantitative and qualitative data with value judgements.

If one determines that it is possible to model Parkinson's disease, one could conversely question whether PD is the best disease to use for developing a model with MCDA. Others have shown that MCDA can be used to choose treatments for other conditions, such as Ferrari et al.'s (2005) model developed to determine the most effective triptan for migraines, Hummel et al.'s (2005) model for tetraplegia, Singh et al.'s (2006) model for pharyngitis, a model for colorectal cancer screening (Dolan and Frisina, 2002) and a model for pyelonephritis (Dolan, 1989). However, most of the models previously developed for medical decision-making using MCDA have been for conditions or treatments that were less complex than Parkinson's disease and which involved fewer criteria and fewer available options. None of the aforementioned studies described problems obtaining trial data, if it was used, and therefore did not have the same limitations that this study had. Nor did the previous studies develop as sophisticated a model which could recommend different treatments for individual patients. This project is the first to tackle such a complex disease with its complicated treatments using MCDA and shows that PD was a suitable disease to be used with this methodology. It also shows that MCDA could be used for other major diseases, where there is a need for models and decision aids to help practitioners deal with complicated decision-making on choice of treatments and importantly to aid in the implementation of evidence-based medicine. Many of these diseases and conditions may be less complicated than Parkinson's disease, and therefore more straightforward to model with MCDA. One advantage of modelling Parkinson's disease with MCDA is that it has shown that it is possible to do so for a complicated disease and therefore models for other diseases can follow the initiative of this project. The development of this model as part of a CDSS means that it also meets the criteria outlined in chapter one for new CDSSs, in that it has been shown to be quick to use, provides a comprehensive functionality and implements evidence-based medicine.

LIMITATIONS OF THE STUDY

There were a number of limitations to the work carried out for this project. Firstly, the criteria that were developed were not comprehensive enough in the range of variables they incorporated. Although practitioners were consulted about the criteria they would use for decision-making in PD, there were still criteria, such as bradykinesia and tremor, which were not listed by practitioners and were therefore not incorporated into the model, as previously discussed. This was something that was highlighted by the expert panel during the validation exercise, as it was felt that if criteria were missing it was not possible for the model to truly represent the patient's situation.

There were limitations with the scoring of the criteria. First of all, there was a problem with obtaining all the necessary clinical trial data from which to calculate the scores. There were additional limitations with the data that was collected on the drugs, such as the lack of uniformity of assessments used in the clinical trials, with different measurement and assessment tools being used and very often different criteria being measured. Additionally, not using the evidence base such as had been used in development of the NICE guidelines (NICE, 2006) to collect all the data on all the drugs meant that there may have been data on some aspects of some drugs that was missing. Therefore, the scores could not necessarily be considered to be completely accurate.

The weights proved difficult to develop. This was for a number of reasons. It was not possible to develop a satisfactory means of pre-determining the weights so the model had to be developed so that the user was choosing their own weights. There were thus then difficulties in phrasing the weights in such a way that any user would understand the methodology of swing-weighting and therefore calculate the weights correctly. Using swing-weighting meant that the weights could be time-consuming for users to choose. Overall this was a necessary part of the methodology, but not a very satisfactory one to include in the model because of the potential difficulties it could cause the user.

The final limitation of the project was that full content validation was not carried out for each stage of development of the model. This in part contributed to the limitations listed above. For example, if the criteria had been validated by an expert panel when they were developed, such as by using the Delphi technique, the criteria that the panel involved in the validation at the end of the project mentioned that were missing, such as bradykinesia, may have been identified at an early stage to be included in the model. Additionally, an expert panel could have validated the scores that were developed, to ensure they represented fairly the way the drugs performed against the criteria. Although this would not have eliminated the problems mentioned previously with obtaining data and the problems with the lack of uniformity in the trials, it may have diminished some of the problems highlighted with the scores. It may have been difficult to have carried out a validation of the weights as these were not pre-determined, but an expert panel could have been involved in validating whether the methodology was understandable and if the wordings used for the weights were clear. In general, content validation of each stage of development of the model would help to ensure that the finished model was as robust as possible. It would also have been useful to have been able to provide a means of explaining to the user why a particular drug was recommended by the model for each patient, but this would have added a level of complexity to the model that would have taken its development beyond the scope of this PhD project. Finally, it could be considered that the scope of the project was too broad. The issues identified in developing a model that could recommend treatments for all Parkinson's disease patients could be considered as too ambitious a project based on the results discussed in this thesis. It would perhaps have been better to have developed a model for one aspect of the disease, such as for early stage patients for example, from which further work could be carried out to develop the same or a similar model for other stages of the disease. However, this study did develop a model and CDSS for Parkinson's disease, which can be considered to be a successful proof of principle. The limitations discussed above could be incorporated into the refinement of the prototype developed here and carried out in future work.

HAVE THE OBJECTIVES BEEN MET?

In chapter one two broad objectives for the project were identified in order to achieve the aim of developing an electronic decision aid to help practitioners choose the most effective treatment for Parkinson's disease. These were:

- To develop a model using multi-criteria decision analysis to be applied to Parkinson's disease
- To develop a computer system to implement the model's functions.

Both objectives can be said to have been met. The model was developed using MCDA and was applied to Parkinson's disease. The aim of helping practitioners to choose the most effective drug treatment was met through development of the model, as the model incorporated evidence-based medicine and the criteria, scores and weights determined the information that was necessary for each patient. A piece of software was successfully developed using Excel and VBA which implemented the model's functions, and through validation of the user's data entry and a thorough testing process the software was shown to meet its objectives to be quick and easy to use and was therefore successful in its development. Therefore both of the objectives of this project were successfully met.

FURTHER WORK

In order to refine the model and increase its sophistication a number of areas of further work would need to be carried out, to take the work developed here as proof of principle into a more refined model and CDSS suitable for use in a clinical setting. In terms of the methodology used, three of the steps of the MCDA model would need further development. A need for a greater number of criteria was established during the validation exercise with the expert panel. The list of criteria established from the two surveys could be reviewed by including an expert panel in the further development of the criteria and a methodology such as the Delphi technique used to ensure that all the expected additional criteria, such as bradykinesia, had been added in to the

model. The scores would also need further refinement. First of all, a comprehensive literature review should be carried out on all the PD drugs to ensure that all the available studies and evidence had been appraised, using for example the same sources as were used in the development of the NICE guidelines. If further data were obtained the measurement scales for the scores may need to be revised and a new set of scores developed for each of the drugs. The issue discussed previously regarding lack of uniformity in the trials is not really a problem that can be solved for this project or subsequent work. However, using all the evidence that is available to determine the scores would at least ensure that the data used to calculate the scores is comprehensive. Other issues identified earlier with the scores, such as the trial data possibly leading to potential bias in the score results could not necessarily be overcome, but may just be a feature of using evidence-based medicine. However, use of the best sources of evidence, such as from the NICE guidelines, would help to ensure that as a minimum the best evidence had been used. Having an expert panel involved in the development and reviewing of the scores could help to ensure that clinicians' value judgements are also incorporated into the model, as has been suggested is the best way to use evidence-based medicine. The weights too may need some modification in their wording in order to make the methodology of swing-weighting easier for users to understand. It is also possible that an alternative means of deciding the weights may need to be considered so that it is quicker and more straightforward for clinicians to use.

It could also be useful to either develop in effect separate 'modules' of the model that apply to the different stages of the disease, such as for early or advanced stage patients among others, or if the model was developed to apply only to early stage patients, for example, further models could be developed for the other stages of the disease.

The issue of content validation throughout the model has been discussed previously. It would be useful to have an expert panel involved in each stage of development of the model and any variation of the CDSS to carry out content validation to ensure that the model is practical and meets the users'

expectations. This would help ensure that the model was robust and could therefore be considered for use in clinical practice.

One area which was not addressed in this project was a means of giving the user feedback on why a particular treatment had been recommended over all the others. This was felt to be beyond the scope and time-limits of this project. However, it is an important issue which would provide a further useful benefit of the decision aid and would particularly benefit less experienced users in clinical practice as well as medical students if it were used as a teaching aid. It would therefore be beneficial to incorporate an algorithm to provide the users with the reasoning behind the model's recommendations in order to further knowledge about why one drug is recommended over another. This is important to help the user learn from the model's recommendations and particularly pertinent for medical students and junior staff so that the model can become an effective learning tool. It could also be useful for more experienced practitioners to improve their clinical practice.

In order to implement the extended functionalities of the model, as discussed above, it would be necessary to refine the software. One possibility could be to develop an expert system to provide additional functionality. A computerised expert system can be developed by obtaining knowledge from a human expert which is then transformed into a format the computer can use to solve similar types of problems. The expert system uses reasoning to apply a set of rules to the knowledge by using some of the rules that human experts use (Aniba et al., 2008). The expert system therefore simulates the judgement and behaviour of the experts and uses their knowledge to provide an analysis for the user.

There are several forms of expert system that have been identified (Liao, 2005), which include rule-based systems, case-based reasoning systems, neural networks and fuzzy expert systems, each of which will be outlined in turn.

- Rule-based systems – these use a set of rules to analyse information about a class of problems and recommend one or more solutions
- Case-based reasoning systems – these systems adapt solutions that have been used to solve previous problems and use them to help solve new problems
- Neural networks – these implement software simulations of parallel processes that process elements connected in a network architecture
- Fuzzy expert systems – this type of system uses fuzzy logic to deal with uncertainty and is used where results often involve grey areas.

An expert system could provide more sophisticated modelling and software which adapts to each patient. For example, by perhaps using either case-based reasoning to adapt previous solutions for patients, or by using a fuzzy expert system which would perhaps deal more effectively with the 'grey' areas of decision-making for Parkinson's disease patients. An expert system would also provide the means of incorporating further functionality than the model developed for this project was capable of, such as recommending dosage amendment or stopping a drug the patient was already taking. It would also be easier to provide feedback to the user regarding the recommended treatment path as a complicated algorithm detailing why a recommendation was being made would already by necessity be part of an expert system and so could be adapted to be returned to the user. This would also aid the confidence of the clinicians using the system in the suitability of the recommendations it made.

However, an expert system is only one suggested path for the future direction of a model for Parkinson's disease. It may be necessary to examine in detail whether it is possible to develop a sophisticated enough model for PD using MCDA, with some of the aforementioned refinements encapsulated. It would also be useful to examine whether an expert system would be the best way to take the model forward. Therefore, further work could be carried out to examine both paths in detail with experts in the two fields involved to compare the two possible routes in which to take this work further forward. Once the

best route has been established it should be possible to develop a more refined and sophisticated model or system which would have good potential for use in a clinical setting.

CONCLUSIONS

Developing this model has shown that MCDA can, with limitations, be used to develop a model for complex diseases. It has also been shown that a model can be developed for Parkinson's disease. Bespoke software can be, and has been, successfully developed to fit the model and implement its function in order to provide a computer decision support system. This model and CDSS show that progress has been made in both the field of MCDA in medicine and in modelling Parkinson's disease. With further refinement a more sophisticated CDSS could be developed that would have great potential for use in a clinical setting, providing clinicians with a time-saving decision aid unique in the field of Parkinson's disease and a means of implementing evidence-based medicine. This is something that could be particularly useful for less experienced doctors and for PDNSs new to prescribing in helping them with their decision-making. It could also provide a means of training junior doctors and medical students in medical schools and help them to develop their skills in decision-making and use of evidence-based medicine. Through this research project progress has been made in both modelling using MCDA and for PD. A model has been developed for the first time for Parkinson's disease and the use of MCDA extended in medicine in a way which has not been done before. Both PD and MCDA have been taken in a new direction and the potential for the use of MCDA in medicine and the modelling of Parkinson's disease been taken forward. Developing this model and CDSS for PD have shown that there is a great potential for future work moving the field of decision support in medicine forward and creating the potential for applying the methodology to other medical conditions.

"The aim of argument, or of discussion, should not be victory, but progress"
Joseph Joub

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APPENDIX I

Data Collection on Parkinson's Disease Drugs

Drug	Criteria	Comparator	Stage of disease	Primary endpoint	Significance level	How performs
Amantadine	Motor fluctuations	Placebo	H&Y II to V	UPDRS IV q39 Mean diary scores Variance of diary scores	P<0.01 P<0.01 P<0.01	"on" time (hrs) 2.4 baseline, 2.1 (15 days), 1.9 (30 days), 2.3(60-240 days) "off" time (hrs) 2.9 baseline, 2.5 (15 days), 2.0 (30 days), 2.4 (60-240 days) (Thomas et al., 2004) UPDRS IV q39 amantadine mean 1 vs placebo 1.5; mean diary scores amantadine 1.03 vs placebo 1.62; variance of diary scores amantadine 1.3 vs placebo 3.3 (Verhagen Metman et al., 1998)
	Cognitive impairment					
	Confusion					
	Hallucinations					ADR (SPC – www.alliancepharma.co.uk) ADR (www.bnf.org)
	Dyskinesias	Placebo Placebo Placebo	Advanced – H&Y 3 to 5 (off) 1 to 3 (on) Advanced H&Y II to V	VAS from diary assessment, cumulative dyskinesia scores calculated UPDRS IV items 32 and 33 UPDRS IV 32-34 Dyskinesia rating scale UPDRS IV 32 & 33	P<0.05 P<0.05 P<0.001 P<0.001 P<0.001	Reduction cumulative dyskinesia score by 53% 11.9 vs 25.6 placebo Dyskinesia duration and disability signif reduced, baseline 3.4 to post-Rx 1.7(Luginger et al., 2000) Baseline score 6.7 compared to 2.0 (15 days), 2.3 (30 days), 6.1 (60-240 days) DRS – 19.6 baseline, 10.5 (15 days), 10.3 (30 days), 18.4 (60-240 days) (Thomas et al., 2004) Amantadine mean 1 vs placebo mean 4 (scale 0 to 4) (Verhagen et al., 1998)
	Postural hypotension					ADR (www.alliancepharma.co.uk)

	Patient's choice					No data
	Mobility					No data
	Depression					ADR (www.alliancepharma.co.uk)
	ADLs	Placebo	H&Y II to V	UPDRS II	P<0.01	Amantadine 8.0 'on' vs 10.6 placebo 'on'; amantadine17.8 'off' vs 21.0 placebo 'off' (Verhagen et al., 1998)
	Cost-effectiveness					No data
	Stage of disease (H&Y)					No data
	Drug contraindications					Hypersensitivity to amantadine or excipients, convulsions, gastric ulceration, severe renal disease, pregnancy, breast-feeding. Use with caution in cardiovascular disorders – congestive heart failure Epilepsy, history of gastric ulceration, pregnancy, breast-feeding (BNF)
	Drug interactions					Increased risk of antimuscarinic side-effects when given with antimuscarinics, increased risk of side-effects when given with bupropion, increased risk of CNS toxicity when given with memantine (manufacturer of memantine advises avoid concomitant use), increased risk of extrapyramidal side-effects when given with methyldopa, metoclopramide, tetrabenazine, antipsychotics, domperidone (BNF)
	Adverse drug reactions					Anorexia, nausea, nervousness, inability to concentrate, insomnia, dizziness, convulsions, hallucinations or feelings of detachment, blurred vision, GI disturbances, livedo reticularis, peripheral oedema, rarely leucopenia, rashes (BNF)
Apomorphine	Motor fluctuations	Placebo	Advanced – with motor fluctuations	UPDRS motor score	P<0.001	Therapeutic indication. Off-state score 39.7 vs 36.3 placebo, on-state score 15.8 vs 36.2 placebo, %change -62 vs -1

						placebo (Dewey et al., 2001)
	Cognitive impairment	DBS	Advanced	California verbal learning test (verbal memory) Corsi block tapping span test (spatial memory)	NS NS	CVLT 45.62 baseline to 53.65 12 mths Corsi 4.90 baseline to 4.25 12 mths (De Gaspari et al., 2006) Contraindicated for dementia (www.apo-go.co.uk/literature/apgamp_spc_v4%20.07.2007.pdf)
	Confusion					ADR – mild confusion (www.apo-go.co.uk) ADR (Dewey et al., 2001) ADR (BNF)
	Hallucinations					ADR (www.apo-go.co.uk) ADR (Dewey et al., 2001) ADR (BNF)
	Dyskinesias	Placebo	Advanced	Dyskinesia score (?UPDRS)	P<0.001	Off-state 0, on-state 1, score change 1 vs 0,0,NA placebo (Dewey et al., 2001) ADR (BNF) Intermittent apomorphine not suitable if severe dyskinesia (www.apo-go.co.uk)
	Postural hypotension					ADR (BNF) Caution advised if pre-existing post hyp (www.apo-go.co.uk)
	Patient's choice					No data
	Mobility					No data
	Depression	DBS	Advanced – H&Y>=3	HDRS-17	NS	Baseline score 10.00 to 12 month score 7.46 (Gaspari et al., 2006)
	ADLs					No data
	Cost-effectiveness					No data
	Stage of disease (H&Y)					No data
	Drug contraindications					Contra-indicated for children under 18 years of age; pts with respiratory depression, dementia,

						psychotic diseases or hepatic insufficiency; intermittent apogo not suitable if severe dyskinesia or dystonia; known hypersensitivity to apomorphine or its excipients Caution with pts with renal, pulmonary or cardiovascular disease, pts prone to nausea & vomiting; pre-existing cardiac disease or pts taking vasoactive medicinal products eg antihpertensives, especially if pre-existing postural hypotension; some pts neuropsychiatric disturbances may be exacerbated Respiratory depression, hypersensitivity to opioids, not suitable if 'on' response to levodopa marred by severe dyskinesia, hypotonia or psychiatric effects, hepatic impairment, breast-feeding (BNF)
	Drug interactions					Potential interaction between clozapine and apogo, clozapine may be used to reduce symptoms of neuropsych complications; caution advised antihypertensive and cardiac active drugs; caution pregnant women/childbearing age; avoid during breast-feeding Effects of apomorphine antagonised by antipsychotics, effects of apomorphine possibly enhanced by entacapone (BNF)
	Adverse drug reactions					Nausea, vomiting, drowsiness, confusion, hallucinations, injection-site reactions, *less commonly*: postural hypotension, breathing difficulties, dyskinesia during 'on', haemolytic anaemia with levodopa, *rarely*: oesinophilia, pathological gambling, increased libido, hypersexuality (BNF)

Bromocriptine	Motor fluctuations	Ropinirole	H&Y I to III	UPDRS III	P=0.086 (NS)	Motor score improvement mean % 31 ropinirole vs 22 bromocriptine 23.1 to 16.94 (Korczyn et al., 1999)
	Cognitive impairment					No data
	Confusion					ADR (BNF)
	Hallucinations					ADR (BNF)
	Dyskinesias	Levodopa DCI/LevodopaDCI and selegiline	H&Y I to V	As ADR		ADR (BNF) After 3 yr follow up incidence of dyskinesia 2% for brom vs 27% levodopa/34% for ldopa/selegiline (PDRGUK, 1999)
	Postural hypotension					ADR (BNF)
	Patient's choice					No data
	Mobility					No data
	Depression					11.3% ropinirole vs 10.2% bromocriptine (Korczyn et al., 1999)
	ADLs	Ropinirole	H&Y I to III	UPDRS III	P=0.009	Mean score ropinirole 5.83 vs bromocriptine 7.28 (Korczyn et al., 1999)
	Cost-effectiveness	Levodopa Pergolide Pramipexole				Generic bromocriptine cost-effective (Shimbo et al., 2001) Pergolide cost saving and more effective than Bromocriptine (Davey et al., 2001) More expensive and less effective than pramipexole (Hoerger et al., 1998)
	Stage of disease (H&Y)	LevodopaDCI/LevodopaDCI and selegiline	H&Y I to V	Disability score – Webster rating scales	P<0.0058 P<0.0002	Significant improvement for levodopa vs bromocriptine (PDRGUK, 1999) Significant improvement for ldpa/selegiline vs bromocriptine (PDRGUK, 1999)
	Drug contraindications					Hypersensitivity to bromocriptine or other ergot alkaloids, toxaemia of pregnancy, hypertension in pregnant women or in peurperium (BNF)

	Drug interactions					hypoprolactinaemic and antiparkinsonian effects of bromocriptine antagonised by antipsychotics, hypoprolactinaemic effect of bromocriptine possibly antagonised by domperidone and metoclopramide, plasma concentration of bromocriptine increased by erythromycin (increased risk of toxicity) and octreotide and possibly increased by macrolides (increased risk of toxicity), risk of toxicity when bromocriptine given with isometheptene and phenylpropanolamine (BNF)
	Adverse drug reactions					Nausea, constipation, headache, drowsiness, nasal congestion, *less commonly:* vomiting, postural hypotension, fatigue, dizziness, dyskinesia, dry mouth, leg cramps, *high doses:* confusion, psychomotor excitation, hallucinations, *rarely*: constrictive pericarditis, pericardial effusion, pleural effusion, retroperitoneal fibrosis, hair loss, allergic skin reactions, *very rarely:* GI bleeding, gastric ulcer, vasospasm of fingers and toes (particularly in Raynaud's), neuroleptic malignant syndrome on withdrawal, pathological gambling, increased libido, hypersexuality (BNF)
Cabergoline	Motor fluctuations	None	H&Y I to IV	CDRS score	P<0.0001	Reduction % time awake with 'severe off' symptoms from mean 30.78 baseline to 17.19 wk 26 (Odin et al., 2006)
				UPDRS III	P<0.05 (wk 16) P=0.06055 (wk 26)	Severity 'off' periods improved from 39.8 baseline to 29.1 wk 16, to 25.5 wk 26
		Placebo	Median H&Y II	UPDRS III	Wk 12 p=0.014, wk 24 p=0.031	Cabergoline grp signif better at wk 12 and wk 24 vs placebo, Cabergoline improved 16% wk 24 from baseline vs 6% placebo
				Patient diaries		'on' time increased Cabergoline grp signif wk 12 and wk 24 vs placebo

		Levodopa	H&Y I to III	UPDRS IV q39 UPDRS III	Wk12 p=0.005, wk 24 p=0.022 Wk 12 p=0.009, wk 24 p=0.012 P<0.01	Cabergoline grp less 'off' time at wk 12 and wk 24 vs placebo (Hutton et al., 1996) Mean scores lower for ldopa grp than cabergoline grp – 13.8 vs 12.9 at 1yr, 18.6 vs 17.2 at 3yrs and 19.2 vs 16.3 at 5yrs (Bracco et al., 2004)
	Cognitive impairment	Levodopa	H&Y I to III	MMSE	NS	No change over time in cognitive function (Bracco et al., 2004)
	Confusion					ADR (BNF)
	Hallucinations					ADR (BNF) ADR (Odin et al., 2006)
	Dyskinesias	None Levodopa	H&Y I to IV H&Y I to III	CDRS score UPDRS II	P<0.001 ??	ADR (BNF) Time 'on with dyskinesias' reduced from 20.67% baseline to 8.57% 26 weeks (Odin et al., 2006) ADR (Odin et al., 2006) Occurred at a lower rate in Cabergoline grp than levodopa grp 9.5% vs 21.2% after 5 years (Bracco et al., 2004)
	Postural hypotension					ADR (BNF)
	Patient's choice	No data	No data	No data	No data	No data
	Mobility	No data	No data	No data	No data	No data
	Depression	Levodopa	H&Y I to III	Zung SDS	NS	ADR (BNF) No change over time in depression (Bracco et al., 2004)
	ADLs	Placebo Levodopa	Median H&Y II H&Y I to III	UPDRS II UPDRS II	Wk 12 p=0.043, wk 24 p=0.032 P<0.02	Cabergoline grp scores significantly better at wk 12 and wk 24 than placebo, improvement 19% from wk 0 vs 4% placebo grp (Hutton et al., 1996) Slight higher improvement for ldopa vs caberg signif only at 12 mths, declined for both groups after that
	Cost-	Levodopa				Cost-effective for patients ≤60 yrs (Smala et al.,

	effectiveness					2003)
	Stage of disease (H&Y)	No data	No data	No data	No data	No data
	Drug contraindications					Pregnancy; breast-feeding; history of pulmonary, pericardial or retroperitoneal fibrotic disorders; cardiac valvulopathy (BNF)
	Drug interactions					Hypoprolactinaemic and antiparkinsonian effects antagonised by antipsychotics, hypoprolactinaemic effect of cabergoline antagonised by metoclopramide and possibly domperidone, plasma concentration of cabergoline increased by erythromycin (increased risk of toxicity) and possibly macrolides (BNF)
	Adverse drug reactions					Nausea, constipation, headache, drowsiness, nasal congestion, *less commonly:* vomiting, postural hypotension, fatigue, dizziness, dyskinesia, dry mouth, leg cramps, *high doses:* confusion, psychomotor excitation, hallucinations, *rarely*: constrictive pericarditis, pericardial effusion, pleural effusion, retroperitoneal fibrosis, hair loss, allergic skin reactions, *very rarely:* GI bleeding, gastric ulcer, vasospasm of fingers and toes (particularly in Raynaud's), neuroleptic malignant syndrome on withdrawal, pathological gambling, increased libido, hypersexuality. Also: dyspepsia, epigastric and abdominal pain, syncope, breast pain, palpitation, angina, cardiac valvulopathy, epistaxis, peripheral oedema, hemianopia, asthenia, paraesthesia, erthyromelalgia, hot flushes, depression (BNF)

Duodopa	Motor fluctuations	Group1: PD meds 3 wks /duodopa 3wks Group 2: duodopa 3wks/ PD meds 3wks	Advanced	Primary: %time 'on' Secondary: %time 'off' and %time 'on with dyskinesias' UPDRS III		'on' increased from 81 to 100%, decrease in 'off' state and no increase in dyskinesia (Nyholm et al., 2005) ADR
	Cognitive impairment		Advanced			Dementia ADR (Nyholm et al., 2005)
	Confusion		Advanced			ADR (Nyholm et al., 2005)
	Hallucinations		Advanced			ADR (Nyholm et al., 2005)
	Dyskinesias		Advanced			No change. ADR (Nyholm et al., 2005)
	Postural hypotension					ADR (BNF - levodopa)
	Patient's choice		Advanced			16 out of 18 (89%) pts completing study chose duodopa infusion vs conventional therapy (Nyholm et al., 2005)
	Mobility					No data
	Depression					No change. ADR (Nyholm et al., 2005) ADR (BNF)
	ADLs	Group1: PD meds 3 wks /duodopa 3wks Group 2: duodopa 3wks/ PD meds 3wks	Advanced	UPDRS pt II	P <0.01	Improvement against conventional meds median 11 and mean 11.1 duodopa vs median 14 and mean 15.3 conventional meds (Nyholm et al., 2005)
	Cost-effectiveness		Advanced			NNT for one year for benefit is 1.1. Yearly drug cost is £28,105 (Solvay, 2008)
	Stage of disease (H&Y)					No data
	Drug contraindications		Advanced			Hypersensitivity to levodopa, carbidopa or any of excipients; narrow-angle glaucoma; severe

						liver and renal insufficiency; severe heart failure; severe cardiac arrhythmia; acute stroke Pregnancy, breast-feeding (BNF) (levodopa)
	Drug interactions		Advanced			Antihypertensives, antidepressants (tricyclic), anticholinergics, dopamine receptor antagonists can reduce therapeutic effect of levodopa, selegiline – serious orthostatic hypotension, see others to adjust doses of. Selegiline – orthostatic hypotension Enhanced hypotensive effect: ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside; amisulpiride manufacturer advises advoidance; risk arrhythmias with volatile liquid GAs; absorption of ldopa poss reduced by: antimuscarinics, oral iron, phenytoin; effects of ldopa antagonised by: antipsychotics, possibly benzodiazipines; agitation, confusion & hallucinations with baclofen; increased risk side effects with buproprion, moclobemide; risk hypertensive crisis with MAOIs; enhanced effect and increased toxicity with selegiline (reduce dose ldopa) (levodopa – BNF)
	Adverse drug reactions					Anorexia, nausea and vomiting, insomnia, agitation, postural hypotension, dizziness, tachycardia, arrhythmias, reddish discolouration of urine and bodily fluids, rarely hypersensitivity, abnormal involuntary movements & psych symptoms (inc hypomania and psychosis) may be dose-limiting, depression, drowsiness, headache, flushing, sweating, GI bleeding, peripheral neuropathy, taste disturbance,

						pathological gambling, increased libido, hypersexuality, pruritus, rash and livery enzyme changes reported, syndrome resembling neuroleptic malignant syndrome reported on withdrawal, very rarely angle-closure glaucoma (BNF - levodopa)
Entacapone	Motor fluctuations	Placebo	Advanced	UPDRS III	P<0.05	Increased proportion daily ON time from 58% to 65% vs placebo 60% to 61%, UPDRS II and III not stat significant vs placebo (fluctuators). (Brooks and Sagar, 2003)
						Mean "on" time increased by 24% vs placebo (Ruottinen and Rinne, 1996)
		Placebo		UPDRS III	P=0.001	Decrease in 'off' time of 0.4
						Pt pop receiving DAs decrease 1.7 to 1.3
			H&Y mean 2.9		P<0.0001	Pop not on Das decrease 1.7 to 1.2
					P<0.0001	At baseline no pts with no 'off' time, at end of
					P<0.0001	study 8% had no 'off' time (Durif et al., 2001)
						Proportion daily 'on' time increased from 62% to
		None				72% vs 59% to 65%
					P<0.05	'Off' time decreased significantly vs placebo
						Fluctuating pts with 5-10 ldopa doses per day
			H&Y 1.5 to IV		P<0.05	increased 'on' time 1.7h vs 0.5h placebo (Poewe
					P<0.05	et al., 2002)
		Placebo				Mean % 'on' time signif higher vs placebo – 5%
			Mean H&Y 2.4		P=0.003	(1997)(PSG, 1997)
					P<0.01	UPDRS III increased after withdrawal from 20.8
						to 23.7 vs placebo 20.2 to 20.3 (Myllyla et al.,
			H&Y all stages	Secondary:	NS	2001)
		Placebo		UPDRS III		UPDRS III not signif different from baseline at
		Placebo				36mths
				UPDRS III		Proportion pts with predictable 'offs' decreased
		None				from 97% to 84% - (Larsen et al., 2003)
	Cognitive impairment					No data
	Confusion					ADR:(Ruottinen and Rinne, 1996), ADR (Durif et

						al., 2001), ADR (BNF)
	Hallucinations					ADR: (Brooks et al., 2003, Poewe et al., 2002, PSG, 1997, Larsen et al., 2003)
	Dyskinesias					ADR: (Brooks et al., 2003, Ruottinen & Rinne, 1996, Poewe et al., 2002, PSG, 1997, Myllyla et al., 2001, Larsen et al., 2003)
	Postural hypotension					ADR : (Larsen et al., 2003, Durif et al., 2001, Myllyla et al., 2001)
	Patient's choice					No data
	Mobility					No data
	Depression					ADR: (Brooks et al., 2003, Larsen et al., 2003)
	ADLs	Placebo Placebo Placebo Placebo None	 H&Y mean 2.9 H&Y 1.5 to 4 H&Y 1.5 to 4 H&Y all stages	UPDRS II UPDRS II UPDRS II UPDRS II UPDRS II UPDRS II UPDRS II	NS P<0.01 P<0.0001 P<0.0001 P<0.05 NS P=0.06 P<0.001 NS	Slight improvement UPDRS II but not stat significant (fluctuators) 12.5 baseline to 12.0 6mths (Brooks et al., 2003) UPDRS II improved from 10.6 to 10 vs reduction 0.1 placebo, (non-fluctuators) (Brooks et al., 2003) Mean score decreased by 1.8 (Durif et al., 2001) Pt pop on DAs change from baseline -1.9 vs -1.5 for pts not on DAs, stat signif compared to baseline but not compared to each other (Durif et al., 2001) UPDRS II score improved from 12.4 to 11.1 vs 12.0 to 12.4 placebo Non-fluctuating pts: improved from 11.3 to 10.3 vs 9.8 to 11.3 placebo (Poewe et al., 2002) 0.8 improvement in score vs placebo (PSG, 1997) UPDRS II score increased after withdrawal from 9.3 to 10.3 vs placebo 9.0 to 8.9 (Myllyla et al., 2001) At 36mths UPDRS similar to baseline (Larsen et al., 2003)
	Cost-effectiveness					Cost-effective – (Nuijten et al., 2001) (Palmer et al., 2002)

	Stage of disease (H&Y)					Unchanged for both groups (Poewe et al., 2002)
	Drug contraindications					Pregnancy, breast-feeding, hepatic impairment, phaeochromocytoma, history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis (BNF)
	Drug interactions					Possibly enhances effects of: adrenaline, apomorphine, dobutamine, dopamine, methyldopa, noradrenaline; Manufacturer advises caution with: tricyclics, moclobemide, paroxetine, venlafaxine; absorption of entacapone reduced by oral iron; avoid use with non-selective MAOIs; possibly reduces plasma concentration of rasagiline; manufacturer advises max dose 10mg selegiline; enhances anticoagulant effect of warfarin (BNF)
	Adverse drug reactions					Nausea, vomiting, abdominal pain, constipation, diarrhoea, urine may be coloured reddish-brown, dry mouth; confusion, dizziness, abnormal dreams, fatigue, insomnia, dystonia, dyskinesia, hallucinations; increased sweating; *rarely* hepatic dysfunction and rash; *very rarely* anorexia, weight loss, agitation, and urticaria; also reported colitis, neuroleptic malignant syndrome, rhabdomyolysis, and skin, hair, and nail discoloration (BNF)
Madopar	Motor fluctuations	Ropinirole	H&Y I to III	UPDRS III	P=0.008	Decrease from baseline of 0.8ropinirole vs 4.8 levodopa (Rascol et al., 2000)
	Cognitive impairment					Dementia ADR (BNF)
	Confusion					ADR (BNF)
	Hallucinations					ADR (Rascol et al., 2000) ADR (BNF)
	Dyskinesias	ropinirole	H&Y I to III	UPDRS		Dyskinesias developed in 20% ropinirole grp vs 45% levodopa grp

					P<0.001 P=0.002	No at risk after 5 yrs: ropinirole 85 vs 45 levodopa Risk disabling dyskinesia signif lower ropinirole grp, hazard ratio to be free disabling dyskinesia 3.02 ropinirole vs levodopa, 8% ropinirole vs 23% levodopa had disabling dyskinesias ADR (Rascol et al., 2000)
	Postural hypotension					ADR (Rascol et al., 2000) ADR (BNF)
	Patient's choice					No data
	Mobility					No data
	Depression					ADR (Rascol et al., 2000) ADR (BNF)
	ADLs	Ropinirole	H&Y I to III	UPDRS II	P=0.08 (NS)	Mean change from baseline 1.6 ropinirole vs 0.0 levodopa (Rascol et al., 2000)
	Cost-effectiveness	Bromocriptine, cabergoline ropinirole				Not cost-effective against bromocriptine (Shimbo et al 2001), cabergoline (Smala et al 2003), or ropinirole (Iskedjian and Einarson, 2003)
	Stage of disease (H&Y)	No data	No data	No data	No data	No data
	Drug contraindications					Pregnancy, breast-feeding (BNF)
	Drug interactions					Enhanced hypotensive effect: ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside; amisulpiride manufacturer advises advoidance; risk arrhythmias with volatile liquid GAs; absorption of ldopa poss reduced by: antimuscarinics, oral iron, phenytoin; effects of ldopa antagonised by: antipsychotics, possibly benzodiazipines; agitation, confusion &

						hallucinations with baclofen; increased risk side effects with buproprion, moclobemide; risk hypertensive crisis with MAOIs; enhanced effect and increased toxicity with selegiline (reduce dose ldopa) (BNF)
	Adverse drug reactions					Nausea, vomiting, taste disturbances, dry mouth, anorexia, arrhythmias, postural hypotension, syncope, drowsiness (including sudden onset of sleep), fatigue, dementia, psychoses, hallucinations, confusion, euphoria, abnormal dreams, insomnia, depression (very rarely with suicidal ideation), anxiety, dizziness, dystonia, dyskinesia, and chorea. *Less commonly* weight loss or gain, constipation, diarrhoea, hypersalivation, dysphagia, flatulence, hypertension, chest pain, oedema, hoarseness, ataxia, increased hand tremor, malaise, muscle cramps, and reddish discoloration of the urine and other body fluids may occur. *Rare* side-effects include abdominal pain, gastro-intestinal bleeding, dyspepsia, phlebitis, dyspnoea, agitation, paraesthesia, bruxism, trismus, hiccups, neuroleptic malignant syndrome (associated with abrupt withdrawal), convulsions, reduced mental acuity, disorientation, headache, urinary retention, urinary incontinence, priapism, activation of malignant melanoma, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, blurred vision, blepharopasm, diplopia, activation of Horner's syndrome, pupil dilatation, oculogyric crisis, angioedema, rash, urticaria, pruritus, flushing, alopecia, exanthema, Henoch-Schönlein purpura, and increased sweating.

						Very rarely angle-closure glaucoma may occur; pathological gambling, increased libido, hypersexuality, and false positive tests for urinary ketones have also been reported. (BNF)
Pergolide	Motor fluctuations	None	H&Y II to V	UPDRS III Patient diaries	P<0.001 P<0.001 P<0.001	Improved from median 32 baseline to 8 at endpoint (Storch et al., 2005) Total motor fluctuations Mean of 10.5h per day baseline to 2.8h per day at endpoint, 'off' hrs per day decreased from 7.3h per day baseline to 1.7h per day endpoint (Storch et al., 2005)
	Cognitive impairment					No data
	Confusion					ADR(BNF)
	Hallucinations					ADR (BNF)
	Dyskinesias	Levodopa None	Early (I to 2.5) H&Y II to V	UPDRS IV UPDRS IV Patient diaries	P<.001 P<0.001 P<0.001	3x as many pts on l-dopa had dyskinesias at 3yr endpoint compared to pergolide (Oertel et al., 2006) Improved from median 10 baseline to 2 at endpoint Reduced from mean of 5.0h per day to 1.4h per day at endpoint (Storch et al., 2005) ADR (BNF)
	Postural hypotension	Levodopa	Early (1 to 2.5)			Difference in proportion of pts in each group with post hypotension not significantly significant (but greater number in pergolide group) (Oertel et al., 2006) ADR (BNF)
	Patient's choice					No data
	Mobility					No data
	Depression	Pramipexole	Mean H&Y III	Zung self-rating depression scale MADRS	P=0.01 NS	Zung score decreased from mean 60.4 to 43.4 vs 59.6 to 49.1 pramipexole (Rektorova et al., 2003)

						Reduction from 11.25 to 10.06 vs 15.11 to 9.28 pramipexole (baseline values different for ppx and prg – authors say cannot exclude bias, be cautious with results) (Rektorova et al., 2003)
	ADLs	Pramipexole	Mean H&Y III	UPDRS II UPDRS VI (Schwab & England)	not given not given	Mean score reduced from 15.5 to 7.2 vs 15.2 to 7.6 pramipexole (Rektorova et al., 2003) Score changed from 70% 1st visit to 85% 6th visit (8 months) vs 72% to 83% pramipexole (Rektorova et al., 2003)
	Cost-effectiveness	Bromocriptine Levodopa		Cost-effectiveness (Markov model) Cost-effectiveness (Markov model)		Pergolide cost saving and more effective than bromocriptine (Davey et al., 2001) Cost-effective for H&Y stage III or more (Shimbo et al., 2001)
	Stage of disease (H&Y)	Levodopa None	Early (1 to 2.5) H&Y 2 to 5	H&Y H&Y	P=0.001	Change from baseline after 3 years – 0.6 perg vs 0.1 l-dopa Improved by 0.5 to 1.5 in 63% pts, 34% had same score (Storch et al., 2005)
	Contraindications					History fibrotic disorders, cardiac valve disorders (BNF)
	Drug interactions					Effects antagonised by antipsychotics; antiparkinsonian effect antagonised by metoclopramide (BNF)
	Adverse drug reactions		Early (1 to 2.5)			Nausea, vomiting, dyspepsia, abdominal pain, dyspnoea, rhinitis, hallucinations, dyskinesias, drowsiness, diplopia, constipation, diarrhoea, tachycardia, atrial premature contractions, palpitation, hypotension, syncope, raynaud's

						phenomenon, cardiac valvulopathy, pericarditis, pericardial effusion, pleuritis, pleural effusion, pleural fibrosis, insomnia, confusion, dizziness, pathological gambling, neuroleptic malignant syndrome, fever, increased libido, hypersexuality, rash (BNF)
Pramipexole	Motor fluctuations	Placebo None	Advanced H&Y I to V	UPDRS II and III SPES	P<0.001	Mean number 'off' hours per day reduced from 6 to 4 for pramipexole group vs 6 to 6 for placebo group Baseline 16.17 to 9.93 endpoint (Lemke et al., 2006)
	Cognitive impairment					No data
	Confusion					ADR (advanced PD) (Lemke et al., 2006) ADR (BNF)
	Hallucinations	Placebo	Early/advanced	UPDRS		Early – 9% vs 2.^% placebo Advanced – 16.5% vs 3.8% placebo Caused discontinuation 3.1% early and 2.7% advanced vs 0.4% placebo both groups Increases risk hallucinations: Early – risk 1.9x > placebo if pt <65 6.8x > if pt >65 Advanced – 3.5x > placebo if <65 5.2x > placebo if >65 ADR (Lemke et al., 2006) ADR (BNF)
	Dyskinesias					ADR (advanced PD) (Lemke et al., 2006) ADR (BNF)
	Postural hypotension	Placebo	Early/advanced			Dopamine agonists impair systemic regulation of BP with resulting orthostatic hypotension, especially during dose escalation. Requires careful monitoring. Reported incidence wasn't greater for pramipexole pts than for placebo group. (pts with significant orthostatic hypotension at baseline excluded from trial).

						(Lemke et al., 2006) ADR (BNF)
	Patient's choice					No data
	Mobility					No data
	Depression	None	H&Y I to V	SPES - depression	P<0.001	Moderate to severe depression baseline 22.5% to endpoint 6.8%, mild depression baseline 46.6% to endpoint 37.6% (Lemke et al., 2006)
	ADLs	None	H&Y I to V	SPES	P<0.001	8.5 baseline to 6.26 endpoint (Lemke et al., 2006)
	Cost-effectiveness					No data
	Stage of disease (H&Y)					No data
	Drug contraindications	placebo	Early/advanced			Hypersensitivity to drug or ingredients Breast-feeding (BNF)
	Drug interactions					Dopamine antagonists (neuroleptics – phenothiazines, butyrophenones, thixanthenes or metoclopramide) may diminish effectiveness of pramipexole Amantadine – may slightly decrease the oral clearance of pramipexole Avoid antipsychotics – antagonism of effect (BNF)
	Adverse drug reactions	Pramipexole vs Placebo – early Pramipexole & levodopa vs Placebo and levodopa – advanced PD	Early/advanced	UPDRS		Nausea, constipation; postural hypotension, hypotension, headache, confusion, drowsiness (including sudden onset of sleep), fatigue, insomnia, dizziness, hallucinations (mostly visual), dyskinesia, peripheral oedema; hyperkinesia, delusions, abnormal dreams, paradoxical worsening of restless legs syndrome, and behavioural changes including pathological gambling, binge eating, hypersexuality, and changes in libido also reported (BNF)
Rasagiline	Motor	Placebo	Early - <= H&Y 3	UPDRS total	P<0.001	Benefit for 1mg and 2mg vs placebo for total

	fluctuations	1mg or 2mg vs 2mg delayed Entacapone and placebo	H&Y <5 in 'off' state	score baseline to 26 weeks, secondary: H&Y, Schwab-England ADL, BDI, timed motor tests, PDQUALIF (TEMPO) Primary: change from baseline to treatment in mean total daily off-time as measured by 24h diaries. Secondary: CGI 'on'; UPDRS III	Not given ? P=0.0001 P=0.0130	UPDRS score Motor subscale -2.71 (1mg) and -1.68 (2mg) both vs placebo Timed motor score: -0.55 (1mg) and -0.36 (2mg) both vs placebo (2002)(PSG, 2002) -1.06 1mg and -0.99 2mg vs 2mg delayed for UPDRS motor (PSG, 2002) Mean total daily off-time reduced from baseline to endpoint by more than 1h, almost three times more than by placebo UPDRS III score -5.64 vs placebo (Rascol et al., 2005)
	Cognitive impairment					No data
	Confusion					No data
	Hallucinations					ADR (BNF)
	Dyskinesias	Entacapone and placebo	H&Y <5 in 'off' state	UPDRS	NS p=0.7711	UPDRS dyskinesia score -0.03 vs placebo (Rascol et al., 2005)
	Postural hypotension					ADR for 2% pts vs 0% placebo grp (PSG, 2002)
	Patient's choice					No data
	Mobility					No data
	Depression	Placebo	<= H&Y 3	BDI	Not given	-0.35 (1mg) and -0.21 (2mg) both vs placebo (PSG, 2002) ADR (BNF)
	ADLs	Placebo Placebo 2mg delayed	<= H&Y 3 <=H&Y 3 <=H&Y 3	UPDRS II Schwab & England UPDRS II	Not given Not given P=0.005	-1.04 (1mg) and -1.22 (2mg) both vs placebo 0.77 (1mg) and 0.39 (2mg) both vs placebo (PSG, 2002) -0.48 (1mg) and -0.96 (2mg) vs 2mg delayed

		Placebo and entacapone	H&Y <5	UPDRS II	P<0.0001	(PSG, 2002) UPDRS II -1.71 vs placebo (Rascol et al., 2005)
	Cost-effectiveness					No data
	Stage of disease (H&Y)	Placebo 2mg delayed	<= H&Y 3 <=H&Y 3	H&Y H&Y	Not given NS	-0.04 (1mg) and -0.04 (2mg) both vs placebo (PSG, 2002 0.08 (1mg) and 0.04 (2mg) vs 2mg delayed (PSG, 2002)
	Drug contraindications					Hepatic impairment, pregnancy, breastfeeding (BNF)
	Drug interactions					Avoid dextromethorphan and sympathomimetics; increased risk of CNS toxicity with antidepressants (SSRIs & Tricyclics); wait 2 weeks before using: fluoxetine, fluvoxamine, MAOIs, pethidine; plasma concentration of rasagiline reduced by entacapone (BNF)
	Adverse drug reactions					Dry mouth, dyspepsia, constipation; angina; headache, depression, anorexia, weight loss, abnormal dreams, vertigo, hallucinations; influenza-like symptoms; urinary urgency; leucopenia; arthralgia; conjunctivitis; rash; *less commonly* myocardial infarction, and cerebrovascular accident (BNF)
Ropinirole	Motor fluctuations	Bromocriptine Levodopa (madopar)	H&Y II-IV H&Y I To III H&Y I to III	>-20% improvement UPDRS III, reduction >-20% off duration per day, UPDRS III	NS NS P=0.008 P=0.086 (NS)	70% reduction UPDRS motor score >-20% vs 63.3 bromocriptine group (no signif difference); 81% reduction in off duration >-20% vs 52.4% bromocriptine group (not stat signif) (Whone et al., 2003) Decrease from baseline of 0.8 ropinirole vs 4.8 levodopa (Rascol et al., 2000) Motor score improvement mean % 31 ropinirole vs 22 bromocriptine (Korczyn et al., 1999)

		Bromocriptine		UPDRS III		
	Cognitive impairment					No data
	Confusion					5 pts as adverse event vs 1 levodopa (Rascol et al., 2000) ADR (BNF) ADR (Korczyn et al., 1999)
	Hallucinations					6 pts as adverse event vs 1 levodopa (Rascol et al., 2000) ADR (BNF)
	Dyskinesias	Levodopa Levodopa	H&Y I to 2.5 H&Y I to III	UPDRS q32 (dyskinesias) UPDRS	p<0.001 P<0.001 P=0.002	3.4% developed dyskinesia vs 26.7% levodopa group (Rascol et al., 2000) ADR (BNF) Dyskinesias developed in 20% ropinirole grp vs 45% levodopa grp No at risk after 5 yrs: ropinirole 85 vs 45 levodopa Risk disabling dyskinesia signif lower ropinirole grp, hazard ratio to be free disabling dyskinesia 3.02 ropinirole vs levodopa, 8% ropinirole vs 23% levodopa had disabling dyskinesias (Rascol et al., 2000)
	Postural hypotension					Hypotension ADR (BNF) ADR (Korczyn et al., 1999)
	Patient's choice					No data
	Mobility					No data
	Depression					6 patients as adverse event vs 7 levodopa (Rascol et al., 2000) 11.3% ropinirole vs 10.2 bromocriptine ADR (Korczyn et al., 1999)
	ADLs	Levodopa Bromocriptine	H&Y I to III H&Y I to III	UPDRS II UPDRS II	P=0.08 (NS) P=0.009	Mean change from baseline 1.6 ropinirole vs 0.0 levodopa (Rascol et al., 2000) Mean score ropinirole 5.83 vs bromocriptine 7.28 (Korczyn et al., 1999)

	Cost-effectiveness	Levodopa		Cost-minimization analysis		Cost-saving from societal perspective, due to avoiding dyskinesias (Iskedjian & Einarson 2003)
	Stage of disease (H&Y)					No data
	Drug contraindications					Pregnancy, breast-feeding; caution: severe cardiovascular disease, major psychotic disorders, hepatic impairment, renal impairment (BNF)
	Drug interactions					Avoid antipsychotics, metoclopramide; metabolism inhibited by: ciprofloxacin; plasma concentration increased by oestrogens (BNF)
	Adverse drug reactions	levodopa				Nausea, vomiting, abdominal pain, dyspepsia; hypotension, syncope, leg oedema; drowsiness (including sudden onset of sleep), dizziness, nervousness, fatigue, dyskinesia, hallucinations, confusion; *less commonly* psychosis, pathological gambling, hypersexuality, and increased libido; *very rarely* hepatic disorders; *also reported* paradoxical worsening of restless legs syndrome (BNF)
Rotigotine	Motor fluctuations	Placebo	Advanced (II to IV)	No daily hours 'off' UPDRS II,III,IV	P<0.0001/0.0031 P<0.0001/0.0012 P 0.0871/0.6499 P<0.0001/0.0078 P 0.001/0.0195 P 0.0185/0.000	"off" time -2.7h/-2.1h vs 0.9h placebo "on"time – 3.1h/2.3h vs 1.1h placebo "on with dyskinesia" - 0.4h/0.1h vs-0.1h placebo "on without dyskinesia" – 3.5h/2.2h vs 1.1h placebo No daily "off" periods - 1.5/-1.3 vs -0.7 placebo UPDRS III -6.8/-8.7 vs -3.4 (LeWitt et al., 2007)

					6	
	Cognitive impairment					No data
	Confusion					No data
	Hallucinations	Placebo	Advanced	UPDRS II and III		ADR - 7%/14% vs 3% placebo (LeWitt et al., 2007)
	Dyskinesias	Placebo	Advanced	UPDRS II and III		ADR - 14%/17& vs 7% placebo (LeWitt et al., 2007)
	Postural hypotension	Placebo	Early	UPDRS II and III	Stat signif	ADR - 2% vs 4% placebo (Watts et al., 2007)
	Patient's choice					No data
	Mobility					No data
	Depression					No data
	ADLs	Placebo Placebo	Early Advanced (II to IV)	UPDRS II UPDRS II	Stat signif P0.0004/0.0023	Improved (?by how much – part II and III scores combined, not broken down) (Watts et al., 2007) Improved (LeWitt et al., 2007)
	Cost-effectiveness					No data
	Stage of disease (H&Y)					No data
	Drug contraindications					Hypersensitivity to rotigotine or components of transdermal system Sulphite sensitivity Treat pts with severe cardiovascular disease with caution – not known to what extent incidence of syncope occurs in these pts Pregnancy, breast-feeding (BNF)
	Drug interactions					Antipsychotics / metoclopramide could diminish effectiveness of rotigotine Possible additive effects, use caution with sedating medication, CNS depressants (benzodiazepines, antipsychotics, antidepressants)

						Manufacturer of rotigotine advises avoid concomitant use of antipsychotics (antagonism of effect) manufacturer of rotigotine advises avoid concomitant use of metoclopramide (antagonism of effect) (BNF)
	Adverse drug reactions					Nausea, vomiting, constipation, dry mouth, diarrhoea, dyspepsia, weight changes, postural hypotension, peripheral oedema, confusion, drowsiness, sleep disorders, dizziness, headache, dyskinesia, asthenia, hallucinations, hyperhydrosis, rash, pruritis, *less commonly:* abdominal pain, anorexia, taste disturbance, palpitation, tachycardia, hypotension, hypertension, atrial fibrillation, syncope, dyspnoea, cough, hiccup, tremor, psychosis, pathological gambling, anxiety, impaired attention, dystonia, paraesthesia, impaired memory, erectile dysfunction, increased libido, arthralgia, visual disturbances, *rarely:* convulsions, loss of consciousness (BNF)
Selegiline	Motor fluctuations	Placebo Placebo Placebo Placebo/tocopherol/ Deprenyl+tocopherol Placebo & levodopa	H&Y I to III H&Y I to III Mean H&Y 2.10 vs 2.11 H&Y dep mean 1.73 /placebo1.78/ Tocopherol 1.63/ dep+toc 1.73	UPDRS III UPDRS III UPDRS III UPDRS III UPDRS III	NS Signif P<0.001 P=0.0006 P<0.05 NS	6mth -1.5, 12 mth 0.7 (Palhagen et al., 2006) Increase 0. depenyl vs 4.1 placebo (total UPDRS score (II&III) increase 0.4 vs 5.8 placebo) (Olanow et al., 1995) Increase deprenyl 0.7 vs 3.8 placebo (Shoulson et al., 2002) Dep +2.1 vs dep+toc -0.5 vs toc -1.4 vs placebo -0.7 (1996)(PSG, 1996) After 60 months: selegiline 17.6 vs 24.1 placebo (Palhagen et al., 2006)

	Cognitive impairment	Placebo	H&Y I to III	MMSE	NS	contraindication – psychosis MMSE score 0.7 6mth, 0.5 12 mth change from baseline (Palhagen et al., 2006)
		Placebo	H&Y mean 2.10 vs 2.11	UPDRS mental	P=0.07	Increase deprenyl 0.6 vs 0.8 placebo (Shoulson et al., 2002)
				Measurement?	P=0.75	Dementia 3.9 deprenyl vs 3.0 placebo (Shoulson et al., 2002)
		Placebo & levodopa	?	MMSE	P=0.74	No difference between treatment groups
	Confusion					contraindication – psychosis ADR (BNF)
		Placebo	H&Y mean 2.10 vs 2.11	UPDRS mental	P=0.07	Increase deprenyl 0.6 vs 0.8 placebo (Shoulson et al., 2002)
				Measurement?	P=0.96	Confusion 6.6% deprenyl vs 6.6% placebo new cases (Shoulson et al., 2002)
	Hallucinations					ADR(BNF) ADR (Shoulson et al., 2002) ADR (Palhagen et al 2006)
	Dyskinesias	Placebo	H&Y mean 2.10 vs 2.11	Measurement?	P=0.006	ADR(BNF) Deprenyl 33.8% new cases vs 19.4% placebo (Shoulson et al., 2002)
	Postural hypotension					ADR (BNF) ADR (Shoulson et al., 2002)
	Patient's choice					No data
	Mobility					No data
	Depression	Placebo	H&Y I to III	HADRS	NS	Hardly any change in HADRS score (no figs given) ADR (Shoulson et al., 2002)
		Placebo & levodopa		HADRS	P=0.016,p=0.0001	Mean scores lower for selegiline and difference increased with time (Palhagen et al., 2006)
	ADLs	Placebo	H&Y I to III	UPDRS II	NS Signif ?? (not given)	6mth 0.0, 12mth 0.5 change Decrease -0.2 vs increase 1.8 placebo (Olanow et al., 1995)
		Placebo	H&Y mean 2.10	UPDRS II	P=0.0045	Increase deprenyl 1.1 vs 2.4 placebo (Shoulson

			vs 2.11			et al., 2002)
				S&England	P=0.053	Schwab & England score deprenyl -2.4 vs -4.5 placebo (Shoulson et al., 2002)
		Placebo/tocopherol/ Deprenyl+tocopherol	H&Y dep mean 1.73/placebo 1.78/tocopherol 1.63/dep+toc 1.73	S&England	P<0.05 (?)	S&E score dep -2.9 vs dep+toc -4.8 vs toc -4.9 vs -3.9 placebo (PSG, 1996)
		Placebo & levodopa		UPDRS II	P<0.05	60 month mean selegiline 9.4 vs 12.1 placebo (Palhagen et al., 2006)
	Cost-effectiveness					No data
	Stage of disease (H&Y)	Placebo	H&Y 2.10 vs 2.11 mean	H&Y stage	P=0.37 (NS)	Deprenyl mean 0.1 vs 0.2 placebo (Shoulson et al., 2002)
		Placebo/tocopherol/ Deprenyl+tocopherol	H&Y dep mean 1.73/placebo 1.78/tocopherol 1.63/dep+toc 1.73	H&Y stage	P<0.05	Deprenyl -0.27 vs deprenyl+tocopherol -0.35 vs tocopherol -0.33 vs placebo -0.19 (tocopherol worst) (PSG, 1996)
	Drug contraindications					Pregnancy, breast feeding. Cautions: gastric and duodenal ulceration, uncontrolled hypertension, arrhythmias, angina, psychosis, s-e ldopa may be increased, reduce ldopa dosage 10-20% (BNF)
	Drug interactions					CNS toxicity: tricyclics; risk serotonin syndrome: citalopram; risk hypertensive crisis: dopamine; max dose 10mg selegiline advised by manufacturer of entacapone; caution advised by manufacturer of escitalopram; increased risk hypertension and CNS excitation: fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine; enhanced effect and increased toxicity: levodopa; enhanced hypotensive effect: MAOIs; effects selegiline enhanced: Memantine; avoid

						use: moclobemide; plasma concentration increased: oestrogens, progesterone; hyperpyrexia and CNS toxicity (avoid use): pethidine; manufacturer advises caution: tramadol (BNF)
	Adverse drug reactions					Nausea, constipation, diarrhoea, dry mouth, postural hypotension, dyskinesia, vertigo, sleeping disorders, confusion, hallucinations, arthralgia, myalgia, mouth ulcers with oral lyophilisate, *rarely:* arrhythmias, agitation, headache, micturition difficulties, skin reactions, also reported chest pain (BNF)
Sinemet	Motor fluctuations	Pramipexole	H&Y I to III	UPDRS III	P<0.001 P<=0.002	-3.9 difference in treatment pramipexole minus levodopa Improvement levodopa group from baseline to each follow up significant vs pramipexole for motor UPDRS score
		Ropinriole	H&Y I to II.5	UPDRS III	Not given	Initial improvements in on-treamtent UPDRS motor scores retained over 2 yrs for ldopa but not ropinirole; mean 'on' UPDRS motor score increased by 0.70 from baseline to endpoint for ropinirole vs decrease by 5.64 levodopa (Whone et al., 2003)
		Pergolide	H&Y I to II.5	UPDRS III	P=0.006 P=0.038 P<0.001	Improvement UPDRS score at 1 year -3.2 pergolide vs -5.2 ldopa, estimate of treatment difference -1.92; time to onset of motor complications in 1st yr greater in pergolide grp than ldopa grp (Oertel et al., 2006) 3yr endpoint ldopa -2.8 vs 2.8 pergolide
	Cognitive impairment					No data
	Confusion					No data
	Hallucinations					ADR (PSG, 2000)
	Dyskinesias					Abnormal involuntary movements – ADR (BNF) Ropinirole grp (3.4%) developed dyskinesias vs

		Ropinirole Pergolide	H&Y I to II.5 H&Y I to II.5	UPDRS q32 UPDRS IVa q32	P<0.001 P<0.001 P<0.001	Idopa (26.7%); Time to develop dyskinesia in favour of ropinirole vs Idopa (hazard ratio 8.28) (Whone et al., 2003) Incidence of dyskinesias 26.0% Idopa vs 8.2% pergolide (Oertel et al., 2006) ADR (Oertel et al., 2006)
	Postural hypotension					Enhanced hypotensive effect: ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside;(interactions from BNF) ADR (BNF) ADR (Oertel et al., 2006)
	Patient's choice					No data
	Mobility					No data
	Depression					ADR (BNF) ADR (Oertel et al., 2006)
	ADLs	Pramipexole Pergolide	H&Y I to III H&Y I to II.5	UPDRS II UPDRS II Schwab & England	P<=0.002 P<0.001 P=0.008	Improvement levodopa group from baseline to each follow up significant vs pramipexole for ADL UPDRS score Improvement -0.6 ldopa vs 2.3 pergolide Ldopa 0.1 vs 0.5 pergolide (Oertel et al., 2006)
	Cost-effectiveness					No data
	Stage of disease (H&Y)					No data
	Drug contraindications					Pregnancy, breast-feeding (BNF)
	Drug interactions					Enhanced hypotensive effect: ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-

						blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside; amisulpiride manufacturer advises advoidance; risk arrhythmias with volatile liquid GAs; absorption of ldopa poss reduced by: antimuscarinics, oral iron, phenytoin; effects of ldopa antagonised by: antipsychotics, possibly benzodiazipines; agitation, confusion & hallucinations with baclofen; increased risk side effects with buproprion, moclobemide; risk hypertensive crisis with MAOIs; enhanced effect and increased toxicity with selegiline (reduce dose ldopa) (BNF)
	Adverse drug reactions					Nausea, vomiting, taste disturbances, dry mouth, anorexia, arrhythmias, postural hypotension, syncope, drowsiness (including sudden onset of sleep), fatigue, dementia, psychoses, hallucinations, confusion, euphoria, abnormal dreams, insomnia, depression (very rarely with suicidal ideation), anxiety, dizziness, dystonia, dyskinesia, and chorea. *Less commonly* weight loss or gain, constipation, diarrhoea, hypersalivation, dysphagia, flatulence, hypertension, chest pain, oedema, hoarseness, ataxia, increased hand tremor, malaise, muscle cramps, and reddish discoloration of the urine and other body fluids may occur. *Rare* side-effects include abdominal pain, gastro-intestinal bleeding, dyspepsia, phlebitis, dyspnoea, agitation, paraesthesia, bruxism, trismus, hiccups, neuroleptic malignant syndrome (associated with abrupt withdrawal), convulsions, reduced mental acuity, disorientation, headache, urinary retention,

						urinary incontinence, priapism, activation of malignant melanoma, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, blurred vision, blepharopasm, diplopia, activation of Horner's syndrome, pupil dilatation, oculogyric crisis, angioedema, rash, urticaria, pruritus, flushing, alopecia, exanthema, Henoch-Schönlein purpura, and increased sweating. *Very rarely* angle-closure glaucoma may occur; pathological gambling, increased libido, hypersexuality, and false positive tests for urinary ketones have also been reported. (BNF)

Stalevo	Motor fluctuations	None	H&Y mean 2.28	UPDRS III	(level of significance set at 0.05) 0.001 P<0.001	31.7% decreased at least one quartile of 'off' time Mean baseline 24.4 to endpoint mean 20.4 (Koller et al., 2005)
	Cognitive impairment					No data
	Confusion					ADR - entacapone (BNF)
	Hallucinations					ADR – entacapone (BNF)
	Dyskinesias			As above	?0.05	8.5% developed dyskinesias, 43.6% pre-existing dyskinesias worsened – majority had improvement in dyskinesia with reduction in stalevo dose ADR – entacapone (BNF)
	Postural hypotension					ADR - levodopa (BNF)
	Patient's choice					No data
	Mobility					No data
	Depression					ADR – levodopa (BNF) Interacts with some antidepressants
	ADLs	None	Mean H&Y 2.28	UPDRS II UPDRS II	0.001 P<0.001	Improved from baseline to endpoint Baseline mean 11.0 to endpoint mean 9.3 (Koller et al., 2005) Improvement general UPDRS scores – not broken down into sections (Myllyla et al., 2006)
	Cost-effectiveness					No data
	Stage of disease (H&Y)					No data
	Drug contraindications					Pregnancy, breast-feeding (BNF) (levodopa) Non-selective MAO-A and MAO-B inhibitors. Concomitant use of selective MAO-A, selective MAO-B inhibitor and entacapone.

						Administer cautiously with products metabolised by COMT (rimiterole, isoprenaline, adrenaline, noradrenaline, dopamine, dobutamine, alpha-methyldopa and apomorphine) (Entacapone)
	Drug interactions					Enhanced hypotensive effect: ACE inhibitors, adrenergic neurone blockers, alpha-blockers, antiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, methyldopa, minoxidil, nitrates, sodium nitroprusside; *amisulpiride manufacturer advises advoidance;* risk arrhythmias with volatile liquid GAs; absorption of ldopa poss reduced by: antimuscarinics, oral iron, phenytoin; effects of ldopa antagonised by: antipsychotics, possibly benzodiazipines; agitation, confusion & hallucinations with baclofen; increased risk side effects with buproprion, moclobemide; risk hypertensive crisis with MAOIs; enhanced effect and increased toxicity with selegiline (reduce dose ldopa) (levodopa – BNF) Possibly enhances effects of: adrenaline, apomorphine, dobutamine, dopamine, methyldopa, noradrenaline; Manufacturer advises caution with: tricyclics, moclobemide, paroxetine, venlafaxine; absorption of entacapone reduced by oral iron; avoid use with non-selective MAOIs; possibly reduces plasma concentration of rasagiline; manufacturer advises max dose 10mg selegiline; enhances anticoagulant effect of warfarin (BNF - entacapone)
	Adverse drug reactions					Anorexia, nausea and vomiting, insomnia, agitation, postural hypotension, dizziness, tachycardia, arrhythmias, reddish discolouration

						of urine and bodily fluids, rarely hypersensitivity, abnormal involuntary movements & psych symptoms (inc hypomania and psychosis) may be dose-limiting, depression, drowsiness, headache, flushing, sweating, GI bleeding, peripheral neuropathy, taste disturbance, pathological gambling, increased libido, hypersexuality, pruritus, rash and livery enzyme changes reported, syndrome resembling neuroleptic malignant syndrome reported on withdrawal, very rarely angle-closure glaucoma (BNF - levodopa) Nausea, vomiting, abdominal pain, constipation, diarrhoea, urine may be reddish-brown, confusion, dizziness, abnormal dreams, fatigue, insomnia, dystonia, dyskinesia, hallucinations, increased sweating, *rarely*: hepatic dysfunction and rash, very rarely: anorexia, weight loss, agitation, urticaria, also reported: colitis, neuroleptic malignant syndrome, rhabdomyolysis, skin hair and nail discolouration (BNF – entacapone)
Tolcapone	Motor fluctuations	Placebo	H&Y I to IV	'off' and 'on' time, IGA, UPDRS III	P<0.01 (200mg) P<0.01 (100mg & 200mg)	100mg -2.3h (NS) 200mg -3.2h vs -1.4h placebo Wearing-off effect (IGA) 68% (100mg) 95% (200mg) vs 37% placebo (Rajput et al., 1997)
		Placebo	H&Y I to IV	'off' and 'on' time, IGA, UPDRS III	P<0.01 (100mg & 200mg) P<0.05 (100mg) 200mg NS P<0.01 (200mg) 100mg NS	'On' time (% change?): 10.8 (100mg & 200mg) vs -0.7 placebo (maintained until month 9 – 200mg only) 'Off' time (% change?): -12.7 (100mg) -9.8 (200mg) vs -4.2 placebo (maintained until month 9 – 200mg & 100mg) UPDRS III score -4.2 (100mg) -6.5 (200mg vs -2.1 placebo (Baas et al., 1997)
	Cognitive					No data

	impairment					
	Confusion					ADR (BNF)
	Hallucinations					ADR (Rajput et al., 1997 ADR (BNF)
	Dyskinesias					Severe dyskinesia contraindication (BNF) ADR (BNF)
	Postural hypotension					ADR
	Patient's choice					No data
	Mobility					No data
	Depression					No data
	ADLs	Placebo	H&Y I to IV	UPDRS II	NS	-0.8 (100mg) 0.2 (200mg) vs -0.3 placebo (Rajput et al., 1997)
	Cost-effectiveness					No data
	Stage of disease (H&Y)					No data
	Drug contraindications					Hepatic impairment, raised liver enzymes, severe dyskinesia, phaeochromocytoma, previous history neuroleptic malignant syndrome, rhabdomyolosis, hyperthermia, breast-feeding. Cautions: renal impairment, pregnancy, reduce levodopa by 30% if on >600mg/day (BNF)
	Drug interactions					Avoid MAOIs (BNF)
	Adverse drug reactions					Diarrhoea, constipation, dyspepsia, abdominal pain, nausea, vomiting, anorexia, xerostomia, hepatotoxicity, chest pain, confusion, dystonia, dyskinesia, drowsiness, headache, dizziness, sleep disturbance, excessive dreaming, hallucinations, syncope, urine discolouration, sweating, neuroleptic malignant syndrome and rhabdomyolysis reported on dose reduction or withdrawal (BNF)

APPENDIX II

Visual Basic for Applications Coding

VBA Coding

```
Private Sub CmdHelpQ4_Click()
  MsgBox "Each criterion needs to be weighed up against all the others to
determine the figure to be given. You must consider the range of effects the
drug can cause for each criterion. For example, when choosing a car cost
may be an important criterion, but if you have £10,000 to spend and the
difference between 1 car and another is only £100 cost becomes less
important than another criterion where the difference is much bigger. In this
case with PD drugs it may be very important for your patient that the drugs
don't cause dyskinesias or postural hypotension: the range of effects the
drugs have on dyskinesias is quite extensive, whereas for postural
hypotension the range is quite small. Therefore, dyskinesias might be given a
high value, whereas postural hypotension might be given a small value even
though both are important for your patient."
End Sub


'prevent the user from closing the form other than by 'close' button
 Private Sub UserForm_QueryClose(Cancel As Integer, CloseMode As
Integer)
   If CloseMode = vbFormControlMenu Then
     Cancel = True
     MsgBox "You must use the 'Close' button to close the form"
   End If
 End Sub



'Carry out multiplication of scores and weights and sum multiplication values
Private Sub cmdCalculate_Click()
   Dim WeightRow As Integer 'weight row
   Dim DrugCol As Integer   'drug column
   Dim DrugRow As Integer   'drug row
   Dim MultiCol As Integer  'column to be multiplied
   Dim MultiRow As Integer  'row to be multiplied
   Dim Result As Double     'result of multiplication
   Dim Rng As Range         'range of multiplication results
   Dim SortResult As String 'result of sort

   If Range("A56").Value = "True" Then

   'start from column C and loop through to column R
   DrugCol = 3
   Do Until DrugCol = 19

      'start from row 2 and loop through to row 12
      WeightRow = 2
      Do Until WeightRow = 13
```

```
        'multiply score by weight, loop down rows and across columns,
position results underneath each column
        Cells(WeightRow + 13, DrugCol).Value = Cells(WeightRow, 2).Value *
Cells(WeightRow, DrugCol).Value
        WeightRow = WeightRow + 1
      Loop
      DrugCol = DrugCol + 1
   Loop

   'sum multiplication values - (no sum function)
   'start from column C, loop through to column R
   MultiCol = 3
   Do Until MultiCol = 19

       'put result of addition 2 rows below scores
       Cells(28, MultiCol).Value = (Cells(15, MultiCol).Value + Cells(16,
MultiCol).Value + Cells(17, MultiCol).Value + Cells(18, MultiCol).Value +
Cells(19, MultiCol).Value + Cells(20, MultiCol).Value + Cells(21,
MultiCol).Value + Cells(22, MultiCol).Value + Cells(23, MultiCol).Value +
Cells(24, MultiCol).Value + Cells(25, MultiCol).Value) \ 100

     MultiCol = MultiCol + 1
   Loop

   'copy rows with names of drugs and results of multiplication and cautions
and comorbidities
   Range("C27:R30").Select
   Selection.Copy

   'paste drug names into row 33, results to row 34, cautions to row 35 and
comorbidities to row 36
   Range("C33:R36").Select
   Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
SkipBlanks _
      :=False, Transpose:=False

   'select drug names, results, cautions and comorbidities and sort in
ascending order
   Range("C33:R36").Select
   Selection.Sort Key1:=Range("C34"), Order1:=xlAscending, Header:=xlNo,
_
      OrderCustom:=1, MatchCase:=False, Orientation:=xlLeftToRight, _
      DataOption1:=xlSortNormal

   'take top 3 results in columns R, Q and P and return their names in
message box with their cautions and comorbidities
   'results 1,2 and 3 return results for top drug with cautions and comorbidities
   SortResult1 = Cells(33, 18).Value
   SortResult2 = Cells(35, 18).Value
   SortResult3 = Cells(36, 18).Value
```

```
    'results 4,5 and 6 return results for 2nd drug with cautions and
comorbidities
    SortResult4 = Cells(33, 17).Value
    SortResult5 = Cells(35, 17).Value
    SortResult6 = Cells(36, 17).Value

    'results 7, 8 and 9 return results for 3rd drug with cautions and
comorbidities
    SortResult7 = Cells(33, 16).Value
    SortResult8 = Cells(35, 16).Value
    SortResult9 = Cells(36, 16).Value

    'show results of sort in ResultsForm - top 3 recommended treatments
    ResultsForm.TextBox1 = SortResult1 & vbCrLf & vbCrLf & SortResult2 &
vbCrLf & vbCrLf & SortResult3
    ResultsForm.TextBox2 = SortResult4 & vbCrLf & vbCrLf & SortResult5 &
vbCrLf & vbCrLf & SortResult6
    ResultsForm.TextBox3 = SortResult7 & vbCrLf & vbCrLf & SortResult8 &
vbCrLf & vbCrLf & SortResult9
    ResultsForm.Show

    Else
      MsgBox "You must select figures for section 4 and click 'submit
responses' before you can receive the recommended treatments"
    End If

End Sub

Private Sub CmdListResult_Click()

If Range("A60").Value = "True" Then

'list the results of all the drugs with their scores in a message box
  SortResult1 = Cells(33, 18).Value
  SortResult1Fig = Cells(34, 18).Value
  SortResult4 = Cells(33, 17).Value
  SortResult4Fig = Cells(34, 17).Value
  SortResult7 = Cells(33, 16).Value
  SortResult7Fig = Cells(34, 16).Value
  SortResult10 = Cells(33, 15).Value
  SortResult10Fig = Cells(34, 15).Value
  SortResult11 = Cells(33, 14).Value
  SortResult11Fig = Cells(34, 14).Value
  SortResult12 = Cells(33, 13).Value
  SortResult12Fig = Cells(34, 13).Value
  SortResult13 = Cells(33, 12).Value
  SortResult13Fig = Cells(34, 12).Value
  SortResult14 = Cells(33, 11).Value
  SortResult14Fig = Cells(34, 11).Value
```

```
  SortResult15 = Cells(33, 10).Value
  SortResult15Fig = Cells(34, 10).Value
  SortResult16 = Cells(33, 9).Value
  SortResult16Fig = Cells(34, 9).Value
  SortResult17 = Cells(33, 8).Value
  SortResult17Fig = Cells(34, 8).Value
  SortResult18 = Cells(33, 7).Value
  SortResult18Fig = Cells(34, 7).Value
  SortResult19 = Cells(33, 6).Value
  SortResult19Fig = Cells(34, 6).Value
  SortResult20 = Cells(33, 5).Value
  SortResult20Fig = Cells(34, 5).Value
  SortResult21 = Cells(33, 4).Value
  SortResult21Fig = Cells(34, 4).Value
  SortResult22 = Cells(33, 3).Value
  SortResult22Fig = Cells(34, 3).Value

  MsgBox "The results for all the drugs are as follows:" & vbCrLf & "1. " &
SortResult1 & " " & SortResult1Fig & vbCrLf & "2. " & SortResult4 & " " &
SortResult4Fig & vbCrLf & "3. " & SortResult7 & " " & SortResult7Fig & vbCrLf
& "4. " & SortResult10 & " " & SortResult10Fig & vbCrLf & "5. " & SortResult11
& " " & SortResult11Fig & vbCrLf & "6. " & SortResult12 & " " &
SortResult12Fig & vbCrLf & "7. " & SortResult13 & " " & SortResult13Fig &
vbCrLf & "8. " & SortResult14 & " " & SortResult14Fig & vbCrLf & "9. " &
SortResult15 & " " & SortResult15Fig & vbCrLf & "10. " & SortResult16 & " " &
SortResult16Fig & vbCrLf & "11. " & SortResult17 & " " & SortResult17Fig &
vbCrLf & "12. " & SortResult18 & " " & SortResult19Fig & vbCrLf & "13. " &
SortResult19 & " " & SortResult19Fig & vbCrLf & "14. " & SortResult20 & " " &
SortResult20Fig & vbCrLf & "15. " & SortResult21 & " " & SortResult21Fig &
vbCrLf & "16. " & SortResult22 & " " & SortResult22Fig

  Else
    MsgBox "You must enter data for all the sections, click 'submit section 2'
and 'submit responses' before you can view the results"
  End If
End Sub


Public Sub CmdReset_Click()

  'Copy original scores from cells C41 to R51
  Range("C41:R51").Select
  Selection.Copy

  'Paste scores back into cells C2 to R12 after poor responses have been
selected
  Range("C2:R12").Select
  Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone,
SkipBlanks _
      :=False, Transpose:=False
```

```
   'set reset_done cell flag to TRUE here
    Range("A54").Value = "TRUE"

End Sub

'Help facility
Private Sub CmdHelp_Click()

 MsgBox "Complete sections 1 and 2 of the page," & vbCrLf & "Click 'Submit
section 2'" & vbCrLf & "Then complete sections 3 and 4" & vbCrLf & "Click
Submit response and Calculate answer." & vbCrLf & "A message box will
show on screen with your result" & vbCrLf & "Click 'List all results' to see all
the drugs with their results" & vbCrLf & "Click 'reset' once you have viewed
your result"

End Sub


'on 'clear' re-set option boxes to null
Private Sub cmdClear_Click()

    OptMotorFlucs.Value = Null
    OptCogImpair.Value = Null
    OptConfusion.Value = Null
    OptHallucns.Value = Null
    OptDyskinesias.Value = Null
    OptDepression.Value = Null
    OptPostHyptn.Value = Null
    OptStage.Value = Null
    OptADL.Value = Null

    TextBoxMotorFlucs.Value = Null
    TextBoxCogImpair.Value = Null
    TextBoxConfusion.Value = Null
    TextBoxHallucns.Value = Null
    TextBoxDyskinesias.Value = Null
    TextBoxDepression.Value = Null
    TextBoxPostHyptn.Value = Null
    TextBoxStage.Value = Null
    TextBoxADL.Value = Null


    'Clear any poor response drugs selected when click 'clear'
    ListBoxPoorResp.Selected(0) = False
    ListBoxPoorResp.Selected(1) = False
    ListBoxPoorResp.Selected(2) = False
    ListBoxPoorResp.Selected(3) = False
    ListBoxPoorResp.Selected(4) = False
    ListBoxPoorResp.Selected(5) = False
```

```
    ListBoxPoorResp.Selected(6) = False
    ListBoxPoorResp.Selected(7) = False
    ListBoxPoorResp.Selected(8) = False
    ListBoxPoorResp.Selected(9) = False
    ListBoxPoorResp.Selected(10) = False
    ListBoxPoorResp.Selected(11) = False
    ListBoxPoorResp.Selected(12) = False
    ListBoxPoorResp.Selected(13) = False
    ListBoxPoorResp.Selected(14) = False
    ListBoxPoorResp.Selected(15) = False
    ListBoxPoorResp.Selected(16) = False

End Sub

'Close application
Public Sub cmdClose_Click()

'test reset cell flag here
If Range("A54").Value = "True" Then
  Unload Me
Else
    MsgBox "You must click 'reset' before you can close the form"
End If

End Sub

'submit data for highest weight into relevant text box in section 4 on 'submit
section 2'
Private Sub CmdSubmit1_Click()

'set reset flag cell
Range("A54").Value = "FALSE"

'set reset flag cell for validation that responses submitted before calculate
answer
Range("A56").Value = "FALSE"

'set reset flag cell to false for validation for list all responses
Range("A60").Value = "FALSE"

'set scores to 0 for any poor responses selected
'Not applicable
    If ListBoxPoorResp.Selected(0) = True Then
      'Do Nothing
    End If
'Co - beneldopa
    If ListBoxPoorResp.Selected(1) = True Then
       Range("C2:C12").Value = 0
    End If
'Co - careldopa
```

```
    If ListBoxPoorResp.Selected(2) = True Then
        Range("D2:D12").Value = 0
    End If
'Stalevo
    If ListBoxPoorResp.Selected(3) = True Then
        Range("E2:E12").Value = 0
    End If
'Duodopa
    If ListBoxPoorResp.Selected(4) = True Then
        Range("F2:F12").Value = 0
    End If
'Ropinirole
    If ListBoxPoorResp.Selected(5) = True Then
        Range("G2:G12").Value = 0
    End If
'Pramipexole
    If ListBoxPoorResp.Selected(6) = True Then
        Range("H2:H12").Value = 0
    End If
'Rotigotine
    If ListBoxPoorResp.Selected(7) = True Then
        Range("I2:I12").Value = 0
    End If
'Pergolide
    If ListBoxPoorResp.Selected(8) = True Then
        Range("J2:J12").Value = 0
    End If
'Bromocriptine
    If ListBoxPoorResp.Selected(9) = True Then
        Range("K2:K12").Value = 0
    End If
'Cabergoline
    If ListBoxPoorResp.Selected(10) = True Then
        Range("L2:L12").Value = 0
    End If
'Apomorphine
    If ListBoxPoorResp.Selected(11) = True Then
        Range("M2:M12").Value = 0
    End If
'Selegiline
    If ListBoxPoorResp.Selected(12) = True Then
        Range("N2:N12").Value = 0
    End If
'Rasagiline
    If ListBoxPoorResp.Selected(13) = True Then
        Range("O2:O12").Value = 0
    End If
'Amantadine
    If ListBoxPoorResp.Selected(14) = True Then
        Range("P2:P12").Value = 0
```

```
    End If
'Entacapone
    If ListBoxPoorResp.Selected(15) = True Then
        Range("Q2:Q12").Value = 0
    End If
'Tolcapone
    If ListBoxPoorResp.Selected(16) = True Then
        Range("R2:R12").Value = 0
    End If


    ActiveWorkbook.Sheets("Sheet3").Activate
    Range("A1").Select
    If IsEmpty(ActiveCell) = False Then
        ActiveCell.Offset(1, 1).Select
    End If


    'Enter weight for chosen criterion with score of 10
    If OptMotorFlucs.Value = True Then
      ActiveCell.Value = 10
      TextBoxMotorFlucs.Value = 10
        ElseIf OptCogImpair.Value = True Then
          ActiveCell.Offset(1, 0).Value = 10
          TextBoxCogImpair.Value = 10
            ElseIf OptConfusion.Value = True Then
              ActiveCell.Offset(2, 0).Value = 10
              TextBoxConfusion.Value = 10
                ElseIf OptHallucns.Value = True Then
                  ActiveCell.Offset(3, 0).Value = 10
                  TextBoxHallucns.Value = 10
                    ElseIf OptDyskinesias.Value = True Then
                      ActiveCell.Offset(4, 0).Value = 10
                      TextBoxDyskinesias.Value = 10
                        ElseIf OptDepression.Value = True Then
                          ActiveCell.Offset(5, 0).Value = 10
                          TextBoxDepression.Value = 10
                            ElseIf OptPostHyptn.Value = True Then
                              ActiveCell.Offset(6, 0).Value = 10
                              TextBoxPostHyptn.Value = 10
                                ElseIf OptStage.Value = True Then
                                  ActiveCell.Offset(7, 0).Value = 10
                                  TextBoxStage.Value = 10
                                    ElseIf OptADL.Value = True Then
                                      ActiveCell.Offset(8, 0).Value = 10
                                      TextBoxADL.Value = 10

                                      Else
                                      'validate that a weight in section 2 has been selected
```

```
                        MsgBox "You must select an option for section 2
before you click 'submit section 2'"

   End If



End Sub

   'Submit values for all other weights into spreadsheet
   Private Sub cmdSubmitWeights_Click()

   ActiveWorkbook.Sheets("Sheet3").Activate
   Range("A1").Select
   If IsEmpty(ActiveCell) = False Then
     ActiveCell.Offset(1, 1).Select
   End If


     'data validation - check input is not non-numeric character, not negative
number, not more than 10 and not blank
     If IsNull(TextBoxMotorFlucs) Or Me.TextBoxMotorFlucs = "" Then
     MsgBox "You must complete a value for motor fluctuations"
       ElseIf IsNumeric(TextBoxMotorFlucs.Value) And
Val(TextBoxMotorFlucs.Value) < 0 Then
       MsgBox "Number must be 0 or more for motor fluctuations"
         ElseIf Val(TextBoxMotorFlucs.Value) > 10 Then
         MsgBox "You must choose a number between 0 and 10 for motor
fluctuations"
           ElseIf Not IsNumeric(TextBoxMotorFlucs.Value) Then
           MsgBox "Enter numerals and not any other characters for motor
fluctuations"
     End If

     If IsNull(TextBoxCogImpair) Or Me.TextBoxCogImpair = "" Then
     MsgBox "You must complete a value for cognitive impairment"
       ElseIf Not IsNumeric(TextBoxCogImpair.Value) Then
       MsgBox "Enter numerals and not any other characters for cognitive
impairment"
         ElseIf IsNumeric(TextBoxCogImpair.Value) And
Val(TextBoxCogImpair.Value) < 0 Then
         MsgBox "Number must be 0 or more for cognitive impairment"
           ElseIf Val(TextBoxCogImpair.Value) > 10 Then
           MsgBox "You must choose a number between 0 and 10 for cognitive
impairment"
     End If

     If IsNull(TextBoxConfusion) Or Me.TextBoxConfusion = "" Then
     MsgBox "You must complete a value for confusion"
       ElseIf Not IsNumeric(TextBoxConfusion.Value) Then
```

9. Would you use this model in clinic yourself or recommend it to colleagues to use?

Yes	No	Not sure
☐	☐	☑

Please give details, for example, would you use it yourself for difficult cases only, would you recommend it for junior colleagues:

B. Software (EPSS)

10. How easy did you find the EPSS to use? Please tick one option

Very easy	Easy	Fair	Difficult	Very difficult
☐	☑	☐	☐	☐

11. Are there any amendments you think could be made to the EPSS to make it easier to use?

Yes	No	Not sure
☑	☐	☐

Please give any suggestions here:

Ability to see all PD drugs rather than need to scroll

12. How well do you think the questions are explained on the EPSS?

Very well	Well	Fair	Poorly	Very poorly
☐	☐	☑	☐	☐

13. How quick was the EPSS to use?

Very quick	Quick	Fair	Slow	Very slow
☐	☑	☐	☐	☐

14. How would you rate your own knowledge and experience of computers?

Very good	Good	Fair	Poor	Very poor
☐	☑	☐	☐	☐

15. Would you be happy to use the EPSS in your clinic or to recommend it to colleagues to use?

Yes	No	Not sure
☐	☐	☑

Please give any details:

Evaluation of Parkinson's disease model and Electronic Prescribing Support System (EPSS)

Please complete both sections:

A. Parkinson's disease Model

1. How do you rate the criteria chosen? Please choose one option

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☑

2. Do you think any important criteria have been missed out?

Yes	No	Not sure
☑	☐	☐

3. How do you rate the way the drugs have been scored against the criteria?

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☑

4. How do you rate the ease or difficulty of weighting the criteria?

Very easy	Easy	Fair	Difficult	Very difficult
☐	☐	☐	☐	☑

5. Do the weights need rewording to improve their clarity?

Yes	No	Not sure
☑	☐	☐

If yes, please give any suggestions here:

6. What is your opinion of the model overall?

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☑	☐

7. Are there any amendments you think could be made to improve the model?

Yes	No	Not sure
☑	☐	☐

8. Do you think this is a suitable methodology for use in PD?

Yes	No	Not sure
☐	☑	☐

Please give details:

NOT SUITABLE IN ITS CURRENT FORMAT; BUT HAS POTENTIAL IF RECOMMENDATIONS MADE.

```
        MsgBox "Enter numerals and not any other characters for confusion"
          ElseIf IsNumeric(TextBoxConfusion.Value) And
Val(TextBoxConfusion.Value) < 0 Then
          MsgBox "Number must be 0 or more for confusion"
            ElseIf Val(TextBoxConfusion.Value) > 10 Then
            MsgBox "You must choose a number between 0 and 10 for
confusion"
      End If

      If IsNull(TextBoxHallucns) Or Me.TextBoxHallucns = "" Then
      MsgBox "You must complete a value for hallucinations"
        ElseIf Not IsNumeric(TextBoxHallucns.Value) Then
        MsgBox "Enter numerals and not any other characters for
hallucinations"
          ElseIf IsNumeric(TextBoxHallucns.Value) And
Val(TextBoxHallucns.Value) < 0 Then
          MsgBox "Number must be 0 or more for hallucinations"
            ElseIf Val(TextBoxHallucns.Value) > 10 Then
            MsgBox "You must choose a number between 0 and 10 for
hallucinations"
      End If

      If IsNull(TextBoxDyskinesias) Or Me.TextBoxDyskinesias = "" Then
      MsgBox "You must complete a value for dyskinesias"
        ElseIf Not IsNumeric(TextBoxDyskinesias.Value) Then
        MsgBox "Enter numerals and not any other characters for dyskinesias"
          ElseIf IsNumeric(TextBoxDyskinesias.Value) And
Val(TextBoxDyskinesias.Value) < 0 Then
          MsgBox "Number must be 0 or more for dyskinesias"
            ElseIf Val(TextBoxDyskinesias.Value) > 10 Then
            MsgBox "You must choose a number between 0 and 10 for
dyskinesias"
      End If

      If IsNull(TextBoxDepression) Or Me.TextBoxDepression = "" Then
      MsgBox "You must complete a value for depression"
        ElseIf Not IsNumeric(TextBoxDepression.Value) Then
        MsgBox "Enter numerals and not any other characters for depression"
          ElseIf IsNumeric(TextBoxDepression.Value) And
Val(TextBoxDepression.Value) < 0 Then
          MsgBox "Number must be 0 or more for depression"
            ElseIf Val(TextBoxDepression.Value) > 10 Then
            MsgBox "You must choose a number between 0 and 10 for
depression"
      End If

      If IsNull(TextBoxPostHyptn) Or Me.TextBoxPostHyptn = "" Then
      MsgBox "You must complete a value for postural hypotension"
         ElseIf Not IsNumeric(TextBoxPostHyptn.Value) Then
```

```
      MsgBox "Enter numerals and not any other characters for postural
hypotension"
        ElseIf IsNumeric(TextBoxPostHyptn.Value) And
Val(TextBoxPostHyptn.Value) < 0 Then
        MsgBox "Number must be 0 or more for postural hypotension"
          ElseIf Val(TextBoxPostHyptn.Value) > 10 Then
          MsgBox "You must choose a number between 0 and 10 for postural
hypotension"
    End If

    If IsNull(TextBoxStage) Or Me.TextBoxStage = "" Then
    MsgBox "You must complete a value for stage of disease"
      ElseIf Not IsNumeric(TextBoxStage.Value) Then
      MsgBox "Enter numerals and not any other characters for stage of
disease"
        ElseIf IsNumeric(TextBoxStage.Value) And Val(TextBoxStage.Value)
< 0 Then
        MsgBox "Number must be 0 or more for stage of disease"
          ElseIf Val(TextBoxStage.Value) > 10 Then
          MsgBox "You must choose a number between 0 and 10 for stage of
disease"
    End If

    If IsNull(TextBoxADL) Or Me.TextBoxADL = "" Then
    MsgBox "You must complete a value for ADL"
      ElseIf Not IsNumeric(TextBoxADL.Value) Then
      MsgBox "Enter numerals and not any other characters for ADL"
        ElseIf IsNumeric(TextBoxADL.Value) And Val(TextBoxADL.Value) < 0
Then
        MsgBox "Number must be 0 or more for ADL"
          ElseIf Val(TextBoxADL.Value) > 10 Then
          MsgBox "You must choose a number between 0 and 10 for ADL"
    End If


    'Put values of weights chosen for rest of criteria
    ActiveCell.Offset(0, 0).Value = TextBoxMotorFlucs.Value
    ActiveCell.Offset(1, 0).Value = TextBoxCogImpair.Value
    ActiveCell.Offset(2, 0).Value = TextBoxConfusion.Value
    ActiveCell.Offset(3, 0).Value = TextBoxHallucns.Value
    ActiveCell.Offset(4, 0).Value = TextBoxDyskinesias.Value
    ActiveCell.Offset(5, 0).Value = TextBoxDepression.Value
    ActiveCell.Offset(6, 0).Value = TextBoxPostHyptn.Value
    ActiveCell.Offset(7, 0).Value = TextBoxStage.Value
    ActiveCell.Offset(8, 0).Value = TextBoxADL.Value



  'set reset flag cell to true as this section has been completed
  Range("A56").Value = "TRUE"
```

```
    'set reset flag cell to true when this section completed for validation of list
results
    Range("A60").Value = "TRUE"

End Sub



'Add list box selections on initialisation
Private Sub UserForm_Initialize()


    'set list box to null on initialisation
    ListBoxPoorResp.Value = ""


    'add medications to combi box list
    With ListBoxPoorResp
        .AddItem "Not Applicable"
        .AddItem "Co-beneldopa"
        .AddItem "Co-careldopa"
        .AddItem "Stalevo"
        .AddItem "Duodopa"
        .AddItem "Ropinirole"
        .AddItem "Pramipexole"
        .AddItem "Rotigotine"
        .AddItem "Pergolide"
        .AddItem "Bromocriptine"
        .AddItem "Cabergoline"
        .AddItem "Apomorphine"
        .AddItem "Selegiline"
        .AddItem "Rasagiline"
        .AddItem "Amanatdine"
        .AddItem "Entacapone"
        .AddItem "Tolcapone"

    End With

    'set cursor to 'poor response' list box on initialisation
    ListBoxPoorResp.SetFocus


End Sub
```

APPENDIX III

Computer Decision Support System Evaluation Questionnaires

Evaluation of Parkinson's disease model and Electronic Prescribing Support System (EPSS)

Please complete both sections:

A. Parkinson's disease Model

1. How do you rate the criteria chosen? Please choose one option

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☑	☐

2. Do you think any important criteria have been missed out?

Yes	No	Not sure
☑	☐	☐

3. How do you rate the way the drugs have been scored against the criteria?

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☑	☐

4. How do you rate the ease or difficulty of weighting the criteria?

Very easy	Easy	Fair	Difficult	Very difficult
☐	☐	☐	☑	☐

5. Do the weights need rewording to improve their clarity?

Yes	No	Not sure
☑	☐	☐

If yes, please give any suggestions here:

6. What is your opinion of the model overall?

Very good	Good	Fair	Poor	Very poor
☐	☑	☐	☐	☐

7. Are there any amendments you think could be made to improve the model?

Yes	No	Not sure
☑	☐	☐

8. Do you think this is a suitable methodology for use in PD?

Yes	No	Not sure
☐	☐	☑

Please give details:

9. Would you use this model in clinic yourself or recommend it to colleagues to use?

Yes	No	Not sure
☐	☑	☐

Please give details, for example, would you use it yourself for difficult cases only, would you recommend it for junior colleagues:

B. Software (EPSS)

10. How easy did you find the EPSS to use? Please tick one option

Very easy	Easy	Fair	Difficult	Very difficult
☐	☐	☑	☐	☐

11. Are there any amendments you think could be made to the EPSS to make it easier to use?

Yes	No	Not sure
☑	☐	☐

Please give any suggestions here:

12. How well do you think the questions are explained on the EPSS?

Very well	Well	Fair	Poorly	Very poorly
☐	☐	☑	☐	☐

13. How quick was the EPSS to use?

Very quick	Quick	Fair	Slow	Very slow
☑	☐	☐	☐	☐

14. How would you rate your own knowledge and experience of computers?

Very good	Good	Fair	Poor	Very poor
☐	☐	☑	☐	☐

15. Would you be happy to use the EPSS in your clinic or to recommend it to colleagues to use?

Yes	No	Not sure
☐	☑	☐

Please give any details:

9. Would you use this model in clinic yourself or recommend it to colleagues to use?

Yes	No	Not sure
☐	☐	☑

Please give details, for example, would you use it yourself for difficult cases only, would you recommend it for junior colleagues:

B. Software (EPSS)

10. How easy did you find the EPSS to use? Please tick one option

Very easy	Easy	Fair	Difficult	Very difficult
☑	☐	☐	☐	☐

11. Are there any amendments you think could be made to the EPSS to make it easier to use?

Yes	No	Not sure
☑	☐	☐

Please give any suggestions here:

12. How well do you think the questions are explained on the EPSS?

Very well	Well	Fair	Poorly	Very poorly
☐	☐	☑	☐	☐

13. How quick was the EPSS to use?

Very quick	Quick	Fair	Slow	Very slow
☐	☑	☐	☐	☐

14. How would you rate your own knowledge and experience of computers?

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☑	☐

15. Would you be happy to use the EPSS in your clinic or to recommend it to colleagues to use?

Yes	No	Not sure
☑	☐	☐

Please give any details:

Evaluation of Parkinson's disease model and Electronic Prescribing Support System (EPSS)

Please complete both sections:

A. Parkinson's disease Model

1. How do you rate the criteria chosen? Please choose one option

Very good	Good	Fair	Poor	Very poor
☐	☐	☑	☐	☐

2. Do you think any important criteria have been missed out?

Yes	No	Not sure
☑	☐	☐

3. How do you rate the way the drugs have been scored against the criteria?

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☑	☐

4. How do you rate the ease or difficulty of weighting the criteria?

Very easy	Easy	Fair	Difficult	Very difficult
☐	☐	☑	☐	☐

5. Do the weights need rewording to improve their clarity?

Yes	No	Not sure
☑	☐	☐

If yes, please give any suggestions here:

Simplify language.

6. What is your opinion of the model overall?

Very good	Good	Fair	Poor	Very poor
☐	☐	☑	☐	☐

7. Are there any amendments you think could be made to improve the model?

Yes	No	Not sure
☑	☐	☐

8. Do you think this is a suitable methodology for use in PD?

Yes	No	Not sure
☐	☐	☑

Please give details:

Make weights more representative of real world experience/priorities