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Special Paper

Quality of Life Assessment in Clinical Trials—Guidelines and a Checklist for Protocol Writers: the U.K. Medical Research Council Experience

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Many clinical trials groups now routinely consider including Quality of Life (QoL) assessment in trials. Indeed, several have policies stating that QoL should be considered as a potential endpoint in all new trials and that if it is not to be evaluated the applicants should justify not doing so. However, inclusion of QoL in clinical trials presents a number of difficult organisational issues, and serious problems in compliance have frequently been reported. Thus, in multicentre clinical trials many of the expected QoL questionnaires fail to be successfully completed and returned, although a few groups have claimed high success rates. However, it is well recognised that if questionnaires are missing, there may be bias in the interpretation of trial results, and the estimates of treatment differences and the overall level of QoL may be inaccurate and misleading. Hence it is important to seek methods of improving compliance, at the level of both the participating institution and the patient. We describe a number of methods for addressing these issues, which we suggest should be considered by all those writing clinical trial protocols involving QoL assessment. These are based upon over a decade of experience with assessing QoL in Medical Research Council (MRC) cancer clinical trials. In particular, we provide a checklist for points that should be covered in protocols. Examples are given from a range of current MRC Cancer Trials Office protocols, which it is proposed might act as templates when writing new protocols.

Key words: quality of life, randomised controlled trials, patient compliance, cancer clinical trials, protocol design

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INTRODUCTION

MANY CLINICAL trials groups routinely consider including Quality of Life (QoL) assessment whenever they design a new trial. Thus, groups such as the U.K. Medical Research Council (MRC), the European Organization for Research and Treatment of Cancer (EORTC), and the National Cancer Institute of Canada (NCIC) all have policies stating that QoL should be considered as a potential endpoint in all new trials, and that if it is not to be evaluated the applicants should justify not doing so [1].

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The MRC Cancer Trials Office has been using patient self-assessed QoL since 1981, when two small-cell lung cancer trials introduced a patient-completed Daily Diary Card [2–4]. Since then, an increasing number of MRC trials have incorporated QoL assessments [5–10]. The early trials used the Daily Diary Card [5, 11], but more recent trials have increasingly used other instruments. The Rotterdam Symptom Checklist (RSCL) [12] has been used in 16 randomised trials covering bladder, colorectal, gastric, head and neck, lung, prostate, renal and testicular cancers. In 11 trials, the RSCL was supplemented with the Hospital Anxiety and Depression Scale (HADS) [13]. More recently, the EORTC QLQ-C30 [14] has been incorporated in 12 trials of colorectal, lung, ovarian, prostate and testicular

cancer. All these trials are large, multicentre, phase III trials, with target accrual of between 260 and 1800 patients.

Hence, QoL research is a fundamental component of many MRC trials. However, the MRC, like many other trials organisations, has experienced compliance problems, and in some trials only approximately half the expected questionnaires were returned to the trials office. This led us to carry out a survey of the administration and compliance issues associated with QoL questionnaires in three multicentre randomised trials in lung cancer and in head and neck cancer [15]. The MRC is also developing, for internal use, a set of guidelines for the administration of QoL assessment in clinical trials, addressing the issues that were revealed by the survey. These build upon those published by other groups [16–18], and cover the many points which should be addressed when implementing QoL assessment in trials, and include specimen documents such as Patient Information Sheets.

These guidelines are complementary to those currently in preparation by the EORTC Quality of Life Study Group, which cover the more general aspects of QoL in clinical oncology trials including selection of trials in which QoL is relevant, selection of instruments, ethical issues, logistic and administrative issues and training workshops for investigators [19].

The objective of this paper is to present specific examples of text that have been used in MRC protocols and which might be used as templates for others who are writing new protocols. Many of the extracts relate to measures specifically intended to improve compliance, but other examples of text cover general QoL issues that we regard as important details to be covered in protocols. We also provide a checklist which will ensure that new protocols will comprehensively cover the many QoL and compliance issues that are of importance. This paper restricts itself primarily to protocol-writing, which is, therefore, covered in detail. MRC protocols aim to be concise, practical documents for participating clinicians, and cover all aspects of day-to-day running of the clinical trials; it is hoped that brevity encourages reading and observance of the content of the protocols.

There is no consensus at present as to the optimal way of presenting all the relevant background information and justification of QoL study design. Thus, whilst it is important to consider the study objectives and details of design, it is unclear how much of this should be incorporated in the working protocol or whether it should be recorded separately. Different approaches are in use in the MRC according to the needs and preferences of different working parties, and according to the nature of the individual trials. In general, in the interest of brevity and clarity, the more general issues concerning aspects such as reasons for the study designs are only infrequently included in the MRC protocols that are written for participants. However, these are important topics and should be addressed in written documents to accompany and supplement the main study protocol, and which are available upon request. These additional documents should comprise part of the package that is also sent to the Protocol Review Committee and to the Local Ethics Committee (Institutional Review Boards).

GENERAL DESIGN ISSUES

It is important to recognise that QoL should only be incorporated in a protocol when it is relevant to do so. In particular, what are the aims of the study, and what is the objective in including a QoL assessment? QoL is not necessarily relevant to all clinical trials. QoL is unlikely to be relevant to most phase I and phase II studies, and it has been suggested [19, 20] that phase III trials can be classified according to the reasons for incorporating QoL assessment: (1) in randomised controlled trials where the (new) treatment is expected to have only a small impact on long-term survival, quality of life may be important (this appears to cover the majority of long-term chronic diseases, including cancer); (2) in equivalence trials, where the disease course in both arms is expected to be similar, but there are expected to be quality of life benefits; and (3) in trials of treatments which are specifically intended to improve quality of life. This includes many palliative trials, for example, trials of palliative radiotherapy for cancer, and trials of bisphosphonates for metastatic bone pain. Most MRC protocols contain a brief statement about the rationale for assessing QoL, aimed mainly at justifying its importance to the participating clinician, although a few do contain more detailed discussion when QoL is the major endpoint. However, all protocols will have been subjected to extensive debate during the design stage, and rigorous justification for either inclusion or exclusion of QoL assessment is demanded by the MRC via its Protocol Review Committees.

What is the most appropriate instrument to use? The choice of instrument may be crucial to the success of a study and many questionnaires exist, not all of which have been extensively validated. Extensive reviews of general [21] and disease-specific [22, 23] questionnaires exist. The choice of instrument must be made with care, and expert advice is important. The MRC Protocol Review Committees require the selection of a QoL instrument to be discussed and justified. This is not normally discussed in MRC trial protocols although, for example, protocols may summarise the reasons for choosing a different instrument from that used in previous MRC trials, or may explain the choice of supplementary disease or treatment-specific modules or questions.

Prior to launching a trial, it is important to consider the provision of training and written instructions for staff responsible for administering the questionnaires. This topic is covered by guidelines being prepared by the EORTC [19] and the MRC [15], and is addressed by documents outside the MRC trial protocols.

Finally, although again not usually part of the main clinical trial protocol sent to participating clinicians, there is a need for documentation of the standard operating procedures (SOP) at the trials office and the intended analysis plan. This should be specified at the inception of the trial, and covers all aspects of the clinical trial. In particular, for QoL it should detail the statistical analysis and interpretation of the clinical trial results when there are missing data. This is important because, as Hopwood and associates [24] have shown, there may be serious problems of bias that arise when the implications of missing data are ignored.

THE NEED TO IMPROVE COMPLIANCE

When QoL is assessed in a clinical trial, it is important to ensure that the information collected is representative of the study patients. However, when data are missing for some

patients, a question arises as to whether patients with missing data differ from those who returned completed forms. As a consequence, missing data presents problems in analysis and interpretation of results [24], and, therefore, the amount of missing data in a trial should be minimised. Compliance is commonly defined as the proportion of QoL forms returned out of those anticipated. Thus, large amounts of missing data are indicated by poor compliance figures. Missing data, and hence low compliance, may arise from many causes, including clinicians or nurses forgetting to ask patients to complete questionnaires, and patients refusing, feeling too ill or forgetting; low 'compliance' does not necessarily imply fault on the part of the patient or their medical staff.

Early MRC experience soon exposed the problems associated with obtaining high compliance rates. The MRC Lung Cancer Working Party [8] found that only 47% of the expected patient Daily Diary Cards were returned, with a third of the patients providing no data at all; however, they noted that there were major differences in compliance rates according to the centre responsible for the patient, providing strong support for the belief that much of the problem is institution compliance rather than patient compliance. Later MRC trials used additional instruments with assessments when the patients attended the clinic. For example, in a lung cancer trial [9], 75% of patients completed baseline RSCL (Rotterdam Symptom Checklist) and HADS (Hospital Anxiety and Depression Scale) questionnaires, with 53% overall compliance. MRC trials usually require completion of a prerandomisation QoL questionnaire, thereby aiming to ensure baseline compliance of nearly 100%—although it is rarely possible to guarantee 100% for logistical reasons. It is hoped that compliance rates during patient follow-up will be improved by adoption of the measures described in this paper, but many of the protocols have only been launched during the last 18 months and the trials are still in early stages.

The definition of compliance used by various trials groups varies, making it difficult to compare reported success rates. Thus, there are no accepted definitions for calculating the number of anticipated forms or the number of acceptable forms received. For example, in cancer trials, some patients will have a short life span, and it is unlikely that QoL forms would be completed until the day of death; therefore, most groups would impose a cut-off point which is some 'reasonable' time prior to death. Similarly, and perhaps more crucially, it is necessary to define a 'window' of acceptability for forms received, since treatment delays may cause some patients to complete their QoL assessment long after it was due. Not only does the definition of an acceptable window differ from group to group, but, in addition, it will depend upon the nature of the trial and the time within the trial. Thus, at baseline, one might decide that forms are only valid if they are completed before therapy commences, but within 3 days before the start of the therapy. Similarly, if an assessment is targeted for 2 months after surgery, a window has to be specified; clearly, a trial group using a window of plus or minus a week might expect to obtain worse values for compliance than if they used a window of plus or minus 2 weeks.

Given the variation in defining compliance, it is slightly surprising to find that the reported experience of other groups appears similar. Many who have incorporated QoL assessments in multicentre clinical trials report serious problems in compliance, especially in palliative trials involving poor prognosis patients, with many of the expected QoL questionnaires failing to be successfully completed and returned [8, 9, 18, 25–28]. Ganz and associates [26], using the Functional Living Index–Cancer (FLIC) scale, reported that 87% of patients returned a baseline questionnaire, but overall only 58% of assessable forms were completed. Finkelstein and associates [25], on behalf of the Eastern Co-operative Oncology Group (ECOG) using the FLIC assessment, achieved a somewhat better level of 76% compliance during second and later cycles of therapy. In the study by Fossa and associates [27], there was "considerable non-compliance". This was thought to be due to the lack of commitment by clinicians, although "lack of time needed to assist patients ... might have been important". Hurny and associates [18] reported a compliance rate of around 50% when using the EORTC QLQ-C30 [14] together with a Linear Analogue Self Assessment (LASA) scale and a mood-adjective checklist (BF-S), and noted that institution, not the patients, appeared to be the major variable contributing to high or low compliance rates; they suggested that pretreatment QoL assessment should be performed as a prerequisite for randomisation, and recommended that there should be a policy of systematic training of staff at participating institutions. Earl and associates [29], in a Cancer Research Campaign trial, used a version of the MRC Daily Diary Card and obtained better compliance than was observed in the MRC trials, but acknowledged that this was probably due to the study being in a single centre with a research nurse assigned solely for this purpose. In another trial, Geddes and associates [28], on behalf of the same group, reported 68% compliance, and opined that patients find it difficult to continue completing the assessment when they become ill with progressive disease, "and this poses a methodological problem for investigators who wish to assess effects throughout an entire treatment programme".

By contrast, very few groups have claimed high success rates, although the NCIC has reported an astonishing overall compliance of above 95% in three trials [17], which they attribute to the development and implementation of comprehensive programmes specifically aimed at encouraging compliance. However, they acknowledge that it remains unclear whether similar success can be obtained with different questionnaires, in different types of trials, in different institutions, and during long-term follow-up. Also, the NCIC used a level of resources which may not be available to other groups conducting international multicentre randomised trials: in one study, "nurses called the patients at home on the appropriate day to remind them to complete the questionnaire". Nevertheless, this study illustrates that given careful planning, and providing adequate resources are made available, it is possible to achieve high compliance.

Why is high compliance important? Unfortunately, it is well recognised that if questionnaires are missing, there may be serious bias in the results of analyses, and the estimates of treatment differences and the overall level of QoL may be inaccurate and misleading [24]. For example, the MRC Lung Cancer Working Party has repeatedly found in successive studies that patients with poor performance status provided less data than those with good performance status [5,

8, 9, 24]. "Fortunately, the level of compliance was similar in the M and NoM series, and thus between-treatment comparisons are likely to remain unbiased. However, the poor compliance raises the question as to whether the results are representative of what patients really feel about their treatment" [5]. Similarly, Hopwood and associates [24] describe another MRC trial, and note that information was provided by 92% of patients whom the clinician assessed as having good performance status (normal activity, no restrictions), through to only 31% of those assessed as very poor (confined to bed or chair). It was subsequently concluded: "At present, given the rapid attrition in lung cancer trials and the rather low levels of compliance in completing questionnaires, there is no entirely reliable way of analysing data longitudinally" [9]. However, other types of patients may respond differently, and Cox and associates [30], illustrating the problems with data for heart transplant patients using the Nottingham Health Profile (NHP) [31], found the reverse effect: those about to die or to be lost to follow-up tended to have poorer QoL scores than those who missed their next follow-up. Cox and associates suggested another reason for poor compliance is that "those experiencing fewer problems may not be so diligent in returning questionnaires".

At best, low compliance raises questions about whether the results are representative, and at worst it may jeopardise interpretation of the main treatment comparisons. This is especially so when there are different compliance rates both according to treatment group and according to patients' performance status, as was found in studies by Geddes and associates [28] and by the MRC lung group [8].

Poor compliance means that there are fewer data items available for analyses, and thus there may be questions about the adequacy of the sample size. However, if this were the only issue, one solution would be to recruit extra patients so as to compensate for the losses due to non-compliance. Unfortunately, this does not address the more serious issue of potential bias in the results; if compliance rates are constant then no matter how much patient numbers are increased, any bias that may be present will merely increase directly in proportion to the sample size. Therefore, the only solution is to aim at better compliance.

Hence, it is important to seek as many methods as possible for improving compliance. In all the reports cited which discussed compliance, a constantly recurring theme was that compliance is an issue at the level of both the participating institution and the patient. Various authors suggested a variety of methods for tackling these issues, based upon their individual experience: Sadura and associates [17] described nine measures that the NCIC has instituted to ensure high compliance, and Hurny and associates [18] provided a table of practical guidelines.

RECOMMENDATIONS FOR WRITING PROTOCOLS

The following points should normally be addressed in all protocols which involve QoL assessment. Examples of the wording used in current MRC trials are given.

Is rationale given for inclusion of QoL assessment?

A section in the protocol should explain the reasons why QoL is being assessed. Some clinicians are less committed to QoL evaluation than others, and so it is important to justify the need for the extra work that the participants are being asked to carry out.

> **An extract from MRC protocol OV05:**
> **Quality of life follow-up**
> *Quality of life is an important endpoint in this study. The timing of treatment may have a considerable impact on patients and the long-term palliation or prevention of symptoms are important factors in the treatment of relapsed disease.* ***It is important therefore that all centres participate in this study.***

Is importance of good compliance emphasised?

The need for good compliance should be stressed, so that participants are aware that a serious effort is being made to ensure completeness of QoL data collection. In those trials where QoL is a major endpoint or even the principal outcome measure, optimal compliance is clearly essential; patients who fail to return QoL data do not contribute information for analysis. In extreme cases, a Data Monitoring Committee (DMC) could recommend early closure of the trial if the level of QoL compliance is unacceptable. Thus, protocols should emphasise the importance of QoL assessment, and should also encourage doctors to emphasise this to patients.

> **An extract from MRC/UKCCCR protocol AB01:**
> *Such data will be an* ***essential*** *source of information for comparison between the two arms in this study.*
> ...
> *It should be emphasised that completion of these forms helps doctors find out more about the effects of treatment on patients' well-being.*

Is a named contact person identified as responsible in each participating centre?

A named person should be identified to serve as the contact at each centre. This person will be responsible for collecting the QoL data and ensuring that the forms are checked and returned to the trials office. This may or may not be the clinician responsible for the patients although, in general, it is recommended that a person other than the responsible clinician should administer the questionnaire to the patient, so that the form may be completed prior to consultation with the doctor. In addition, it has been suggested that patients try to please their doctor or nurse, and thus the responses may be slightly distorted if the person responsible for managing their treatment is present whilst they complete the forms.

> **An extract from MRC protocol LU20:**
> *A named person in each centre must be nominated to take responsibility for the administration, collection and checking of the QoL forms. This may or may not be the clinician responsible for the patients.*

Are there written guidelines for the person administering the questionnaires?

The MRC is developing written guidelines aimed at those administering the questionnaires in the clinical setting.

These attempt to address the issues of poor compliance at the level of the participating institute. The topics covered range from suggestions about adopting a sympathetic approach towards patients who may be feeling particularly ill or may have just been informed of recurrence of disease, for example, through to instructions about the need to ensure backup staff for times when the normal QoL personnel are on leave or absent. Advice is provided about checking the forms, including procedures for patients who fail to complete answers for all questions; this may arise because they have not understood what is required, or because they do not wish to respond to particular questions (". . . explain the relevance and importance of those particular questions, and the confidentiality of the information"). Questions which give particular problems are discussed; for example, the question on the RSCL about decreased sexual interest: "Some patients have omitted to answer because they find it embarrassing and often irrelevant, whereas it is included as an indicator of the general health and well-being of the patient", and the question about loss of appetite: "patients may be confused between inability to eat due to symptoms such as dysphagia or inability to eat because of lack of appetite; it is the latter meaning which is required in this instance".

An extract from MRC protocol LU20:
An information pack is sent to all participating centres detailing the procedures for quality of life assessment and providing guidelines for ensuring optimal compliance.

Are all forms checked for completion whilst patient still present?

When clinical data are missing from a form, it is frequently possible to retrieve the information from hospital notes. QoL is different; once the patient has left the hospital it will be too late to retrieve missing or unclear information, except by contacting the patient by telephone or post. Therefore, there should be a statement about the need for the forms to be checked before the patient has left the clinic, and any action to be taken in the event of missing data.

An extract from MRC protocol LU20:
The questionnaire must be collected before the patient leaves and ***checked to ensure that all questions have been answered;*** *if necessary go back to the patient immediately and ask him or her to fill in any missing items.*
If a questionnaire assessment is missed because of administrative failure, the patient should be contacted by telephone or letter and asked to complete and return a mailed questionnaire as soon as possible.

Timing of assessments

Are baseline assessments specified to be pre-randomisation? Most trials will require a baseline assessment of QoL in order to evaluate changes in the patient's well-being during or after treatment. This assessment should be made before the patient has been informed of the randomised treatment allocation, otherwise knowledge of the treatment assignment may cause different levels of, for example, anxiety within the two treatment groups. Furthermore, by ensuring that QoL is assessed before randomisation and made a randomisation eligibility criterion, we can try to ensure that form completion is 100%.

An extract from MRC protocol TE19:
Randomisation
Patients should be randomised by telephoning the MRC Cancer Trials Office. The person telephoning will be asked to confirm the eligibility criteria have been met, and that the patient has completed their initial quality of life questionnaires.

Is timing of follow-up assessments specified (valid window)? Clearly, the general timing of the assessments must be specified—for example, 2 weeks after surgery. However, a more precise specification might specify a window within which assessments are valid—for example, at least 2, but not more than 3, weeks after surgery.

An extract from MRC protocol RE03:
The Rotterdam Symptom Checklist should be completed by the patient ***before*** *randomisation, at 6 weeks, 12 weeks, 6 months and 1 year.*
An extract from MRC protocol CR06:
Most patients are expected to keep to their protocol treatment time schedule, but to allow for occasional delays; a window of 1 week around each 6 week timepoint will be accepted.

Is timing of follow-up assessments specified (before/whilst/after seeing clinician)?

Generally it is advisable for QoL to be assessed before the patient is seen by the clinician. Usually this is a convenient time for the clinic (whilst the patient is in the waiting room), it means that the patient will not have been affected by anything occurring during their consultation, and it enables the clinical follow-up form to include the questions "Has QoL been assessed? If not, why not?"

An extract from MRC protocol TE18:
Follow-up
The patient should complete the questionnaires whilst waiting to be seen in the clinic—this should be done in a quiet area.

Patients should also be encouraged to request their QoL forms upon arrival at the clinic, since this will help to prevent QoL assessments being forgotten and there is usually suitable time to complete the forms whilst waiting to be seen by the clinician.

An extract from an MRC Patient QoL Information Leaflet—ICON3:
If you are not given a questionnaire to complete when you think it is due, please remind your doctor. You can, of course, decline to fill in a questionnaire at any time.

A more general issue related to timing is that the EORTC QLQ-C30 and RSCL relate to "the past week"; in many trials the patient attends hospital 3 or 4 weeks after the previous cycle of chemotherapy or radiotherapy, and thus assessments at these times may not always include the period during which therapy was received. The timing of the QoL assessments should relate to the specific question which the trial addresses. If, for instance, it were thought important to assess the effects of radiotherapy immediately

after therapy or at a time when the patient is not expected to attend the clinic, it might be possible to provide patients with pre-paid envelopes and ask for the questionnaires to be completed on a certain day and returned by post.

An extract from MRC protocol RE03:
It is important to explain to the patient that the Rotterdam Symptom Checklist (RSCL) refers to how they have been feeling ***during the past week,*** *...*

Is it specified whether help and/or proxy assessments are permitted?

Many publications have suggested that nurses, doctors and family members often underestimate the impact of those items which most distress the patient [32–40]. Therefore, it is important that the patients should complete the QoL questionnaire themselves. Furthermore, it has also been shown that patients may be influenced by the opinions of others when completing questionnaires [41–43]. Thus, it is advisable that the patient should only receive help when it is absolutely necessary, and doctors, nurses and spouses should all be discouraged from offering help unless it is really needed.

However, patients may be unable to complete the questionnaire by themselves or have difficulty understanding the questions. In these cases, help should be provided. Assisted completion is better than total absence of data or the return of information which is incorrect because of misapprehension. Similarly, a few patients may be too ill or too distressed to be able to complete the forms, in which case someone familiar with the patient and their feelings may act as a proxy. Proxies are typically a 'significant other' such as a partner, spouse or close family member, but may include a member of staff such as a nurse who knows the patient well. In some trials, such as trials involving advanced malignancies of the brain, it might be anticipated that the majority of patients will be unable to complete questionnaires and it may be appropriate to make extensive—or even exclusive—use of proxy assessment as a standard. In general, however, proxy assessment is acceptable only as the last resort, and remains controversial. The clinical follow-up forms (see later) should also record the need for help or completion by a proxy.

The instructions to the patients should ask them to complete the forms on their own, that is, without conferring with others.

An extract from MRC protocol CR06:
The patient should complete the questionnaire without conferring with friends or relatives, and all questions should be answered even if the patient feels them to be irrelevant.

Will QoL forms be used to influence therapy or patient management?

There are different opinions on the value of having QoL forms available for use by the treating clinician, or whether they should be confidential. For example, many patients, despite suffering serious toxicity and side-effects, may be keen for their therapy to be continued. It is often claimed that such patients may be reticent about revealing the level of their QoL and the side-effects of treatment if they believe that their responses might cause their treatment to be reduced or terminated. Also, it has been claimed that many patients try to 'please' their clinician and nursing staff, and tend to report more positively than they feel. Although evidence for this remains scanty, there is some implicit support from studies which have shown differences between QoL assessments completed by self-administered questionnaire versus interview-administered questionnaire [41–43], in which interview-assisted completion resulted in reduced reporting of QoL impairments. A tendency for 'yes saying' or response acquiescence when filling in QoL questionnaires has also been noted in some patients [44]. Therefore, to obtain 'true' responses it could be an advantage if patients could be assured that the QoL information is confidential and will not be seen by the clinician, and in some trials pre-stamped envelopes which are addressed to the trials office are supplied. Alternatively, in some centres, clinicians and nurses make use of the QoL forms in order to assist with the management of patients. A spin-off advantage of this to the trial's organisation is that it may increase compliance with form completion. There are both advantages and disadvantages to observing confidentiality and assuring the patient that this is the case, but from the point of view of guaranteeing bias-free interpretation, there are arguably grounds to maintain—and assure the patient of—confidentiality. Whether or not the forms remain confidential, or are used to influence therapy, should be standardised and specified.

An extract from a Patient QoL Information Leaflet—CR05:
You will be given a folder of questionnaires and some reply-paid envelopes in which to return them. We would like you to complete one of these questionnaires just before you go to hospital at the start of each course of chemotherapy, for other treatment or at a routine check-up.
(The reply-paid envelopes are addressed to the MRC Cancer Trials Office)

Patient consent information leaflet: is QoL assessment explained?

The Patient Consent Information Leaflet is typically given prior to requesting Informed Consent. In addition to explaining the nature of randomised trials and discussing issues of relevance to the consent process, this should also explain to the patient the reasons for evaluating QoL, and indicate what this will involve. It should mention the frequency and timing of measurements.

If QoL is the primary endpoint in a trial it may be appropriate to include it as a condition on the patient consent form. Patients who refuse to contribute towards the primary endpoint of a trial should be considered ineligible.

Extracted from the Patient Consent Information Leaflet of MRC protocol TE20:
PATIENT INFORMATION LEAFLET
We will also ask you to fill in a form, which assesses your quality of life, before you receive treatment and at three, six, twelve and twenty-four months after your treatment starts. The quality of life questionnaire is a standard form that is used for other cancer patients and allows us to compare quality of life across various cancers. Because of this, there are some questions that may not seem relevant to your disease. However, please try to answer them all.

Patient QoL information leaflet: is there a leaflet for the patient to take home?

The Patient QoL Information Leaflet is a detailed document that the patient may take away and refer to. It introduces the reasons for using questionnaires, explains aspects of the QoL assessment, and attempts to answer queries which patients commonly ask. The MRC Lung Cancer Working Party uses a general leaflet to cover all trials, whilst some other MRC working parties tailor the QoL Information Leaflet to suit their specific trials. See specimen of the latter in the Appendix.

Randomisation checklist: is QoL completion a prerandomisation eligibility condition?

Completion of the initial QoL assessment is often made a prerequisite for randomisation. Not only does this provide baseline QoL data for all patients, but it also ensures that patients understand the procedure and, by implication, agree to participate in the study of QoL.

An extract from MRC protocol LU20:
RANDOMISATION CHECKLIST
ELIGIBILITY (please tick to confirm)
☐.....
☐.....
☐.....
☐ *Patient's consent to participate in the trial, and patient willing and able to complete SF-36 questionnaires*
☐ *Patient has completed the first SF-36 questionnaire*
☐.....
☐.....
TO RANDOMISE, TELEPHONE THE CANCER TRIALS OFFICE...

Clinical follow-up forms.

Do clinical follow-up forms ask whether QoL assessment has been completed? This question, "Has patient completed QoL forms?", serves as a reminder to the clinician and should protect against patients leaving the hospital before completing the questionnaire.

Do clinical follow-up forms ask about reasons for any missing QoL data? In the event of refusal or other non-compliance—for example, if the patient feels too ill to complete the questionnaire—it is important to obtain details regarding the reasons. There should be a question "If no, give reasons. . . . . ". This information is of value when deciding how to report and interpret results from patients for whom QoL data are missing.

An extract from MRC protocol ICON4:
FOLLOW-UP FORM
Has patient completed Quality of Life form ☐ Yes ☐ No
If ***NO***, *please state reason:*

Do follow-up forms ask whether help was needed? It should be documented if significant help was required in order to complete the questions, or if they were completed by a proxy. Therefore, provision should be made for recording this information on the study forms, together with the reasons such as whether the patient was unable or unwilling to fill in the questionnaire.

Suggested text for a protocol:
FOLLOW-UP FORM
Quality of Life (QoL)
If help was required completing the QoL forms please give details:

CONCLUSIONS

Poor compliance with completion of QoL forms continues to bedevil randomised clinical trials, leading to serious problems of analysis and interpretation. In some instances, the potential for bias in the analyses may even render the results uninterpretable. There are, however, emerging signs that trials organisations, patients and clinicians are all becoming more aware of the importance of QoL as an important endpoint in cancer clinical trials, and thus assessment of QoL is incorporated in an increasing proportion of new protocols.

Checklist for Including Quality of Life in Protocols

Study code and name ☐.....
.....

Are the following points addressed in the protocol:

1. ☐ Is rationale given for inclusion of QoL assessment?
2. ☐ Is importance of good compliance emphasised?
3. ☐ Is a named contact-person identified as responsible in each participating centre?
4. ☐ Are there written guidelines for the person administering the questionnaires?
5. ☐ Are all forms checked for completion whilst patient still present?
6. ☐ Timing of assessments:
   a. ☐ Are baseline assessments specified to be pre-randomisation?
   b. ☐ Is timing of follow-up assessments specified (valid window)?
   c. ☐ Is timing of follow-up assessments specified (before/whilst/after seeing clinician)?
7. ☐ Is it specified whether help and/or proxy assessment are permitted?
8. ☐ Will QoL forms be used to influence therapy or patient management?

and in the forms and other leflets:

9. ☐ PATIENT CONSENT INFORMATION LEAFLET (Pre-Consent Form): Is QoL assessment explained?
10. ☐ PATIENT QoL INFORMATION LEAFLET: Is there a leaflet for the patient to take home? (See specimen in Appendix)
11. ☐ RANDOMISATION CHECKLIST: Is QoL completion a pre-randomisation eligibility condition?
12. ☐ CLINICAL FOLLOW-UP FORMS:
    a. ☐ Do follow-up forms ask whether QoL assessment has been completed?
    b. ☐ Do follow-up forms ask about reasons for any missing QoL data?
    c. ☐ Do follow-up forms ask whether help was needed?

Completed by..... Date.....

This increasing awareness and acceptance of the value of QoL should in itself help to improve compliance. However, QoL assessment is an area in which there are a large number of issues which need to be addressed in a protocol, and it remains far too easy to omit some necessary details. Hence the use of a checklist (see Example in box), accompanied by detailed examples, is important. By adopting the procedures described, and provided they are accompanied by adequate resources and training, it should be possible to ensure that the level of compliance is optimised.

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APPENDIX

PATIENT QoL INFORMATION LEAFLET

Example from MRC protocol CR06: QUALITY OF LIFE QUESTIONNAIRES— AN EXPLANATION

About your questionnaires

We are concerned to find out more about how patients feel, both physically and emotionally, during and after different treatments. In order to collect this information, brief questionnaires have been designed that can be completed by patients themselves. We would like you to complete questionnaires before, during and after your treatment at this hospital.

The questionnaires refer to how you have been feeling ***during the past week*** *and are designed to assess your day to day well-being, as well as to monitor any side-effects you may be experiencing. Your questionnaires will be sent to the Medical Research Council where they will be treated in confidence and analysed together with those from patients in other hospitals to help plan future treatments.*

We enquire about a wide range of symptoms as the questionnaires are designed for use in many different areas of research, but please feel free to discuss any symptoms or concerns with your doctor.

Completing the questionnaires

If possible, complete the questionnaires on your own. Please try to answer all the questions but do not spend too much time thinking about each answer as your first response is likely to be more accurate. If a question is not applicable to you, please write alongside 'not applicable' or 'N/A', but do not leave any question blank.

When you attend hospital for the first time, you will be asked to complete a questionnaire. We would like you to complete further questionnaires each time you come into hospital for an assessment. If you are not given a questionnaire to complete, please remind your doctor. You can, of course, decline to complete a questionnaire at any time without affecting your relationship with your doctor; however, the questionnaire will help us to acquire the knowledge to improve the treatment of patients with your condition.

Thank you for your help