Advice on PRO/QOL information for **Grant Applications**

An adaptation of the SPIRIT-PRO guidelines

Prepared by the Sydney QOL Office for Australia's Multi-site Collaborative Cancer Clinical Trials Groups

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PLEASE NOTE: IF YOU ARE PREPARING A FULL PROTOCOL FOR ETHICS, YOU SHOULD DOWNLOAD THE SPIRIT-PRO CHECKLIST AND ENSURE ALL SPIRIT-PRO GUIDELINE RECOMMENDATIONS ARE INCLUDED. FULL PROTOCOL SUBMITTED FOR REVIEW BY THE QOL OFFICE MUST INCLUDE A COMPLETED SPIRIT-PRO CHECKLIST.

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Key points

Primary or secondary HRQL/PRO endpoints?

- If a patient-reported outcome (PRO) is a primary endpoint:
    - the whole SPIRIT-PRO applies, but available page- or word-limits will dictate how much detail can be included in the project plan section of the grant application.
- If health-related quality of life (HRQL) is the primary endpoint, you should identify which specific aspects of HRQL (e.g. which symptoms and/or aspects of functioning) are of particular relevance, given the proposed intervention(s) and patient population(s).
    - the whole SPIRIT-PRO applies to those key PROs.
- If HRQL or specific PROs are secondary or exploratory endpoints, there will be less space available, and less detail will be required.

Integrate throughout

- Even if HRQL/PROs are secondary outcomes, mention them in the summary, background, objectives/hypotheses, endpoints/outcomes, assessment methods, and significance.
- This indicates relevance, and supports need for PRO-specific budget items.
- Most of these sections may require only a few sentences about HRQL and/or specific PROs, and sometimes they can be mentioned in the same sentences as survival.
- More space may be required for Methods – including stating the questionnaire(s), providing references for their validity (if space permits), and outlining the PRO assessment schedule.
- Ensure all aspects of HRQL highlighted as important in the Background are assessed by the HRQL/PRO questionnaire(s) you say you will use; and ensure consistency throughout the grant application about which questionnaires will be used.
- Cross-check that your questionnaire(s) cover the HRQL-relevant symptoms, aspects of functioning, etc that you have mentioned in the Background to close the loop – so a reviewer knows that you are assessing all domains of HRQL that are of importance and relevance in this patient population.

General note re terminology

- Patient-reported outcomes (PROs) are the outcomes per se, e.g. fatigue.
- Patient-reported outcome measures (PROMS) are the questionnaires used to assess the target PRO, e.g. FACT-Fatigue.
- Health-related quality of life (HRQL) is a multidimensional PRO, and HRQL questionnaires (e.g. QLQ-C30) are PROMs.
- The International Society for Quality Of Life research now recommends using the term health-related quality of life (rather than simply quality of life, which is a much broader construct encompassing issues beyond disease and treatment), and the abbreviation HRQL rather than HRQoL or QoL. You might like to change this throughout.

Specific points

Background and rationale

A good case must be made for HRQL/PRO assessment, with impacts on specific PROs clearly described, backed up with references. Briefly summarize PRO findings in relevant studies, as this provides a rationale for PRO assessment.

> **Tip** To find suitable background references for HRQL/PROs, run a quick search, e.g. via OVID, using suitable search terms for the disease-term (i.e.cancer site/stage) and 'quality of life' or 'patient reported outcome' or the 'symptom' of interest.
>
> e.g. in OVID: (bowel cancer.ti,ab) AND ((quality of life.ti,ab) OR (physical function$.ti,ab) OR (pain.ti,ab))

If a PRO is the primary endpoint, a more detailed literature search/review will be warranted.

Example text:

> *[Treatment] has been shown to decrease quality of life experienced by [population] with [disease] treated with [treatment] [REF]. A [proposed regimen] will lessen the burden of treatment and have important quality-of-life benefits with respect to [specific symptoms/function]. No randomised clinical trials have previously addressed this.*
>
> *HRQL is an essential consideration in this complex clinical setting, where a cascade of events reduce patients' quality of life in a multitude of ways [REF]. This starts with the burden of disease, causing symptoms such as [LIST] and psychological distress [REF]. [Treatment] may cause fatigue and pain [REF].*

Objectives and Hypothesis

If a PRO is your primary endpoint, state specific PRO objectives and hypotheses, i.e. specifying relevant PRO concepts/domains and/or symptom(s) of particular interest, given the disease, intervention and patient population.

- If HRQL is your primary endpoint, your objectives and hypotheses should specify which specific aspects of HRQL (e.g. which symptoms and/or aspects of functioning) are of particular relevance, given the proposed intervention(s) and patient population(s).

When PROs are secondary or exploratory endpoints, objective should be stated briefly.

Example text:

> *[specific symptoms/function] of [population] with [disease] will be longitudinally assessed and compared among the treatment arms.*
>
> *[population] randomised to receive [regimen x] will report poorer [specific symptoms/function] compared to [population] who receive [regimen y].*
>
> *To clarify the HRQL and specific morbidity differences between patients having [treatment A and B].*

Comparator group

A comparator group is always advisable for HRQL/PRO research, as PROs are subjective, so a suitable comparator group facilitates interpretability. In particular, patients' perceptions of their functional ability and symptom experience can change over time (response shift, coping, adaptation). While a placebo-controlled blinded randomised design provides the most robust comparator, this is not always possible.

In a non-randomised Phase II trial, a suitably defined control cohort can provide a useful comparator. The most scientifically robust option is a contemporaneous control group, with data collected prospectively with the same PRO/HRQL questionnaires at comparable time points. If this is not feasible, there are other options. First, historical data (e.g. from published papers), if available from a comparable patient group using the same questionnaires assessed at similar time points, may provide an informative historical comparator. Other options are normative data (from a general population) or reference values (from patient populations), although these are not available for many PRO/HRQL questionnaires. Note however that both these options may be confounded by population-level shifts over time in patient demographics and health care parameters. Potential confounding due to differences in patient characteristics (e.g. age, sex, co-moridities) can only be adjusted for those characteristics that have been measured, and only if individual patient data are available. For population norms, individual data are rarely available, but if the PROs are reported by age and gender groups, they can be adjusted to the age and sex distribution of your trial patient group, using standard epidemiological methods. This is important to do, as age and sex are known to be associated with systematic differences in many PROs.

Outcomes/Endpoints

Specify the PRO concepts/domains of relevance in the specific research context (i.e. given patient population, expected toxicities and benefits of intervention(s). In RCT, these will be used to evaluate the impact of intervention. E.g., specific symptom(s) and/or aspects of function.

Assessment schedule

- The PRO assessment time-points should be well-planned and clearly described in relation to treatment (and corresponding times for controls in non-randomised studies).
- These can often be included in the table describing all study assessments.
- Ensure the selected time-points are clinically informative, capturing maximum expected treatment effects, acute and long-term.
- Baseline should always be included; be specific about timing of baseline relative to start of treatment.
- End of treatment is often informative.
- Assessment should continue until patients are expected to have recovered/stabilised.
- During treatment/short-term recovery, avoid use of standard periodic assessment, e.g. 3 monthly, as this may miss peaks and troughs of impact.
- Long-term: After patients are expected to have recovered/stabilised, periodic assessment is reasonable, and often coincides with standard follow-up clinic attendance for other trial endpoints.

PRO questionnaires and data collection methods

State the HRQL/PRO questionnaire to be used and provide the most relevant reference (e.g. development and/or validation, in your patient population if available) if space permits.

- Cross-check that your questionnaire(s) covers the HRQL-relevant symptoms, aspects of functioning, etc that you have mentioned in the Background – so a reviewer knows that you are assessing all domains of HRQL that are of importance and relevance in this patient population.
- Mention mode-of-administration and setting, e.g. "electronically, in clinic".
- If a proxy is required, mention, and select a questionnaire that is validated for proxy completion.

Example text:

> *HRQL will be assessed with the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) questionnaire, which includes 37 items assessing 4 aspects of well-being (physical, functional, emotional, social/family), as well as a bone transplant-specific subscale. The FACT-BMT is valid (REF), responsive to change (REF) and well-suited to assess the endpoints of interest in the proposed study due to the clinical relevance of scale items. A preference-based measure of HRQL, the EQ-5D-5L (REF), will also be used to estimate health utility scores and combined with survival endpoints to calculate quality-adjusted life years for incorporation in health economic analyses. The FACT-BMT and EQ-5D-5L will be administered at baseline, Day 100, and 6, 12, 18 and 24 months, at clinic appointments.*

Statistical methods

Sample size and power calculations for PRO endpoints (whether primary or secondary) can be based on effect size (mean difference between groups divided by SD at baseline).

Example text:

> *For the HRQL study aiming to detect a difference between [treatment A and B] groups of 0.2 standard deviations of a continuous scale such as fatigue or physical symptoms, with 80% power at a two-sided alpha level of 5%, the required sample size is 790 patients. To allow for attrition at a rate of 5% per year, 1020 patients are required to participate in the quality of life study.*
>
> *If the study shows no difference in the risk of tumour recurrence, the study will also have sufficient power to determine whether [experimental treatment] reduces [side effects] and improves [relevant aspect(s) of function].*

Specific power calculations can be reported in terms of [xx%] power to detect an effect size of [0.xx].

Analysis methods: Briefly state HRQL/PRO analysis methods, plans for addressing multiplicity/type 1 (α) error and missing PRO data.

Example text:

Rates and reasons for missing PRO data will be described. PROs will be analysed with [linear mixed models] to accommodate the repeated measurements and any missing assessments. Significance levels will be adjusted for multiple testing.

HRQL/PRO expertise on your team

- Like health economics and statistics, HRQL/PRO research involves particular theories and methodologies. Your application will be strengthened by the inclusion of one or more investigators with the requisite education, training, experience and expertise.

Budget

Statistician costs

- HRQL data are complex – multiple domains and timepoints must be analysed, sophisticated statistical modelling is typically required to allow for repeated measures and missing data, and good graphs/figures need to be produced to facilitate comprehension and interpretation of the wealth of data. So be sure to allow sufficient budget for the statistician for the HRQL analysis, even if these PROs are secondary endpoints.
- Here is a rough guide to what a clinical trial organisation would typically charge for a statistician's input/involvement in a study with HRQL as an endpoint – noting these figures would cover survival, response and toxicity, but if there were additional lab values or pharmacokinetics, additional budget would be required. There are some factors which may change depending on the complexity of other endpoints or PRO measures, but this is ball-park starting point.

  - Protocol $5,000-$8,000
  - Statistical analysis plan (SAP) $7,000-$10,000
  - Analysis and manuscript collaboration $15,000-$25,000 depending on number of measures and graphs required (say between 3-15)
  - Reporting (attend quarterly meetings with investigators during the study accrual and follow up/ trial management meetings, preparation of 1 report with details about data completeness yearly) $5,000/year.

HRQL/PRO expertise

- Other staff costs may be required to include HRQL/PRO expertise. If you do not have such expertise on your team, please contact the QOL Office for advice. <qol.office@sydney.edu.au>

Questionnaire costs

Allow for any licensing costs

- Many but not all PRO questionnaires are available for free for studies led by academic researchers/clinical trials groups.

Anticipate translations

- Check what languages will be needed (e.g. most common non-English languages in your target patient population), then cross-check against translations available. If languages you need are not yet available, you can create new translations, although this must be done according to best-practice guidelines and in consultation with the instrument developer, e.g. the EORTC Quality of Life Group has Translation Guidelines and are the developers of the EORTC suite of HRQL questionnaires. Allow budget for any new translations needed, including independent bilingual translators and professional proof-readers, as per EORTC Guidelines.

- If you need further advice on determining potential costs for your chosen questionaires, contact qol.office@sydney.edu.au.