Patient-Reported Outcome Measures (PROMs): Identifying UK Research Priorities

Report of a MRC Workshop
12th January 2009, Royal College of Physicians, London
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Executive Summary

Improving the methodology underpinning the application and evaluation of Patient Reported Outcome Measures (PROMs) in health research has been identified as an area of specific interest to Medical Research Council, which leads the Office for Strategic Co-ordination for Health Research (OSCHR) methodology work stream research.

In order to develop a managed programme of research in this area, MRC held a Workshop in January 2009 which aimed to identify priorities for UK research. The Workshop brought together leading UK researchers, patient organisations and the lay public, plus key stakeholders who have interests and needs with regards the use of PROMs in their decision making.

The key research issues to emerge from the Workshop were:

• strengthening the underpinning evidence for the core content of PROMs both within disease-specific measures and in mapping onto generic measures.
• re-assessing the relevance of the EQ-5D
• addressing gaps in the current repertoire of PROMs instruments available e.g. end-of-life, childhood issues.
• developing guidelines for the use of PROMs in research and developing a framework for reporting the experimental design, protocol and analysis plan for PROMs, and
• improving understanding of the impact of changes in PROMs on health functioning, capability or utility.
• demonstrating the utility of PROMs in clinical research and decision making

Given the breadth of issue to arise from the workshop and following consideration by the MRC-NIHR Methodology Research Programme Panel, MRC will issue Highlight Notice to stimulate high quality methods research in this area. In addition, the need to refresh the EQ-5D will be addressed through a separate call for proposals that MRC is also taking forward to underpin the methodological research needs of NICE.
1. Background

Patient reported outcome measures (PROMs)\(^1\) are an assessment of health status and health-related quality of life that comes directly from the patient. They are used increasingly in the evaluation of health care technologies and healthcare services and they also contribute to regulatory decision making in these settings. Ensuring a sound research base underpins the development and application of PROMs methodology is therefore vital in enabling these measures to have maximum impact on research outcomes and health care decision making.

PROMs have been identified as an area of specific interest to the UK OSCHR (Office for Strategic Co-ordination for Health Research) methodology work stream, which the Medical Research Council (MRC) leads on behalf of the other OSCHR partners (Annex 1). MRC has therefore agreed to develop a managed programme of methods research in this area, taking into account the activities and needs of key UK stakeholders i.e. academic researchers, industry, Government and regulatory agencies as well as patients and the public.

The Workshop represented the first stage in this initiative and aimed to engage key stakeholders in outlining the research opportunities and key priorities for UK PROMs research.

2. Aim and Scope of Workshop

The aim of the Workshop was to identify future UK research priorities in PROMs research taking into consideration:

- current national and international activities,
- UK research strengths and expertise and
- the needs of key UK public and commercial sector stakeholders for further research.

3. Workshop Format

The Programme for the Workshop is provided at Annex 2 and the list of attending delegates is given at Annex 3. It began with plenary presentations from key stakeholders about the needs and drivers in applying PROMs in their decision making and was followed by a series of presentations from the UK academic community about the challenges and opportunities of using PROMs in different research settings. Patient input was provided via a discussion paper developed by various patient interest groups and was available to all delegates (Annex 4; see summary by Mr Kent below). Thereafter, in breakout groups, the workshop delegates discussed, in light of the plenary discussions, the main needs and opportunities for UK PROMs research.

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\(1\) FDA - A PRO is a measurement of any aspect of a patient’s health status that comes directly from the patient (i.e., without the interpretation of the patient’s responses by a physician or anyone else).

EMEA (CHMP, 2005): Any outcome based on a patient's perception of a disease and its treatment(s) scored by the patient himself is called a Patient-Reported Outcome (PRO). PROs are a large set of patient-assessed measures ranging from single item (e.g., pain VAS, overall treatment evaluation, and clinical global improvement) to multi-item tools. Multi-item tools can be mono-dimensional (e.g., measuring a single dimension such as physical functioning, fatigue, and sexual function) or multi-dimensional questionnaires measuring several of the following: symptoms, functional status, satisfaction, well-being, or health-related quality of life (HRQL). In general terms, PROs provide information on the patient’s perspective of a disease and its treatment."
3.1 Summary of Plenary Presentations

Keynote address: Issues in relation to the science underpinning PRO measures and their use to inform decisions in health services

Professor Ray Fitzpatrick, Professor of Public Health and Primary Care, University of Oxford

The purpose of the meeting is to help the UK health research community identify research priorities and opportunities in relation to patient-reported outcome measures. My introductory talk will aim to distinguish between issues regarding PROMs that at one extreme are no longer controversial and unresolved and issues at the opposite extreme where little is known and the scientific opportunities are therefore greatest. To pursue this approach, the talk will aim to categorise issues into three levels: (i) low or modest uncertainty (ii) intermediate level uncertainty (iii) highest level of uncertainty (and by implication of highest scientific priority).

1. Issues of broad agreement and low uncertainty
   - Typical content, format of PROMs
   - Desirable attributes (validity, responsiveness etc)
   - Methods of developing PROMs

2. Issues of intermediate level uncertainty
   - Added value of PROMs in clinical trials
   - Ways of improving interpretability
   - Role of and need for models and theories
   - How to evaluate instruments comparatively
   - Relationship between preference and non-preference measures

3. Issues of high uncertainty (and potentially of highest scientific priority)
   - Impact of information from PROMs on decisions of different key parties: patients and public, service providers, managers and commissioners of services
   - Role of non-fixed format item banks

Routine Use of Patient Reported Outcome Measures in the NHS

Dr Alan Glanz, Principal Research Manager, Policy Research Programme, R&D Directorate, Department of Health
Dr David Nuttall, System Management and New Enterprise, Department of Health

The Department of Health (DH) sees an important role for routinely collected PROMs in the NHS. Lord Darzi’s Next Stage Review confirms this role. The DH PROMs programme is developing evidence based systems for routine collection of PROMs for patients undergoing certain elective procedures – for implementation in the NHS from April 2009 - and for patients with long-term conditions managed primarily in community settings – for piloting in spring 2009. The DH programme includes use of condition-specific and generic PROMs.

Key issues for the development of the programme and for the research agenda include how PROMs can be used in the context of performance management, quality improvement, patient care planning and measuring health gain from investment in health services.
NICE Health Technology Appraisals: the impact of patient reported outcomes?

Professor David Barnett, Chair NICE Appraisals Committee, University of Leicester

The NICE appraisals methodology relies on inputs from all stakeholders on the clinical and cost effectiveness of individual health care technologies. This uniquely internationally includes submissions from patient/carer organisations. The remit of the Appraisals Committee is to consider these qualitative inputs on patient experience alongside the quantitative submissions of ‘scientific’ evidence received from other consultees and come to a balanced judgement on the recommendation of the use of the technology within the NHS. The qualitative inputs are often unstructured and whilst this does not diminish their relevance it inevitably makes it more difficult to combine with the other inputs and so may lessen their impact. The challenge is to ensure the inclusion of patient reported outcomes is undertaken systematically as part of the assessment/appraisal process. Examples of where the patient evidence on quality of life or impact of treatment on the disease process has influenced the appraisal outcome will be illustrated and suggestions for future research into patient evidence made.

PROs and drug evaluation process

Dr. Mira Pavlovic-Ganascia, Head of Scientific Advice Unit at the French Medicines Agency, Vice-Chair of the Scientific Advice Working Party of the European Medicines Agency (EMA)

Several working parties have been working on behalf of the Committee of Human Medicinal Products (CHMP) at the EMEA. The role of the Efficacy Working Party (EWP) is to elaborate guidelines for clinical development of medicinal products in different fields of medicine. In some of the EMEA/EWP guidelines, patient reported outcomes (PRO) and health related quality of life (HRQL) have been mentioned as a part of drug development programme either as efficacy variables (primary, secondary, supportive), safety variables, or measures useful for benefiting risk assessment, but neither define HRQL nor PRO in general nor recommend how to assess HRQL/PRO claims in marketing authorisation applications. The impression of both regulators and pharmaceutical companies has been that HRQL/PRO claims have been granted rarely and on a case by case basis.

For all these reasons the EMEA EWP has decided to draft a specific reflection paper on HRQL/PRO assessment in registration trials. The aim was to define the place and to give a recommendation for the use and assessment of PRO, in particular HRQL, in the drug evaluation process. In addition, the definitions of PRO and HRQL, frequently used interchangeably both by sponsors and regulators were also provided. With the recent release of the EMEA reflection paper on HRQL and of the FDA guidance on patient-reported outcomes, these patient-based measures have gained acknowledgment of their value in the drug evaluation process. The two papers issued by regulatory authorities set the principles of the assessment of PRO and HRQL in clinical trials and the requirements for gaining a specific claim based on these measures. However, it

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2 CHMP reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. EMEA/CHMP/EWP/139391/2004
might be still too early to know whether these recommendations have been put into practice by sponsors from one side and whether they have already had an impact on the assessment of medicinal products and PRO/HRQL-related claims by regulators. The given examples show a rather disparate picture. The review of new trials and marketing authorisation requests will test whether the EMEA reflection paper on HRQL is a useful tool for sponsors for gaining HRQL claims in the drug development process.

A patient and family perspective on PRO measures

Mr Alastair Kent, Director, Genetic Interest Group

In September 2008* a group of representatives for patient support organisations with experience and expertise in commissioning research met to discuss patient reported outcome measures. There was unanimous agreement on the importance of PROMs as a contributory factor to the delivery of relevant, effective and cost efficient high quality biomedical research –especially, but not exclusively, in the field of clinical trials. PROMs are not seen as a complete answer to the issue of capturing outputs from research, and there are potential problems arising from some aspects of their use, but they will add value when used in a timely and appropriate way. The workshop delegates emphasised the importance of involving patient representatives in the planning of research studies and in the selection and design of PROMs. A number of key issues were identified that contribute to the development of relevant PROMs and to their introduction into research projects and clinical trials. These will be outlined at the January workshop.

* Following the meeting in September 2008, the participants developed a joint paper outlining the key issues discussed and which formed the basis for Mr Kent’s presentation at the Workshop (Annex 4).

The design and use of PRO measures in orthopaedic surgery

Professor Andrew Carr, Director NIHR Musculoskeletal Biomedical Research Unit, University of Oxford and Nuffield Orthopaedic Centre NHS Trust

The vast majority of orthopaedic procedures are performed for non life threatening conditions where abolition of pain and improvement in function are the stated aims. Considerable deficiencies exist in the available evidence base for most orthopaedic procedures. Using the context of orthopaedics and joint replacement surgery this talk will describe the design and use in clinical trials, registers and audits of PROs (The Oxford Scores). The relationship of outcome data to patient expectations and satisfaction will be discussed. Difficulties exist in defining success and failure in the context of case-mix variation and other selection artefacts. Possible ways of introducing the widespread use of PROs will be discussed.

Embedding clinically meaningful and accurate PROs into RCTs

Professor Jane Blazeby, MRC CONDUCT Hub in Trials Methodology Research, University of Bristol
Despite the widespread inclusion of PROs into RCTs over the past two decades, it is uncertain whether the results have influenced clinical decision-making. This presentation will consider why this is happening and possible areas for research to overcome the barriers for effectively measuring PROs in RCTs. Key areas that need further work include: developing methodology to select primary and secondary PROs during trial design and ensuring that measurement of these endpoints is reliable and accurate using well-designed studies and instruments. The methodological challenges of minimising missing data and understanding how missing data may influence PRO results and interpretation are important. More work and understanding of the minimally important differences in PROs from commonly used instruments and methods to interpret and report PROs alongside clinical outcomes from trials is needed. Finally work to overcome cultural barriers regarding the value of PROs and their importance in clinical-decision making alongside clinical data is needed. This includes development of methods to communicate multi-dimensional PROs from RCTs to clinicians, patients and health care providers.

Using patient-reported outcome measures in observational studies in health

Professor Suzanne Skevington, WHO Centre for the Study of Quality of Life, University of Bath

Observational designs can be helpful in developing complex interventions (MRC, 2008). These types of studies have been important in finding out that patients do want to share their experiences of health care with their providers, and are often willing to complete questionnaires with this in mind. Such studies have also assisted in understanding why health professionals do not use high quality patient-reported outcome measures to assist their clinical practice. The results point to ways in which the measures themselves could be changed to make them more user friendly to patients and providers. Also what procedures need to be put into place to increase the chances of their routine use in health care. Utilising selected examples of different observational designs (sequential cohort, longitudinal, quasi-experimental, survey), this talk will consider recent studies where information has been collected that could help to implement the feedback of health-related quality of life information, with the aim of benefiting the quality of communication in the consultation, health care decision-making, patient management, patient satisfaction etc. Research and clinical priorities for this field generally, and within the NHS, will be discussed.

Patient reported outcomes for economic evaluation: the key issues

Professor John Brazier, Health Economics and Decision Science, School of Health and Related Research, University of Sheffield

Patient Reported Outcomes (PROs) and other measures of outcome have been widely used in economic evaluation. The main use of PROs in economic evaluation has been to provide descriptions of health for valuing on the zero to one scale used to calculate Quality Adjusted Life Years (QALYs). These health state values are a crucial component of many economic evaluations, particularly those focusing on interventions aimed at improving quality of life.

The use of PROs in economic evaluation raises an additional list of research issues to those usually considered with PROs. These include: what should be valued (e.g. health or well-being, functioning or capability), how well does the QALY
describe preferences, how should health be described (e.g. generic or condition specific, how appropriate is the EQ-5D across different conditions), what should be the methods of valuation (e.g. SG vs. TTO, experience vs. preferences), and problems of synthesizing health state utility values and adaptation for use in economic models. These questions include researchable empirical questions into PROs (such as the validity of different descriptive systems) and more philosophical issues (such as whose values).

PROMIS: Promises, Challenges and Opportunities

Professor Susan Yount, Center for Outcomes Research and Education (CORE) at North Shore University Health System, Northwestern University

The Patient Reported Outcomes Measurement Information System (PROMIS) grant, funded by the U.S. National Institutes of Health, was tasked with goals of (1) developing and testing a large bank of items measuring PROs for clinical research relevant to a range of chronic diseases; (2) creating a computerized adaptive testing (CAT) system for efficient, psychometrically robust assessment of PROs, and (3) creating a publicly-available system to allow researchers access to a common repository of items and CAT. This presentation will describe the challenges encountered, PROMIS accomplishments to date, and products currently available to researchers as well as those to be available by the end of funding. In addition, an overview of the objectives for the second generation of PROMIS funding (2009-2013) will be provided. Most importantly, opportunities for international collaboration and partnership will be presented.

3.2 Breakout Sessions

The discussions of the 4 breakout groups were guided by the following questions:

1. What are the key issues faced by users when applying PROMs to decision making?
2. What methodological research is required to improve the PROM technology to increase its utility and validity in the future with regards to: a) the generation and validation and b) the interpretation of PROMs?
3. In the light of what has been discussed, could you please identify 3 issues you would select as a priority for future research?

4. Summary of the key issues arising from the Group discussions and the final plenary feedback session

Users’ Needs

Within the context of the meeting the term ‘users’ was applied in its broadest sense, and encapsulated patients/public, healthcare professionals and regulatory authorities. The groups discussed generic requirements of PROMs and also specific user requirements.

- Delegates agreed that decision makers and the research community required validated, reliable and generalisable PROM instruments in order to maximise the impact and effectiveness of these measures in decision making. Currently PROMs tend to be developed and validated on a bespoke basis for individual research studies and regulatory decisions, and there is little data available to
be able to compare the outputs of PROMs across research studies or regulatory decisions.

To achieve greater consistency and reliability all groups noted that greater consensus was required about what the key patient-important domains were and what validated measures/items best addressed these. This was required for both generic and disease-specific PROMs to ensure consistency and comparability across research studies and decision making.

- The groups identified the following areas where existing PROMs may not meet the specific needs of a particular population or patient group: end of life issues, children and mental health.

- To enhance the interpretability of PROMs, stakeholders needed to be able to communicate the impact of changes in PROMs data into information that was meaningful to the user of the data in terms of the functioning or capability.

- The impact and utility of PROMs as a tool in decision making both at the regulatory and individual patient level needed to be evaluated. There was also a consensus that all users (pharma/industry, regulators, healthcare professionals and patients) should be working collectively towards developing PROMs or specific measures that could satisfy their various requirements.

- There was a need to evaluate the impact of different settings/contexts on the generation of PROMs data, particularly the collection of PROMs in routine practice rather than under more tightly defined conditions in clinical trials which most PROMs instruments were originally designed for.

- A series of systematic reviews was suggested focussing on the utility and impact of PROMs in research, clinical practice and decision-making. In particular it was suggested that it would be useful to systematically review the research evidence to determine instances where the use of PROMs had been shown to be ‘useful’, ‘not useful’ or ‘possibly useful’ in affecting patient outcomes. Such an analysis could help to highlight factors in study design or other areas that could be used to inform future research including when the use of PROMs is not considered appropriate. Such a study could also help to highlight those PROMs tools which have been most successful in demonstrating an impact.

**NICE**

- Generalisability was considered to be especially important for NICE (National Institute of Health and Clinical Excellence) which used the EQ-5D\(^3\) to calculate QALYs (quality-adjusted life years). Although easily generalisable, it might not be particularly sensitive to disease-specific or patient-important outcomes. The key issue was how to improve the trade-off between the requirement for generalisability whilst trying to increase sensitivity by introducing key disease-specific measures.

  It was generally agreed that research could be undertaken to develop tools to bring together consistent domains from generic measures whilst incorporating some disease-specific measures (such an approach is already being developed by the EORTC for cancer trials).

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\(^3\) EQ-5D is a standardised instrument for use as a measure of health outcome; it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys to calculate QALYs.
• Also with regards to the use of EQ-5D by NICE, the groups discussed whether
the utility of the measure obtained should be based on patients’ perception or
societal values. It was noted that NICE’s policy was that it should be based on
societal values, however the groups agreed that there may be merit in further
research to establish whether the EQ-5D still reflects society’s view given that
it was developed over 10 years ago.

Patients
• There needed to be better patient engagement throughout the process of
PROM design, validation and reporting. By improving patient engagement,
response rates should increase and the patient-important outcomes would
become clearer to researchers.

Healthcare Professionals
• Healthcare professionals needed better tools/training to assist them in effective
implementation and use of PROMs in clinical decision making. Such schemes
would need to educate clinicians in how to access and interpret PROM data
both in assessing an individual’s performance against a PROM and in guiding
them on treatment options based on PROM data in the research literature.
Guidance was also required in assisting health professionals about how to give
meaningful feedback to an individual (e.g. what does the result of a clinical
trial mean for an individual patient’s treatment).

• Specific educative guidance and tools would also assist patients and patient
advocacy groups in improving the level of consideration given to PROMs
outcomes.

Developments in PROMS methodology

i) Generation and Validation of PROMs

• Better design of PROMs based studies, particularly RCTs, were discussed. It
was recognized that the selection of PROMs was not always decided “a priori”,
based on the PROM research question to be addressed, but rather on what
measures were available or could be collected. Guidance to assist researchers
in ensuring that during the design of their studies they defined the key
variables to be measured and subsequently ensured that the PROMs they
selected actually measured the chosen variables was proposed as a key
research need.

• Delegates considered that existing PROMs were often poorly defined or not well
described. This led to inconsistency across measures with similar variables
using different items. Also there was often a lack of agreement over what the
content of the domains within measures should be. It was suggested that
future research should focus on creating a consensus about the content of
different domains and improving existing PROMs rather than creating new
measures (>3000 PROMs instruments are already available).

This consensus work, particularly if it involved using a combination of generic
and disease-specific measures, would help build up the evidence base of
validated, reliable and generalisable PROMs that would assist users in their
decision making.

• Delegates noted that there were standardised approaches and frameworks to
developing PROMs available, however it was not known which of these
approaches were superior, how they might be improved, or whether they were generalisable to other disease areas.

- The groups discussed whether there was potential within the NIH PROMIS initiative\(^4\) to take forward this work and develop standardised measures/items in PROMs. Delegates agreed that further consideration should be given to the scope for UK engagement with the PROMIS initiative. If shown to be successful, the use of web-based technology could also be extended to the UK setting.

- There was a need to explore the use of web-based technologies and PROMs. It was recognised that web-based PROMs tended to have a better response rates but it was unclear whether their application could be generalised.

ii) **Interpretation of PROMs**

- The issue of interpretability of PROMs data was raised and particularly the differing needs of end-users in accessing and interpreting PROMs data to aid decision making (see User needs section).

- Further research was required to understand the significance of changes in PROMs data. For example, further research on the minimum important difference (MID) was required and specifically what changes in PROMs meant in terms of changes in functioning, capability or utility.

This information would be helpful for policy makers in evaluating RCT or observational data, and also individual clinicians when informing patients about either their own PROM data, or the impact of different treatment strategies on an individual’s quality of life.

- Normative data to assess PROMs responsiveness and sensitivity was lacking (even in the best studies in areas such as cancer).

- The groups also considered that there are methodological research issues around dealing with missing data in PROMs, including methods to reduce the volume of missing data and analytical methods to handle missing data.

- Further guidance was required on approaches to combine clinical and PROMs data (e.g. survival and quality of life data) and how this should be communicated to patients and decision makers.

- Many agreed that a more consistent and standardised approach to reporting PROMs data in the context of RCTs would improve the use of PROMs data. To assist in cross-study analysis and decision making, it would be useful to develop an agreed framework on how and when to report the experimental design, protocol and analysis plan for PROMs.

\(^4\) The PROMIS programme is funded by NIH and has used computer technology and advances in measurement theory to develop an improved tool for measuring PROs. The broad objectives of PROMIS are to: (1) develop and test a large bank of items measuring PROs; (2) create a computerized adaptive testing system that will allow for efficient, psychometrically robust assessment of PROs in clinical research on a wide range of chronic diseases; and (3) create a publicly-available system that can be added to and modified periodically, and that will allow researchers to access a common item repository and a computerized adaptive test (CAT).
In the longer term such an approach could help to raise the standard of study design of PROMs within trials. The groups agreed that any work in this area should be informed by guidance the EMEA and medicine regulators already have in place around standards for PROMs.

**Key Research Issues**

The breakout and plenary feedback sessions highlighted the following key areas for further research:

- To strengthen the underpinning evidence for the core content of PROMs both within disease-specific measures and in mapping onto generic measures. The suggestion was that was methodological research was required to draw on existing PROMs and define the most appropriate domains within PROMs instruments. This would enhance the consistency and generalisability of these tools in research and decision making.

- To re-assess the relevance of the EQ-5D.

- To address gaps in the current PROMs instruments available e.g. end-of-life, childhood issues.

- To develop guidelines for the use of PROMs in research e.g. in study design, particularly RCTs; and develop a framework for reporting the experimental design, protocol and analysis plan for PROMs.

- To improve understanding of the impact of changes in PROMs on health functioning, capability or utility. This included tools for accessing and interpreting PROMs for clinical decision makers and also further research around the minimum important difference which would have to include the generation of normative data/ reference values; benchmarks and thresholds.

- To demonstrate the utility of PROMs in clinical research and decision making (including assessing different disease sites and populations of interest), through systematic reviews of existing evidence in order to demonstrate and identify factors influencing the utility of PROMs.

**5. Next Steps**

The Workshop report was considered by the MRC/NIHR Methodology Research Programme Panel. In light of discussions at the Workshop and the issues to arise in the Workshop report, the Panel agreed that the most appropriate mechanism to develop a managed programme in the area was to issue a Highlight Notice. The Highlight Notice will seek to encourage investigator-led research specifically around generalisable methods development underpinning i) the generation and validation of PROMs and ii) the interpretation of PROMs.

The specific issue about re-assessing the EQ-5D will also be taken forward but through a call for proposals focussing on addressing NICE’s methodological research needs, which is planned for May 2009.
OSCHR Methodology work stream

The mission of the Office for the Strategic Coordination of Health Research (OSCHR) is to facilitate more efficient translation of health research into health and economic benefits in the UK through better coordination of health research. It brings together the main public funders of UK health research; the Medical Research Council (MRC), National Institute of Health Research (NIHR), Welsh Office for Research and Development and the Chief Scientist’s Office in Scotland.

Methodology research is one of the five areas of joint working between the OSCHR Partners which MRC leads on behalf of the OSCHR partners. The MRC and NIHR are working together to strengthen the UK’s position as a leader in the methods that underpin health sciences research. The initiatives planned will ensure that UK health research is built on the best methodological evidence base.

Scope of the Methodology Work Stream

- Research tools for the design and analysis of primary, descriptive and evaluative studies, including biomedical science, experimental medicine, randomised trials, cohorts and other designs, of health, health care, health services and health policy.

- Research tools for the design and analysis of secondary studies, involving reviews and evidence synthesis of both descriptive and evaluative studies of biomedical science, health, healthcare, health services and health policy.

- Theory and methods in the disciplines underpinning research in the health sciences for example: health economics, modelling and decision science, biostatistics and quantitative methods, qualitative analysis and mixed methods, bio- and health informatics, epidemiology, behavioural sciences, medical anthropology, medical sociology, health psychology, organisational/management science and bioethics.

- Methodologies to accelerate the translation of discovery science into experimental medicine, evaluative studies and clinical benefit including new trial designs, improved methods to improve the conduct of clinical trials and assessment of risk efficacy, safety and other issues related to regulatory approvals for new medicines, devices and diagnostics.

- Methodological toolkits and best practice guidelines for areas of medical research.

- Measurement and validation of patient-based outcomes of health and satisfaction.

Methodology work stream activities

MRC/NIHR Methodology Research Programme (MRP)

This programme is jointly funded but managed by the MRC. It supports research across the breadth of the methodology work stream remit. Its focus is on methods development research where the outputs have generalisable applicability beyond that of a single case-study.
The MRP supports both investigator-led research and needs-led research. The needs-led research programme involves taking forward the methodological research needs of stakeholders who have interests and needs in methods development research (e.g. Departments of Health across the UK, regulators and industry).

Funding opportunities for both investigator-led and needs-led methods research can be found at: 
http://www.mrc.ac.uk/Fundingopportunities/Initiatives/MRP/index.htm

**MRC Hubs in Trials Methodology Research (HTMR)**

To support the national methodological platform in clinical trials research, MRC has committed £16 million to create a UK-wide network of Hubs focussing on trials methodology research. The Hubs, in Birmingham, Bristol, Cambridge, Edinburgh, Liverpool, London, and Oxford include methodological research expertise across a range of research issues and therapeutic areas. They also provide:

- Effective links with regional and national clinical trials units.
- Support and advice to the clinical trials research community on methodological issues.
- Training programmes.

NIHR has provided £3.5m per year in a rolling programme of additional support to underpin Clinical Trials Units in England and provide stability and research capacity (methodological and clinical) for late phase trials. This funding will also enable work with the Hubs in their methodological research.

**Targeted Initiatives**

MRC will develop managed research programmes that address areas which underpin the broader translational research agenda and have a strong user focus, including:

- **Fast-tracking the process for drug development**
- **Patient-based outcomes initiative**
- **Methods development for National Institute for Health and Clinical Excellence (NICE) appraisals and evidence syntheses**

**Research Capacity and Training**

MRC has a number of personal award and training schemes specifically aimed at training the next generation of methodology researchers. Further details are available at:

http://www.mrc.ac.uk/Fundingopportunities/Fellowships/index.htm
http://www.mrc.ac.uk/Fundingopportunities/Studentships/index.htm
Annex 2

Patient Reported Outcomes (PROs):
Identifying UK Research Priorities

Workshop Agenda

Plenary Sessions
Chair: Tim Peters

09.30 Welcome – context, purpose, planned outputs
Professor Tim Peters (Chair MRC/NIHR Methodology Research Programme; Department of Community Based Medicine, University of Bristol)

09.45 Keynote address: Issues in relation to the science underpinning PRO measures and their use to inform decisions in health services
Professor Ray Fitzpatrick (Public Health and Primary Care, University of Oxford)

10.15 Patient reported outcomes in decision-making: needs and drivers from the users’ perspective
- Routine Use of Patient Reported Outcome Measures (PROMs) in the NHS
  Alan Glanz, Principal Research Manager, Policy Research Programme, R&D Directorate, Department of Health
  David Nuttall, System Management and New Enterprise, Department of Health

- National Institute for Health and Clinical Excellence (NICE) Health Technology Appraisals: the impact of PROs on decision making
  Professor David Barnett (Chair of the NICE Appraisal Committee, University of Leicester)

- PROs and drug evaluation process
  Dr. Mira Pavlovic (Head of Scientific Advice Unit at the French Medicines Agency, Vice- Chair of Scientific Advice Working Party at the European Medicines Agency EMEA)

- A patient and family perspective on PRO measures
  Dr. Alastair Kent (Director, Genetic Interest Group)

- The design and use of PRO measures in orthopaedic surgery
  Professor Andrew Carr (Nuffield Department of Orthopaedic Surgery, University of Oxford)

12.00 Use of patient reported outcome measures in various research settings – challenges and opportunities
• Embedding clinically meaningful and accurate PROs into RCTs  
  Professor Jane Blazeby (Department of Social Medicine, University of Bristol)

• Using patient-reported outcome measures in observational studies in health  
  Professor Suzanne Skevington (Department of Psychology, University of Bath)

• PROs for economic evaluation: the key issues  
  Professor John Brazier (School of Health and Related Research, University of Sheffield)

• PROMIS: Promises, Challenges and Opportunities  
  Dr. Susan Yount (Director of Research Operations, Centre on Outcomes, Research, and Education, Northwestern University, Scientific Project Director at NIH PROMIS)

13.00  Lunch

Breakout Sessions

14.00  • What are the key issues users face when applying PRO measures to decision making?

• What methodological research is required to improve the PRO technology to increase its utility and validity in the future with regards: a) the generation and validation and b) the interpretation of PRO measures?

• In the light of what has been discussed, could you please identify 3 issues you would select as a priority for future research?

15.30  Coffee Break

Summary Session  
  Chair: David Armstrong

16.00  Summary of the breakout sessions  
  Rapporteurs

16.30  Closing Remarks  
  Professor David Armstrong (MRC Strategy Board; Department of General Practice, King’s College London)

17.00  Close
Annex 3

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Annex 4

PATIENT REPORTED OUTCOME MEASURES:
PATIENT AND FAMILY ISSUES AND PERSPECTIVES
A DISCUSSION PAPER

Introduction
This paper arises from a preparatory meeting of patient representatives with expertise in commissioning, planning and participating in biomedical research held at the MRC on 30th September 2008. Those attending represented a wide range of different diseases (rare and common) including cancer, diabetes, and a number of rare genetic disorders such as epidermolysis bullosa and cystic fibrosis (the list of participants is attached in Appendix 1)

All present welcomed the MRC’s interest in patient reported outcome measures (PROMs) and appreciated the opportunity to participate in discussions about the development of MRC’s interest in this important issue at the point of formulation of policy and practice, rather than being asked to comment on outcomes after the event. We take this as evidence of a genuine commitment to real partnership working on behalf of the MRC.

Working assumptions and requirements
For PROMs to be able to contribute added value to biomedical research it will be essential for them to meet the following criteria:-
- Reproducibility
- Validity
- Responsiveness to changes that matter to the patient
- Interpretability
- Acceptability (to patients)
- Feasibility of administration/capture of data

It is also likely that the collection of PROM data will require a degree of trade off between rigour and comprehensiveness on the one hand, and willingness of patients to complete the activities required in order to collect the data. As one patient put it “we want research to enable us to live, rather than living to enable research”.

Applicability
Patient (or Carer) Reported Outcome Measures have the potential to be relevant to most, if not all, disease areas into which medical research is undertaken. People should not necessarily be excluded from having their views and feelings taken into account because they are children, mentally incompetent, demented, suffering from a different/divergent reality (e.g. schizophrenia) or for some other reason. Tools to capture the experiences of these patients (and of those who may provide care for them) need to be developed.

Objection to PROMS
Arguments against using PROMs include:
- that it is better to rely on independently verifiable observations
- they are too difficult to interpret
- they disrupt the research process
- their collection is too intrusive for patients/subjects
None of these objections were held to be valid per se, although they can all become so under certain circumstances. This is particularly relevant in circumstances where PROMs are not developed in the context of a partnership process with representatives of those who ultimately stand to benefit from the research proposal. If there has not been proper patient and carer consultation in the development of PROMs then there is indeed a danger that PROMs will be seen as tokenistic - a response to political rhetoric rather than evidence of a genuinely collaborative approach to ensuring best value for the investment of research money (whether arising from public, private or voluntary sources).

**Developing PROMs**

When generating tools for the capture of PROMs that work and which would add value to the research process, it is important to take account of the following issues (n.b. This is not in priority order, nor is it intended to be definitive).

- **Timing**: Patient input to setting the research question to be addressed, as well as to the forming of outputs, can facilitate the design of tools and the capture of relevant PROMs. Patient input into setting the question can enhance payback in a number of ways.
- **On the impact of the research process and on the experience of receiving care and support**
- **On the trend to complexity in R&D and the demands this makes on research subjects (focusing investigations on what they need to know, rather than what it would be nice to know)**
- **What (if any) tangible results patients might anticipate seeing as a result of their participation (making the recruitment of subjects easier and more honest)**
- **The need for more complete use of data**: It was said that as much as 80% of data generated by research is not used. Patients who volunteer for research are usually eager to see the greatest possible benefit arising from their participation, maximising the return on investment and reducing the likelihood of others suffering in future. Unused data is wasted data and it should not be collected unless there is a view as to why it is necessary. PROMs, targeted on patient relevant outcomes will potentially reduce the collection of data that is not used, and enhance the quality and the contribution of that which is, to boost research outcomes.
- **Patient responses to interventions are frequently situation specific**: Two people with the same disease will respond to its impact differently depending on external factors that may have nothing to do directly with the manifestation of the condition in their body. Nor will the same person respond in a consistent manner to the impact of a disease throughout the course of their life (the response to terminal cancer at 35 might be very different to the response that the same patient might make to the same disease had it occurred at age 80).
- **For PROMs to add value they must be capable of capturing the importance of subjective benefit to the patient resulting from the intervention study, and also of the value to third parties/parents/carers etc. Quality of life measures that are able to capture these (things such as palliation of symptoms, making pain more bearable etc.) often appear to be neglected or discounted by those making cost and clinical effectiveness calculations.**
- **Data captured by PROMs must be acceptable to and useable by regulatory agencies such as EMEA, MHRA, NICE etc. Issues arising from the operation of the regulatory process and the uses to which different types of data are put could be fed into patient groups. This would help ensure that regulators are using relevant data in their deliberations, allow the identification and removal**
of inappropriate tools, and help define issues such as the level of risk patients are prepared to tolerate in the expectation of a given level of benefit.

- Carer perceptions of the value of a particular benefit (e.g. maintenance of intellectual capacity compared with activities of daily living with dementia). However, it will be important for these perceived benefits to be viewed as outcomes in their own right, rather than proxies for patient views, as emphasised above. For example, measuring, and weighing, the differing perspectives of patients and children of ‘benefit’ can be challenging in this context. Significant progress has been made in developing materials for conveying complex concepts to people with learning disabilities in recent years. These are transferable, with adaptation, to research and also for use with children.

- Cultural and social issues arising from ethnicity, use of English when not the mother tongue, religious or moral codes, family structures and customs etc. will need to be addressed sensitively (NB. this applies to the researcher as well as the research subject).

- Research and regulatory conservatism (as expressed in a reluctance to use “softer” end points, for example), together with a willingness of patients to cope and not to “make a fuss,” can underplay the potentially substantial advances to be made by using PROMs data in planning and delivering health gain.

- Issues of timing can be important, as the value of a change measured by a PROM may not be apparent (either to the patient or to the researcher) immediately following the intervention. A small change in function can make a big difference to the quality of life if it permits the resumption of activities previously enjoyed or deemed to be important by the patient/research subject (e.g. restoring a degree of independence). As with any research, follow-up remains an important component of delivering robust results.

- Compliance with research protocols may be enhanced by the selection of relevant PROMs, as projects will be seen to be collecting evidence that is of clear value to patients.

**Conclusions**

It is clear that Patient Reported Outcome Measures are an important component in undertaking high quality research, and that these should sit alongside other indicators (clinical end points, biomarkers etc) used to determine the results of biomedical research. Measures to capture PROMs (and also to establish their transferability within and between diseases) need to be developed, and all stakeholders will need training and support if they are to fulfil the potential they have to add value to research and development programmes targeting serious unmet medical needs. However, PROMs are only likely to deliver their potential benefits as part of a wider programme of user involvement in research; in particular, it will be important for patients and carers to be involved in the design of PROMs and research questions to ensure that research is addressing the right questions as well as measuring the right outcomes. PROMs alone cannot fulfil the important role of ensuring research is delivering the maximum benefits for patient care.

Alastair Kent (on behalf of the patient focus group)
3\textsuperscript{rd} November 2008
## Appendix 1

**Patient-Reported Outcomes: Identifying UK Research Priorities**

*Patients’ Perspectives*

**30 September 2008**  
*Medical Research Council, 20 Park Crescent, London W1B 1AL*

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