MPe Myeloma Patients Europe

CONSILIUM SCIENTIFIC

REPORT

ASSESSMENT OF QUALITY OF LIFE DATA IN MYELOMA CLINICAL TRIALS BETWEEN 2011 AND 2021

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ABOUT MYELOMA PATIENTS EUROPE

Myeloma Patients Europe (MPE) is an umbrella organisation representing 49 myeloma and AL amyloidosis patient groups and associations from across Europe and further afield. Our mission is to provide education, information and support to members, and to advocate at European, national and local levels for the best possible research and equal access to the best possible treatment and care. Together, we support thousands of myeloma and AL amyloidosis patients, and their caregivers, every day.

This project is part of the MPE Patient Evidence department, which was established to generate evidence important to myeloma patients and their families. The department aims to understand more about what gaps exist within the myeloma landscape and how to best generate evidence for these gaps. It works alongside MPE's Policy and Access team to anticipate the questions that need to be asked (and the data required) to improve healthcare and medicines access, reduce inequalities and improve patient outcomes across Europe. MPE commissioned Consilium Scientific, an external research agency, to conduct this research. Please visit: www.mpeurope.org.

ABOUT CONSILIUM SCIENTIFIC

Consilium Scientific is a non-profit research and educational organisation dedicated to informing and enacting health policy change in the UK and around the world. Consilium Scientific is working to build a world where clinical research is founded on integrity, transparency and methodological rigour to enable evidence and accessible healthcare for all. For more information about Consilium Scientific, including details of their research and analysis, please visit: https://consilium-scientific.org.

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1. INTRODUCTION

Myeloma is a rare, incurable disease that is the second most prevalent haematological malignancy after lymphoma (Kazandjian, 2016). Incidence and mortality rates vary significantly between individual countries due to disparities in access to quality health care (Ludwig et al., 2020). The global incidence rate of myeloma is 2.1 per 100,000 per year (Ludwig et al., 2020), whereas the incidence rate in Europe ranges from 4.5 to 6.0 per 100,000. (Moreau et al., 2017). The survival for myeloma patients has improved substantially over the last two decades (Kvam and Waage, 2015), but patients face a range of treatment and disease-related events and symptoms, which can negatively influence their quality of life (QoL) (Sonneveld et al., 2013; Kvam and Waage, 2015). Enhanced QoL has been shown to promote prognosis, making QoL measurement a meaningful factor of myeloma patient treatment (Gadó and Domján, 2013). Past studies have indicated that QoL evaluations in clinical trials are very modest (Kvam et al., 2009; Sonneveld et al., 2013; Kvam and Waage, 2015).

QoL is defined by the World Health Organization as *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."* This can relate to health and other factors, including relationships and leisure activities (WHO 2012). Health Related Quality of Life (HRQoL) is more specifically defined as a *"multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological and social aspects of life"* (FDA 2009).

Patient-reported data regarding their QoL and HRQoL can be generated during a clinical trial or treatment – this is known as patient reported outcomes (PRO). A PRO is a report that comes directly from the patient about the status of their health condition without any interpretation by clinicians or anyone else (FDA 2009). PROs are usually collected using validated instruments (usually questionnaires) known as PRO measures or "PROMs", which patients are provided with at set time points in a clinical trial. Typically, HRQoL is always categorised as a PRO, as it can only be described by a patient (FDA 2009).

There is an increasing consensus that the collection of QoL and HRQoL data using validated PROMs is important to understand the full impact a disease or treatment has on a patient and their daily lives. This type of data can also assist with regulatory and reimbursement decisions and in patient decision-making in healthcare systems.

The National Institute for Health and Care Excellence (NICE), the European Medicines Agency (EMA) and the American Society of Clinical Oncology (ASCO) have all emphasised the need to enhance the quality of QoL trial outcomes to better inform health technology assessment (HTA) and regulatory decisions (Kyte et al. 2019). Often, poor reporting is a result of researchers' lack of expertise in handling QoL data that reveals psychological or physical discomfort (Cruz Rivera et al., 2022). Avoiding reporting of problematic data not only introduces bias into a trial's outcomes but also has repercussions for patient treatment and future participation since it heightens patients' confusion (Cruz Rivera et al., 2022). HTA organisations are potentially in a unique position to promote greater QoL data gathering by adopting uniform evidence standards (Kleijnen et al.,2017).

Despite the need for QoL data collection, earlier Myeloma Patients Europe (MPE) research on clinical trial insights for Central and Eastern Europe established that data collection on QoL and HRQoL is lacking in myeloma clinical trials.

To understand this issue further, in this report we analyse and present the findings on QoL and PRO measures (PROMs) used and reported in clinical trials and published literature in myeloma between 2011 and 2021.

This report brings together the evidence, identifies practices in QoL data collection over the past 10 years, identifies gaps and issues with research quality, and proposes solutions to improve the inclusion of QoL data in myeloma clinical trials. Additionally, we present findings on the trials conducted in Europe (where at least one trial location was a European country) and analysis of myeloma appraisals at NICE, specifically focusing on the QoL aspects.

This report provides recommendations for the myeloma patient community and other stakeholders (clinicians, pharmaceutical firms, research institutions, charities and reimbursement bodies) to enhance the collection, reporting, justification and utility of QoL data in myeloma research and clinical practice.

Agreed definitions need to be improved and disseminated to improve consistency. For the purposes of this report, we include both QoL and HRQOL assessment in clinical trials, through the use of PROMs, under the umbrella term "QoL."

1.1 ABBREVIATIONS

AE	Adverse Event
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol-dimension Questionnaire
ERG	Evidence Review Group
FACT-G	Functional Assessment of Cancer Therapy-General
HRQoL	Health-Related Quality Of Life
HTA	Health Technology Assessment
MM	Multiple Myeloma
MTA	Multiple Technology Appraisal
MyPOS	Myeloma Patient Outcome Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PROMs	Patient Reported Outcome Measures
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SCT	Stem Cell Transplantation
SD	Standard Deviation
SLR	Systematic Literature Review
STA	Single Technology Appraisal
TA	Technology Appraisal
TTD	Time-to-Treatment Discontinuation
TTP	Time To Progression

2. KEY FINDINGS

2.1 CLINICAL TRIALS 2011 – 2021

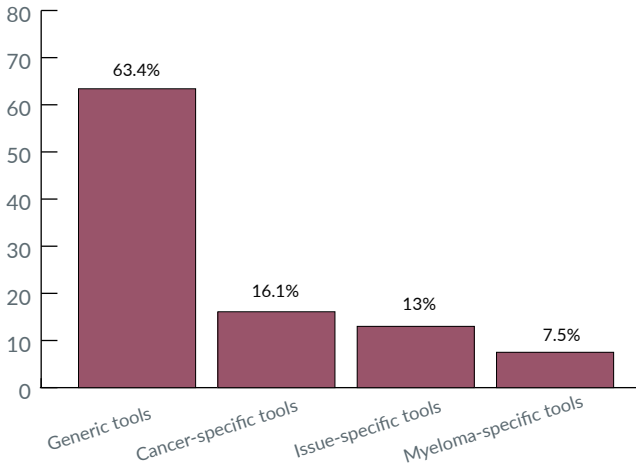
This part of the project explored whether QoL data was collected in global and European myeloma clinical trials run between 2011 and 2021.

- **Overall picture:** We identified 1,557 myeloma clinical trials conducted globally, of which 525 trials were, or are, being conducted in at least one European country.
    - According to the protocol analyses: 521 trials (33%) out of 1,557 trials globally intended to collect QoL data and 215 trials (41%) out of 525 European trials intended to collect QoL.
- **QoL data according to trial sponsor:** The data analysis according to the trial sponsor showed that for any sponsor type (i.e., industry, academic, charity), QoL data collection is/was performed in fewer than 50% of clinical trials. Industry-sponsored trials collect QoL data more often (in 44% of trials) than other sponsors.
- **QoL data according to disease stage:** The vast majority of myeloma clinical trials are/were conducted in relapsed/refractory (n=681, 44%) and newly diagnosed (n=391, 25%) population groups. Both population groups collected QoL data in about one-third of the trials (33% and 37%, respectively).
- **QoL data according to trial phase:** Most trials (45%) are/were in phase 2 and 1/2, in both global and trials conducted in Europe; the collection of QoL data in these phases was 40% and 34%, respectively. More phase 3 and 2/3 trials were conducted in Europe (18%) compared to global trials (10%), and the collection of QoL data in phase 3 and 2/3 trials was higher in trials conducted in Europe (61%) than in global trials (56%).

2.2 LITERATURE REVIEW

This part of the project explored QoL data in a literature search.

- 266 articles that focused on myeloma and measurement of QoL were identified. 192 were primary research (PR – from the clinical trial) articles (72%), 59 were secondary research (SR – studies based on published literature) articles (22%), and 15 articles were economic evaluation (EE) articles (6%).
- QoL was a primary endpoint in 54% of the PR articles. None of the EE articles identified whether the QoL measure was a primary, secondary or exploratory endpoint.
- The literature search identified 93 different QoL instruments, known as PROMs. 59 (63%) of these instruments were generic tools, 15 (16%) were cancer-specific, 12 (13%) were issue-specific and seven (8%) were myeloma-specific tools.
- The most used PROMs in all three types of



PROMs used in 93 clinical trials identified in the literature search

research were generic tools (24%). A combination of cancer and issue-specific (18.4%, n=49), generic, cancer, myeloma and issue-specific (17%, n=46), generic, cancer and issue-specific (15%, n=40) and cancer and myeloma-specific (12%, n=32) were also used. The least used PROMs were myeloma-specific tools (5%).

2.3 NICE APPRAISALS

This part of the project explored the generation and presentation of QoL data in myeloma to support health technology assessment (HTA) conducted by NICE, the HTA body in England.

- We identified 14 myeloma NICE appraisals between 2011 to 2021 that analysed data from 26 clinical trials. 25 trials were phase 3, of which only nine trials collected QoL data as a secondary endpoint. The remaining trials did not collect QoL data at all.
- Of the 14 appraisals analysed, 10 appraisals included QoL data collected in the main clinical trial(s) and four used data collected in dedicated QoL studies.
- The most common PROM used in the appraisals was EQ-5D-3L (n=12), followed by EORTC QLQ-C30 (n=7) and EQ-5D-5L (n=4). The least common was EORTC-MY20 (n=3). To calculate utility values, eight out of the 14 appraisals used EORTC QLQ-C30 and EORTC-MY20 to map onto EQ-5D.
- The Committees found that the QoL data presented in five TAs raised “significant issues” and complicated the decision-making process.
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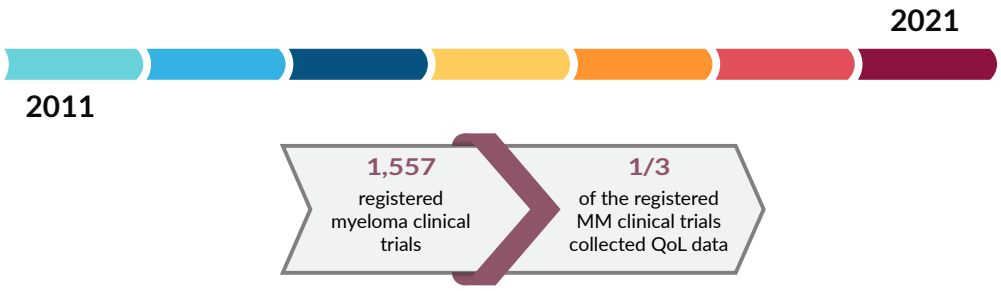

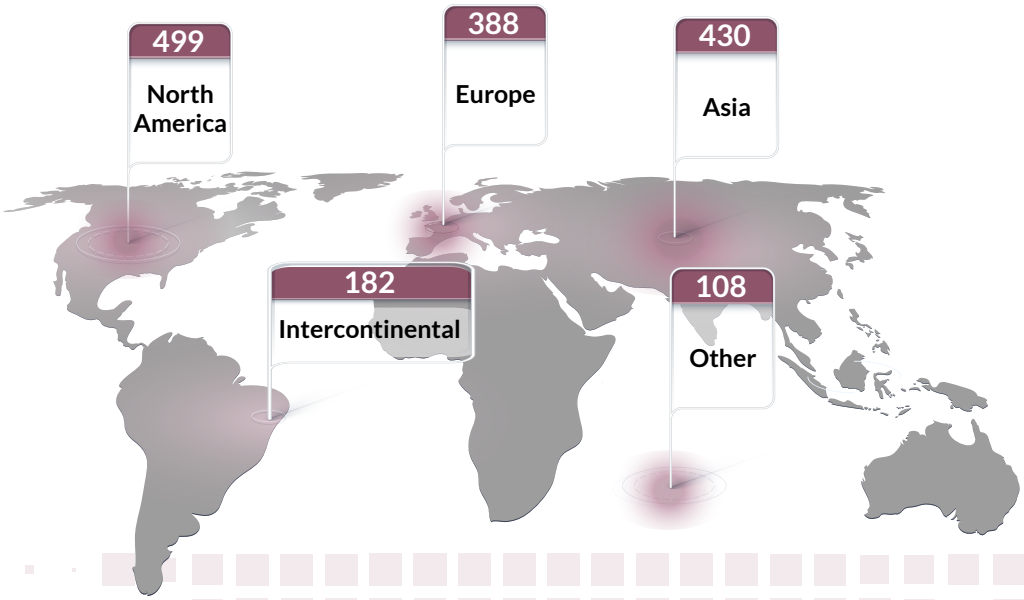

3. RECOMMENDATIONS

1. **Researchers should assess feasibility of collecting QoL data in all clinical trials and, at least, from phase 2. Stakeholders should take account of the following:**
    - Whilst collecting QoL data in phase 1 clinical trials is often important, it can be particularly relevant for cell and gene therapies, as these technologies may enter clinical practice without phase 2 or 3 trials. This QoL data could potentially be supplemented by evidence generated in the real-world. Whilst phase 1 data may not always be useful for regulatory or reimbursement purposes, it is important data to contribute to our overall understanding of how a medicine impacts on quality of life.
    - If the trial is not powered on QoL, investigators must ensure that QoL is designated as a secondary or exploratory endpoint.
    - For the above to happen, ethics committees could potentially include QoL data collection as a question or requirement unless the investigators can justify this is not necessary. The SPIRIT-PRO Extension (2018) and the SPIRIT (2013) give consensus recommendations for elements that should be included in trial protocols in which PROMs are important primary or secondary outcomes. In addition, global reporting rules with open access are obtainable through the CONSORT PRO Extension (2013), or if a newer version becomes available, it should also be utilised. Stakeholders should be encouraged to adopt the expanding array of open-access training materials and guidelines for PROMs to promote future comprehensiveness and uniformity of PROMs design and reporting, and enhance high-quality research (Kyte et al., 2019).
    - Baseline QoL must be measured, and the frequency of PROM administration should not be overwhelming to patients but still often enough to be informative to capture relevant changes. The developers should seek clinical and health economist input in establishing such a schedule. Patient advocacy groups and patients should also be involved in the selection of QoL instruments and PROMs, including in the review of clinical trial protocols, to ensure the measurement (including PROM and frequency) are acceptable.
    - Ideally, where measuring QoL, two forms of PROMs should be utilised simultaneously (Churruca et al., 2021), with at least one being a generic and one a myeloma-specific tool. There are limitations to using both generic and disease/condition-specific PROMs, and the selection of tools needs to be carefully considered with the involvement of patients – where possible/relevant. Even though generic PROMs may lack sensitivity to disease/condition-specific outcomes, they provide generalisation and comparison across conditions, allowing for a more comprehensive application at an organisational or system level. Disease/condition-specific PROMs, on the other hand, offer more face validity, reliability and sensitivity to changes in the patient's state and are thus best suitable for monitoring treatment results at an individual level.
    - There is a lack of QoL data in all myeloma populations, particularly in relapsed/refractory and newly diagnosed patients; consider funding appropriately designed QoL studies in these populations.
    - QoL data should be submitted to registries and published alongside the full results of clinical trials. It is vital that patient-friendly summaries are developed to assist with interpretation and decision-making.

2. **Researchers, patients, and clinicians should collaborate on developing a comprehensive, user-friendly online database of myeloma PROMs.** QoL is subjective and assessing QoL data can be a complex process. It is, therefore, necessary to reduce the ambiguity of the evaluation to produce relevant and consistent outcomes. This can be accomplished by using validated instruments and mapping algorithms. The database should include information about appropriate tools, as well as assist researchers and clinicians in accessing, selecting, and understanding the construct of the instruments' measurement.
3. **Clear and aligned European-level guidance and principles for manufacturers and academic researchers should be developed on how to select relevant instruments, and collect, analyse and report QoL data to support regulatory and reimbursement decisions.** This requires multi-stakeholder involvement, including regulators and representatives from health technology assessment. It would also build on the ongoing work of SISAQOL-IMI and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) on Patient Focused Drug Development and QoL.
4. **An international, multi-stakeholder steering group comprising patients, clinicians, PRO methodologists, regulators and policymakers would be beneficial in establishing a consistent approach to collecting and assessing QoL data in myeloma specifically.** Although different regions and countries may have different healthcare needs, values and systems, creating and exchanging information within and beyond these committees is the best practice for future collection of QoL data. Committees can create frameworks for developing integrated approaches to QoL assessment that benefit patients and administrators by (1) establishing PROMs that correspond to the needs of stakeholders; (2) selecting instruments that are valid, reliable and scored on a common scale across multiple health and social domains; and (3) training and supporting research staff to standardise QoL and PRO data presentation for accurate interpretation (Calvert et al., 2019).

> **For cell and gene therapy, QoL data must be collected from phase 1. For all other myeloma drugs, this data should be collected in (at least) phase 2 and phase 3**

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