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

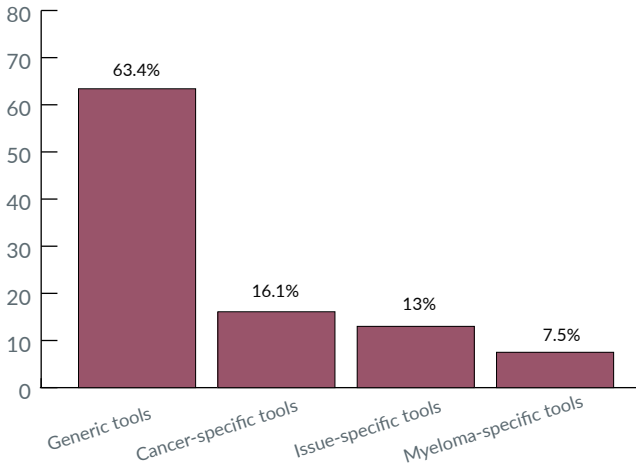
This part of the project explored whether QoL data was collected in global and European myeloma clinical trials run between 2011 and 2021.

- **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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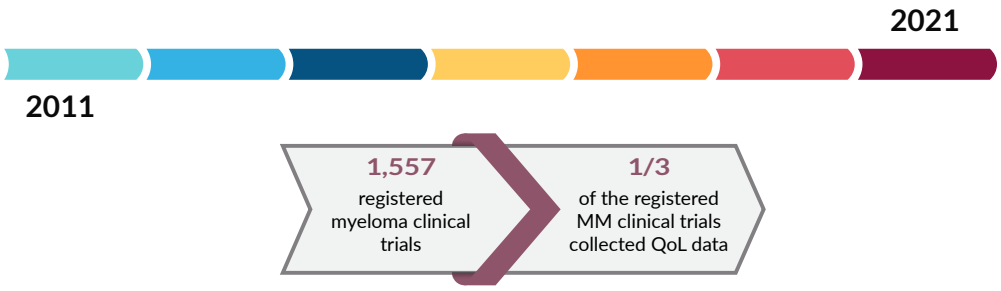
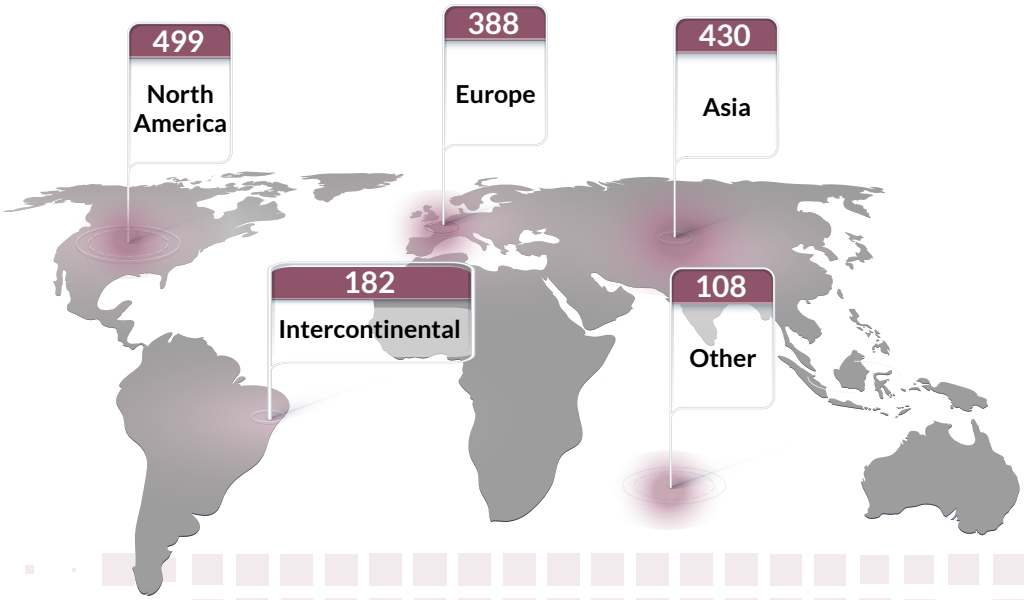




3. RECOMMENDATIONS

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**

4. BACKGROUND

4.1 THE IMPORTANCE OF QOL DATA IN MYELOMA

Myeloma is a rare incurable cancer that is the second most prevalent haematologic malignancy after lymphoma (Kazandjian, 2016), accounting for 1% of all cancers (Padala et al., 2020). 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).

While survival for individuals with high-risk myeloma (15-25%) remains low (Kazmi et al., 2015), survival for patients with standard-risk myeloma has improved substantially over the last two decades, and people living with myeloma for 10-15 years is now common (Kvam and Waage, 2015). This is because treatment for myeloma has significantly improved in recent years, resulting in increased overall survival (OS) with the advent of newer, more focused treatments and sufficient supportive care (Sonneveld et al., 2013). Nevertheless, patients with myeloma face a range of disease-related events and symptoms, the emotional and social impact associated with a cancer diagnosis, and severe side effects of these therapeutic agents, all of which can negatively influence on a patient's quality of life (QoL) (Sonneveld et al., 2013; Kvam and Waage, 2015). Additionally, evidence suggests that people with myeloma are more likely to report symptoms and issues than those with other blood cancers (Osborne et al., 2012).

Treatment choices are influenced by patients' perceptions of their health status and the impact that treatment may have on their overall QoL, which may vary for each individual (Fragola, 2020). Therefore, it is critical to determine which variables have the greatest influence on the patient since better knowledge of these factors can aid in managing symptoms and allow for necessary treatment modifications to avoid additional deterioration in QoL (Fragola, 2020).

While researchers' primary focus has been on improving the OS in myeloma and other cancers, assessing QoL is a critical component in providing patient-centred care in this population (Kvam and Waage, 2015; Fragola, 2020). According to Gadó and Domján (2013), research demonstrating a decrease in QoL in patients with myeloma has concluded that QoL evaluation should become a standard aspect of clinical treatment and that clinical trials should incorporate QoL as a primary endpoint. Enhanced QoL has been shown to promote prognosis in patients with myeloma, making QoL measurement a meaningful factor of patient therapy (Gadó and Domján, 2013).

Although researchers are increasingly considering QoL evaluations in clinical trials, past studies have indicated that the amount of QoL evidence on myeloma therapies is very modest (Kvam et al., 2009; Sonneveld et al., 2013; Kvam and Waage, 2015). Regrettably, there are no standard assessment tools or core outcome measures for assessing QoL in clinical studies (Fragola, 2020). Additionally, the 'weaknesses and inconsistencies' of analysis and presentation of QoL data regularly confound the interpretation of the effect of the therapy on QoL in myeloma. Furthermore, while it is critical that QoL outcomes should affect clinical decision-making, the evidence has had little influence on published therapy guidelines (Sonneveld et al., 2013; Kvam and Waage, 2015).

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). Additionally, cancer patients have demanded a larger availability of high-quality QoL trial data to assist them in understanding what their life will be like during and after a particular medication, as well as how long they may live (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 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. In addition, QoL research may not reflect the opinions of marginalised communities such as the elderly, socioeconomically vulnerable groups and ethnic minorities, which might compromise the scientific credibility of the findings (Cruz Rivera et al., 2022).

Regulators regard QoL to be an essential outcome of healthcare interventions in the medical product evaluation process. Both the EMA and the European Network for Health Technology Assessment (EUnetHTA) provide researchers with QoL recommendations in the form of freely accessible guidance documents that can be used to develop trial protocols. These publications provide guidance on a variety of topics, including the types of QoL measurements that are appropriate for demonstrating the relative efficacy of the product, how to adequately collect QoL data and the interpretation of outcomes (i.e. EMA,). Even though HTA guidelines stipulate QoL data should be a meaningful endpoint for new anti-cancer therapies in Europe, evidence reveals the contrary. HTA organisations are also concerned about the methodological limitations and quality of QoL data collection. Therefore, HTA organisations are in a unique position to promote greater QoL data gathering by adopting uniform evidence standards (Kleijnen et al.,2017).

4.2 INSTRUMENTS USED TO ASSESS QOL

QoL is a complicated and ambiguous concept, and its assessment is highly reliant on the instruments used and the way patients, carers and researchers perceive the outcomes. While life expectancy is easily quantifiable, QoL is subjective.

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), while 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). For the purposes of this report, we use QoL to cover both QoL and HRQoL data.

Patient reported data on their QoL can be generated during a clinical trial or treatment – these are 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 interpretation by clinicians or anyone else (FDA 2009). PROs are usually collected through the use of validated instruments (usually questionnaires) known as PRO measures or 'PROMs', which patients are provided with at set time points in a clinical trial (Kvam and Waage, 2015). Typically, HRQoL is categorised as a PRO as it can only be described by a patient (FDA 2009). Wider QoL data can also be generated using symptom assessments or validated QoL instruments that can be completed by others, including carers or healthcare professional.

Numerous PROMs have been created to evaluate patient-reported QoL in clinical practice, ranging from generic preference-based measures to disease or symptom-specific instruments. A systematic review by Osborne et al (2012) identified 39 myeloma studies that validated 13 multidimensional PROMs. Even though no instrument is complete in terms of patient-centred concerns, the evaluation indicated that the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) has an 'extensive psychometric validation, followed by its myeloma-specific module (EORTC QLQ-MY24 / EORTC QLQ-MY20)' (Osborne et al., 2012).

4.3 GENERIC INSTRUMENTS

Generic PROMs are developed to evaluate QoL in a diverse population, both with and without chronic illness. Although these instruments are used to assess QoL across many disease groups, they may not be sensitive enough to identify changes in QoL within a specific disease. Additionally, normative data can be generated by applying these measurements to healthy individuals. The data may then be used to compare the disease burden of a particular condition to that of other chronic diseases and healthy controls. Two frequently used generic PROMs for QoL are the SF-36 and the EQ-5D (Wells et al., 2011). The NICE methods guide recommends the use of EQ-5D (NICE position statement on use of the EQ-5D-5L value set for England).

4.4 DISEASE-SPECIFIC INSTRUMENTS

Disease-specific PROMs are designed to explore issues related to a given disease. These tools focus on changes in QoL over a period of time or as a result of therapy, which generic measures are not sensitive enough to pick up. Cancer-specific and myeloma-specific tools fall into this category. The two most commonly used tools in cancer and myeloma patients are EORTC QLQ-30 and EORTC QLQ-MY20, respectively (Wells et al., 2011).

4.5 ISSUE-SPECIFIC INSTRUMENTS

PROMs that are issue-specific, such as system- or organ-specific tools, may also be seen in a wider context. These tools are neither generic nor disease-specific and measure a particular aspect of QoL, such as neuropathic pain or cognitive assessment. One of the benefits of this type of questionnaire is that it may be used to assess a variety of illnesses. Examples include DN-4 and TUGT (Wells et al., 2011). Usually, these instruments are combined with disease-specific and or generic QoL instruments in clinical studies.

Furthermore, it is essential that QoL measures are gathered in a manner that respects and safeguards both patients and investigators, and gives meaningful information about how interventions are perceived by participants (Cruz Rivera et al., 2022). For example, Denmark uses AmbuFlex telemedicine to organise outpatient appointments for chronic diseases in which patients complete PROMs from home to assess the necessity for a consultation, thus minimising unnecessary outpatient visits (Hjollund, 2019). In clinical trials, researchers should ensure that modern technologies are used to facilitate QoL data collection.

4.6 PRIMARY RESEARCH

Primary research is original or first-hand research undertaken by the author(s) of the article. The author(s) uses some research methodology (clinical trials, case studies and surveys) to gather new information, which is then published, analysed and evaluated in that source.

4.7 SECONDARY RESEARCH

Secondary research is second-hand research, whereby the author of the article did not generate the research data, but gathered existing data produced by someone else (systematic reviews and meta-analysis). This new information is then reported, analysed and interpreted by the author.

5. METHODOLOGY

The sections that follow outline the methodology used to undertake a comprehensive evaluation of QoL data present in myeloma clinical trials and published research. In addition, we analysed the clinical trials and the relevant literature to investigate the key concerns with the QoL data.

5.1 CLINICAL TRIAL ANALYSIS FOR QOL DATA COLLECTION

5.1.1 Identification of all clinical trials registered between 2011-2021 in myeloma (ongoing and completed)

Data for this project was extracted from publicly available registries. A comprehensive registered clinical trial search in three databases (NCT, WHO and EUCTR) was conducted in December 2021 and updated in February 2022. The scoping period was from 1st January 2011 to December 2021. The three trial registries were searched using the keywords 'myeloma, mieloma, myelom, myélome, Kahler disease, myelomatosis'. Relevant parameters for this study were extracted using proprietary Python code from the XML files downloaded from the NCT registry. The parameters from the WHO registry were obtained using the proprietary java code. The parameters from the EUCTR were also obtained using the proprietary java code.

5.1.2 Data cleaning and extraction

WHO registry pools data from 18 international clinical trial registries, including NCT and EUCTR; however, the quality of records in WHO is often lacking. Since most clinical trials are registered in NCT and/or EUCTR, we repeated the searches in these main databases to a) ensure that we did not miss any clinical trials as search algorithms across registries differ and b) ensure we had access to the complete record.

Duplicate trials were identified by primary identification numbers with priority given to NCT numbers and a list of other possible identifications, for example, EUCTR, DRK and JPRN. NCT, EUCTR, DRK and JPRN numbers are unique identification codes assigned to each clinical study registered on their respective databases. After any duplicates were removed from each database, the data was cleaned to confirm that only myeloma trials remained; trials that included myeloma with other cancers or malignancies were excluded. Data was further cleaned to replace null values, misspellings or format errors. The data from all three registries was merged and any missing data was imputed, where possible, using proprietary coding and manual rechecks.

5.2 COMPREHENSIVE LITERATURE OVERVIEW OF QOL PUBLICATIONS IN MM

5.2.1 Identification of academic literature

A systematic literature search of Embase, Ovid Medline and Web of Science was performed in December 2021. The systematic literature search was from 1st January 2011 to December 2021. Detailed methodology and search criteria are presented in annex 9.6 of this report.

Three researchers conducted a comprehensive search strategy to identify all relevant articles. Articles (full text, abstract only, conference proceedings and poster presentations) were included if they addressed haematological malignancies and QoL. Mendeley was used to remove duplicates and the articles were manually screened further to ensure only the relevant ones remained.

The title and abstract were screened and the articles were included if:

- they were published between 2011 and 2021
- they were available in the English language
- myeloma was stated
- QoL was mentioned

The included articles were separated into three categories: primary research (i.e., a clinical trial), secondary research (i.e., studies based on published literature) and economic evaluation. Each category was then subdivided into articles discussing myeloma only, and myeloma and other haematological malignancies. A second researcher independently verified the lists.

5.2.2 Data extraction

Three researchers extracted parameters of interest for each included myeloma-only article. Another researcher verified the extracted data.

Primary research

Extracted data for primary studies included the trial registration number, article type (full paper, conference proceedings, abstracts poster presentation), article title, year of publication, lead authors, study lead, journal published in, study objective, population type (e.g. newly diagnosed, relapsed/refractory, relapsed, mixed), number of enrolment, intervention (drug name, procedure, therapy), study type (interventional, observational, registry, systematic review), study phase, study duration, randomisation, PROM used, frequency of QoL measurement, QoL as an endpoint (primary, secondary, exploratory) and conclusion of QoL data (impact on QoL or other relevant comments).

Secondary research

Extracted data for secondary articles included title, article type (full paper, conference proceedings, abstracts, poster presentation), year of publication, lead authors, study lead, journal published in, article type (review, qualitative analysis etc.), study objective, population type (e.g. newly diagnosed, relapsed/refractory, relapsed, mixed), QoL instrument used, QoL as an endpoint (primary, secondary, exploratory) and conclusion of QoL data (impact on QoL or other relevant comments).

Economic evaluation

The extracted data for economic evaluation articles included the title, article type (full paper, conference proceedings, abstracts, poster presentation), year of publication, lead authors, study lead, journal

published in, study objective, model structure, randomisation, population type (e.g. newly diagnosed, relapsed/refractory, relapsed, mixed), intervention, cost-effectiveness, PROM used, QoL as an endpoint (primary, secondary, exploratory) and conclusion of QoL data (impact on QoL or other relevant comments).

PROMs

The extracted information on PROMs was further analysed to classify them as generic, disease-specific (cancer-specific or MM-specific) and issue-specific.

Details of PROMs are presented in this report's annexes (Table 1).

5.3 IDENTIFICATION OF ALL NICE APPRAISALS OF MYELOMA

We investigated the critical issues with the evidence submitted in the technology appraisals (TAs) to the NICE Appraisal Committee (AC) that supported the decision-making process. NICE commissions the Assessment Group (AG) or the Evidence Review Group (ERG), an independent academic group with no vested interest, to review the evidence on the clinical and cost-effectiveness summited by the pharmaceutical company. The AC considers all the evidence (AG/ERG report, company's submission, expert opinion and patient groups) in the decision-making process.

5.3.1 Technology appraisal identification

Our review was conducted on multiple technology appraisals (MTAs) and single technology appraisals (STAs) published by NICE between 2011 and 2021. The analysis focused on two key issues: (1) feedback from AR/ERG on the quality of QoL evidence submitted and (2) overall quality of QoL evidence submitted to the AC for decision-making. Data for this research was extracted from publicly available documents on the NICE website (nice.org.uk). These documents included:

- Final Appraisal Determination (FAD) document
- Assessment Report (AR) Or Evidence Review Group's Report (ERG)

We analysed the AR/ERG and AC critiques of the company's submission and did not re-evaluate the evidence submitted to NICE. Therefore, the conclusion of this review on the quality of QoL evidence submitted to NICE is based on aggregated data and presents a qualitative analysis.

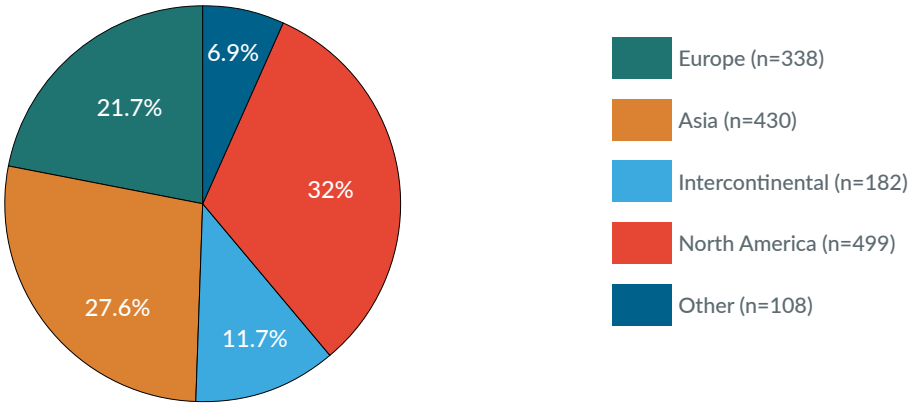
6. RESULTS

6.1 CLINICAL TRIAL ANALYSIS FOR QOL DATA COLLECTION

6.1.1 Identification of clinical trial publications

Location

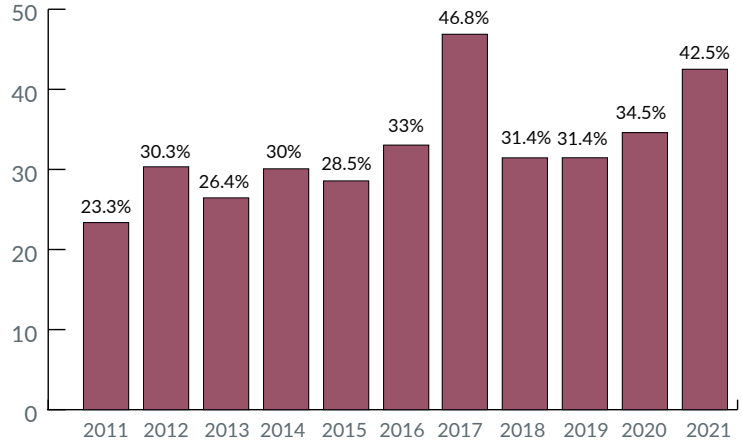
Between 2011 and 2021, 1,557 registered clinical trials in the myeloma population were identified. Over one-fifth of the trials were conducted exclusively in European countries (22%, n= 338), whereas 1,032 were conducted outside of Europe; just under one third in North America (32%, n=499), over a quarter in Asia (27%, n=430), one tenth intercontinental (12%, n=182) and a small fraction were conducted in other countries (7%, n=108). Of the 1,557 trials, 525 were performed in at least one European country and just over two-fifths (n=215, 41%) of these collected QoL data. In the trials conducted outside of Europe (n=1,032), less than a third (n=306, 30%) of the trials collected QoL data.



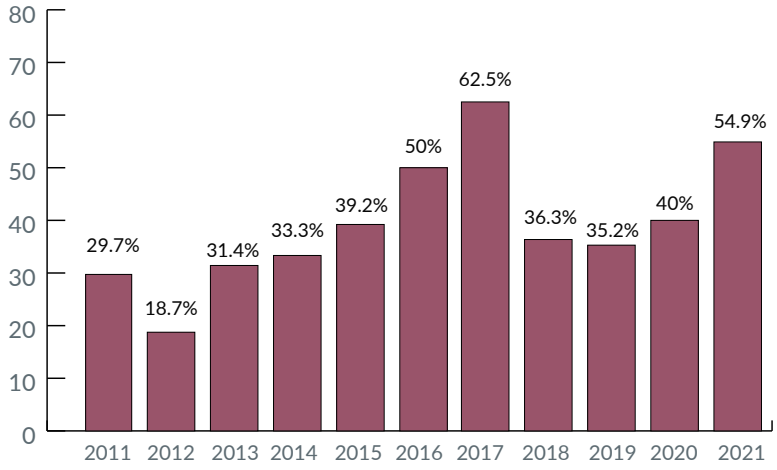
Percentage of all registered myeloma trials by location

Period

We analysed registry data provided by the trial investigators; hence, the data present represents an intention to gather QoL data, rather than actual QoL data collection. Although, from 2011 to 2021, there has been a steady growth in the collection of QoL data in clinical trials, the collection is low regardless of the year. Out of 1,557 clinical trials identified, 521 (33%) trials intended to collect QoL data as per protocol. In 2011, the least quantity of QoL data was gathered (n=25, 23%). The greatest QoL data was obtained in 2017 (n=75, 47%), followed by 2021 (n=73, 43%). A similar trend was seen in the trials that were conducted in at least one European country. In 2012, the lowest amount of the QoL data was gathered (n=12, 19%), while the largest amount of the QoL data was obtained in 2017 (n=39, 63%), followed by 2021 (n=28, 55%).



Percentage of all registered myeloma trials by year which QoL data was collected



Percentage of European registered myeloma trials by year which QoL data was collected

6.1.2 QoL in all myeloma global clinical trials (n= 1,557)

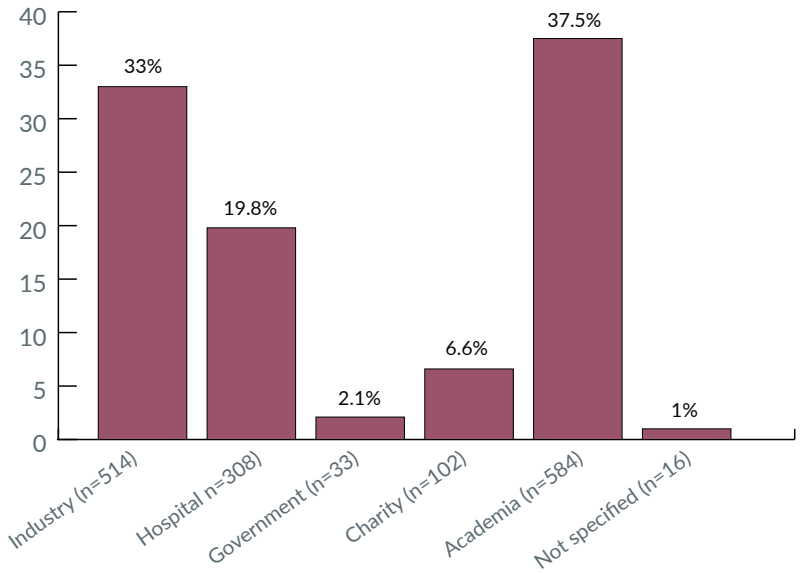
Sponsors

A clinical trial sponsor is a person, company, institution, group or organisation that oversees or pays for a clinical trial and collects and analyses the data (National Cancer Institute).

For this research, we refer to the following as trial sponsors:

- **Industry:** the pharmaceutical industry
- **Hospital:** any sponsor organisation where the word 'hospital' appears in any language. This can also be classified as 'Charity' or as 'Academia', or both
- **Charity:** Organisations such as MPE, Myeloma UK and Myeloma Canada
- **Academia:** an institution or group of collaborative clinical researchers associated with academic institutions, or where the name of the organisation includes the word 'University'

- **Government:** Agencies such as the National Institutes of Health (NIH) and the National Institute for Health and Care Research (NIHR)



Percentage of all registered myeloma trials by sponsor

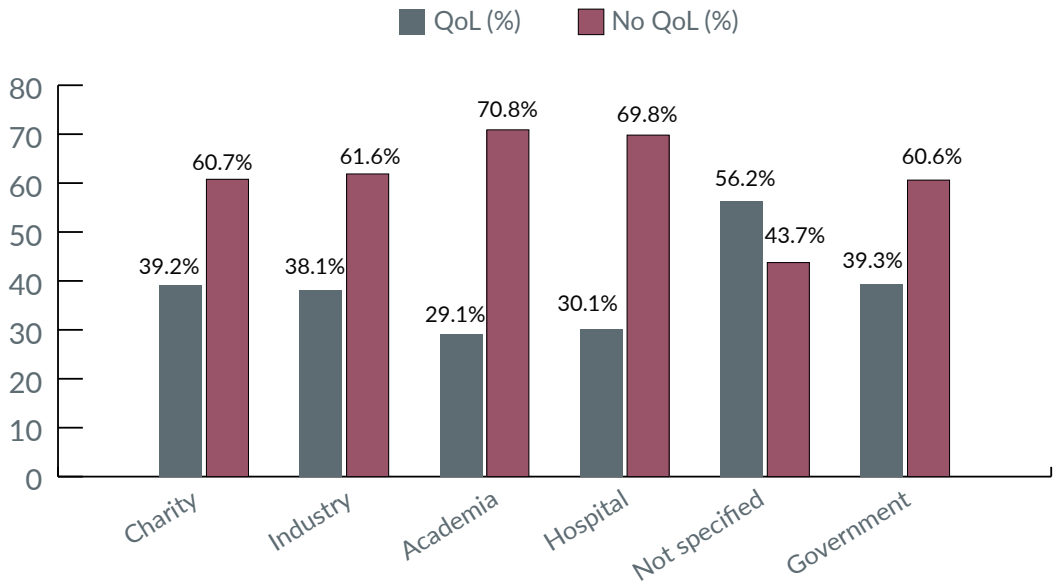
A large proportion of the registered trials were sponsored by academia (38%, n=584), followed by the pharmaceutical industry (33%, n=514) and then hospitals (20%, n=308). Fewer trials were financed by charities (7%, n=102) and government institutes (2%, n=33). However, the collection of QoL data is relatively homogeneous among sponsors, ranging from 29% to 40%. Academia-sponsored trials collected QoL data in less than a third (29%, n=170) of the clinical trials they conducted, whereas government institutes (40%, n=13), charity (39%, n=40), the pharmaceutical industry (38%, n=196) and hospital (30%, n=93) supported trials performed marginally better.

The collection of QoL data can be attributed to the stage of the trials conducted by the sponsors. Nearly three-fifths (n=340, 58%) of trials conducted by academia were in phase 2 and 1/2 (n=261, 44%), phase 3 and 2/3 (n=40, 7%) and phase 4 (n=39, 7%). Of these trials, only 75 (29%) phase 2 and 1/2 trials, 21 (53%) phase 3 and 2/3, and six (15%) phase 4 trials collected QoL data. However, the pharmaceutical industry conducted 277 (54%) trials that were in phase 2 and 1/2 (n=198, 39%), phase 3 and 2/3 (n=68, 13%) and phase 4 (n=11, 2%). Only 79 (40 %) phase 2 and 1/2 trials, 45 (66%) phase 3 and 2/3 and five (46%) phase 4 trials collected QoL data.

Hospitals performed 170 trials (55%) that were in phase 2 and 1/2 (n=146, 47%), phase 3 and 2/3 (n=16, 5%) and phase 4 (n=8, 3%). Only 51 (35%) phase 2 and 1/2 trials, six (38%) phase 3 and 2/3 trials and one (13%) phase 4 trial collected QoL data.

Government institutes conducted the fewest phase 2 and1/2, and phase 3 and 2/3, trials in the global arena (n=25, 75%). Of these, only 22 (36%) were in phase 2 and 1/2, and three were in phase 3 and phase 2/3 (9%). Only eight (34%) phase 2 and 1/2 trials, and one (33%) phase 3 and 2/3 trial collected QoL data.

Charities conducted the most trials in terms of the percentage (n=83, 81%) of phase 2 and 1/2 (n=61, 60%), phase 3 and 2/3 (n=21, 21%) and phase 4 (n=1, 1%). QoL data was only collected in 21 (34%) phase 2 and 1/2, and 10 (48%) phase 3 and 2/3 trials.



Percentage of all registered myeloma trials by sponsor which collected QoL data

Study type

For this research, we referred to the study types as follows:

Observational studies are trials where researchers observe the effect of a risk factor, diagnostic test, treatment or other intervention without trying to change who is or isn't exposed to it. E.g., cohort studies and case-control studies (Institute for Work & Health).

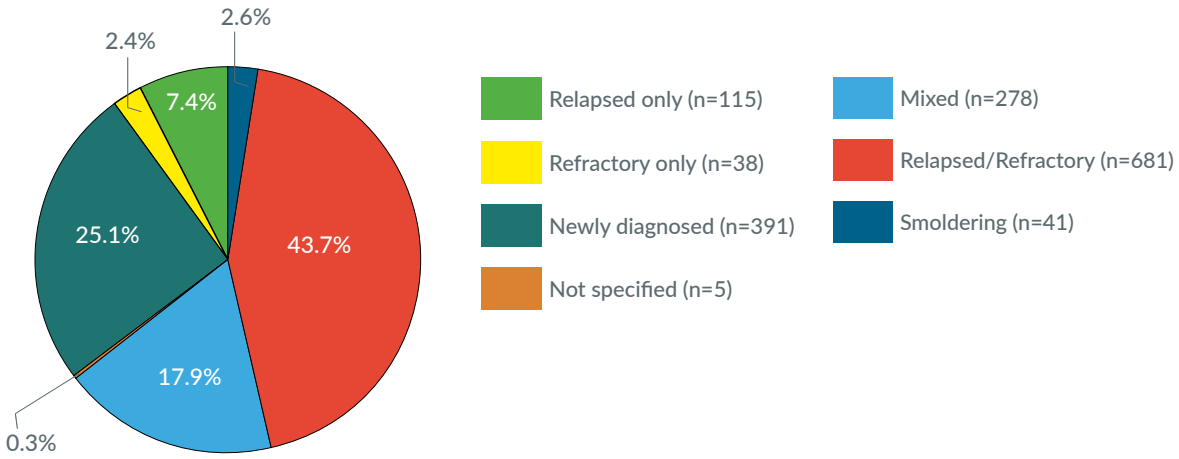
Intervention studies are trials where researchers introduce an intervention and study the effects. E.g. randomised controlled clinical trials (RCT), meaning the subjects are grouped by chance (Institute for Work & Health).

The vast majority of trials are interventional in nature (85%, n=1325) and one-third collected QoL data (33%, n=478). There are far fewer observational studies (15%, n=232), with less than one-fifth of those collecting QoL data (19%, n=43)

Population

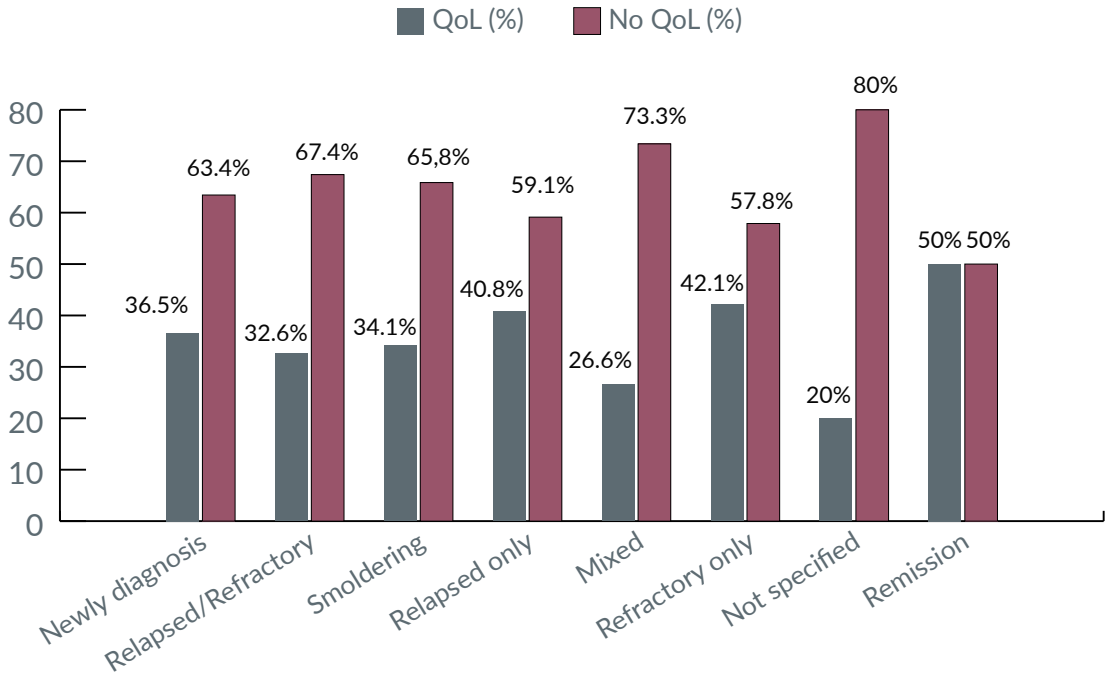
For this research, we referred to the following as population groups:

- **Smoldering myeloma** (or asymptomatic myeloma) is an early form of myeloma that usually progresses to active myeloma, but at a slow rate (Myeloma UK)
- **Relapse** is the term used after someone has responded well to treatment, but the condition has returned later (Myeloma UK)
- **Refractory** disease refers to when myeloma stops responding to treatment (Myeloma UK)
- For this research we referred to a **mixed population** of myeloma patients that were newly diagnosed, relapsed and/or refractory.



Percentage of all registered myeloma trials by population

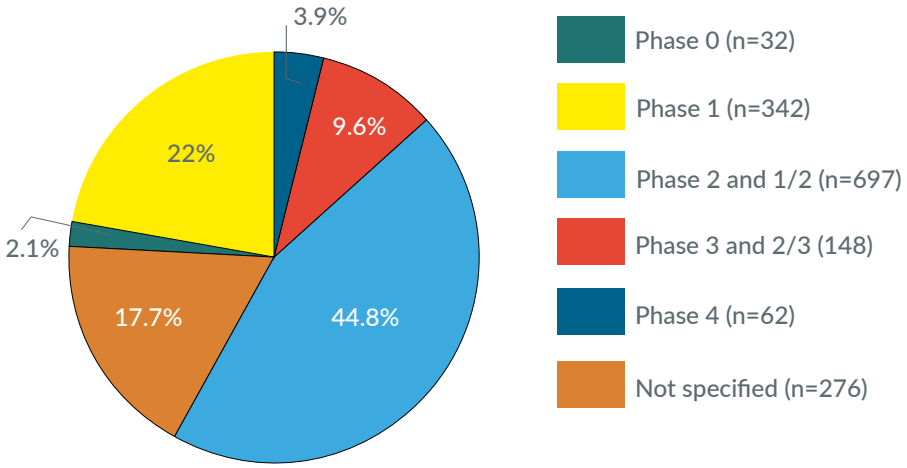
The population of myeloma patients investigated in clinical trials were relapsed/refractory (44%, n=681), newly diagnosed (25%, n=391), a mixed population (18%, n=278) or relapsed only (7%, n=115). Refractory only (2%, n=38) and smoldering myeloma (3%, n=41) patients were studied less often. The gathering of QoL data in all population groups ranged from 27% to 42%. However, both relapsed/refractory and newly diagnosed population groups collected QoL data in roughly one-third of the trials (33% and 37%, respectively).



Percentage of all registered myeloma trials by population which collected QoL data

Phases

Global trials had a substantial proportion of trials in phase 2 and 1/2 (45%, n=697). However, phase 1 trials were more prevalent in global trials (22%, n=342) than in European trials. Only around a tenth of trials were phase 3 and 2/3 (10%, n=149). Almost one-fifth of studies did not explicitly state a phase (17%, n=264), and a small percentage were phase 0 trials (2%, n=32). Phase 3 and 2/3 trials collected the most significant proportion of QoL data (56%, n=83), whereas phase 0 trials collected the least amount of QoL data (9%, n=3). In phase 2 and 1/2 (34%, n=239) and phase 1 trials (33%, n=112), QoL data collection was around one third.



Percentage of all registered myeloma trials by phase

Type of PROM and endpoints

QoL outcomes are usually collected as secondary endpoints, and our analysis confirmed this. We found that around one-third of the trials (N=521, 34%) included QoL as an outcome measure. Among these 521 trials, 186 of them (36%) selected QoL as a primary endpoint, 374 trials (72%) selected QoL as a secondary endpoint and 21 trials (4%) selected QoL as other (exploratory) endpoints. It is important to note that QoL in some trials is an outcome measure in more than one endpoint; that is, different QoL measurements can occur within the same trial to explore more than one type of endpoint.

A total of 38 different PROMs (generic tools, n=21, 55%; cancer-specific, n=9, 24%; myeloma-specific, n=5, 13%; and issue-specific tools, n=3, 8%) were identified. Most trials used a combination of different instrument types.

The most popular choice of instruments used where QoL was a **primary endpoint** were:

- PRO-CTCAE (n=149, 67%),
- EORTC QLQ-C30 (n=19, 9%),
- EORTC QLQ-MY20 (n=13, 6%).

The most popular choice of instruments used where QoL was a **secondary endpoint** were:

- EORTC QLQ-C30 (n=226, 29%),
- PRO-CTCAE (n=212, 27%),

- EORTC QLQ-MY20 (n=104, 14%),
- EQ-5D-3L (n=67, 9%),
- EQ-5D-5L (n=68, 9%).

The most popular choice of instruments used where QoL was **another (exploratory)** endpoint were

- PRO-CTCAE (n=13, 36%),
- EORTC QLQ-C30 (n=6, 17%)
- EORTC QLQ-MY20 (n=4, 11%).

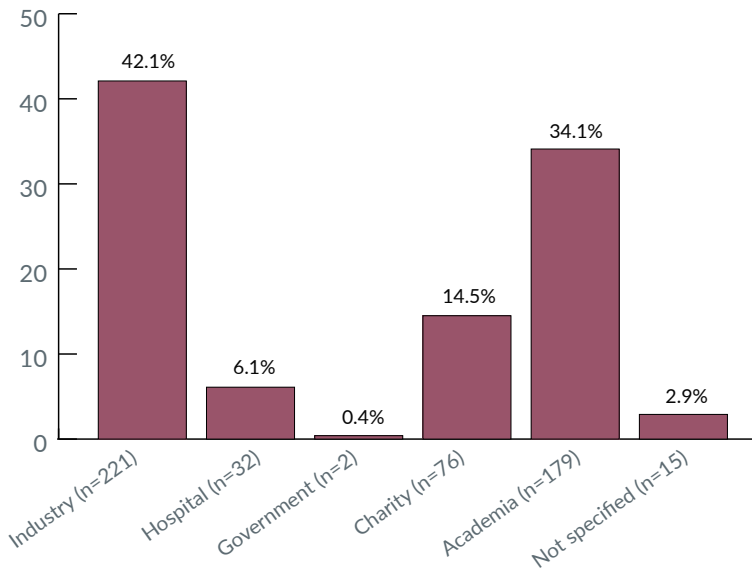
Objectives

In a considerable number of trials (70%, n=1084), the primary objective was to assess treatment regimens, although just under two-fifths provide data on QoL in addition to the primary objective (39%, n=423). Just over half of these trials (n=551, 51%) were in phase 2, phase 3 and phase 4 (phase 2, n=399, 37%; phase 2/3 n=8, 1%; phase 3 n=115, 11%; phase 4, n=29, 3%). The remainder of the trials either did not explicitly declare their objective (23 %, n=357) or were of a mixed character (7%, n=116). Neither of the latter categories gathered much data on QoL; 19% (n= 67) if the objective was not specified, and in mixed, 25.49% (n=30).

6.1.3 Myeloma clinical trials conducted in Europe (n= 525)

Sponsors

A large proportion of the registered trials were sponsored by the pharmaceutical industry (42%, n=221), followed by academic institutes (34%, n=179) and charities (15%, n=76). Hospitals (6%, n=32) and government organisations (0.4%, n=2) funded comparatively few trials in Europe. A similar trend followed with the collection of QoL data among sponsors. For trials sponsored by the pharmaceutical industry, QoL data was collected in 44% (n=98) of them. Collection of QoL data from government-funded projects was 0% (n=0). Charities (39%, n=30), academia (39%, n=69) and hospital (31%, n=10) sponsored trials collected QoL data from fewer than 40% of those trials they sponsored. Data collection from European trials showed an initial upward trend over the scoping period (2011-2021), peaking in 2017, but this trend has generally declined.



Percentage of registered European myeloma trials by sponsor

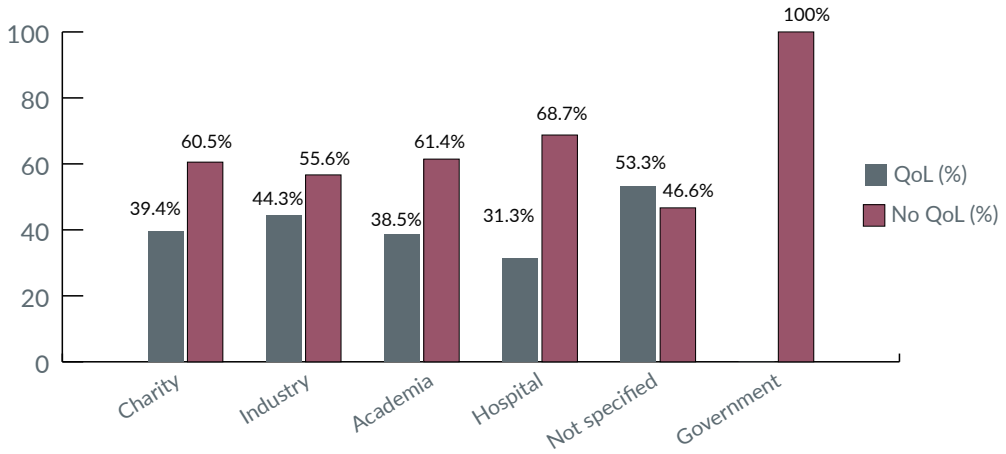
Similar to global trials, the collection of QoL data can be attributed to the stage of the trials conducted by the sponsors. The industry conducted 136 (62%) trials that were in phase 2 and 1/2 (n=88, 40%), phase

3 and 2/3 (n=47, 21%) and phase 4 (n=1, 0.5%). Collection of QoL was only present in phase 2 and 1/2 (n=31, 42%) and phase 3 and 2/3 (n=35, 75%).

Over 63% (n=113) of the trials conducted by academia were in phase 2 and 1/2, (n=83, 46%), phase 3 and 2/3 (n=25, 14%) and phase 4 (n=5, 3%). Of these, collection of QoL data was seen in 60% or less of the trials (phase 2 and 1/2, n=35, 42%; phase 3 and 2/3 n=15, 60%; phase 4 n=2, 40%).

Charity institutes conducted 62 trials (82%) in phase 2 and 1/2 (n=44, 58%), phase 3 and 2/3 (n=17, 22%) and phase 4 (n=1, 1%). Of these, only 23 trials (32%) either in phase 2 and 1/2, (n=15, 34%) or phase 3 and 2/3, (n=8, 47%) collected QoL data.

Hospitals undertook 19 trials (59%) that were in phase 2 and 1/2 (n=12, 38%), phase 3 and 2/3 (n=5, 16%) and phase 4 (n=2, 6%). Of these, only five trials (26%) that were either in phase 2 and 1/2 (n=4, 33%) or phase 3 and 2/3 (n=1, 20%) collected QoL data. Government institutes conducted onephase 2 and 1/2 trial (50%), and one phase 3 and 2/3 trial (50%). Neither of these phase trials collected QoL data.



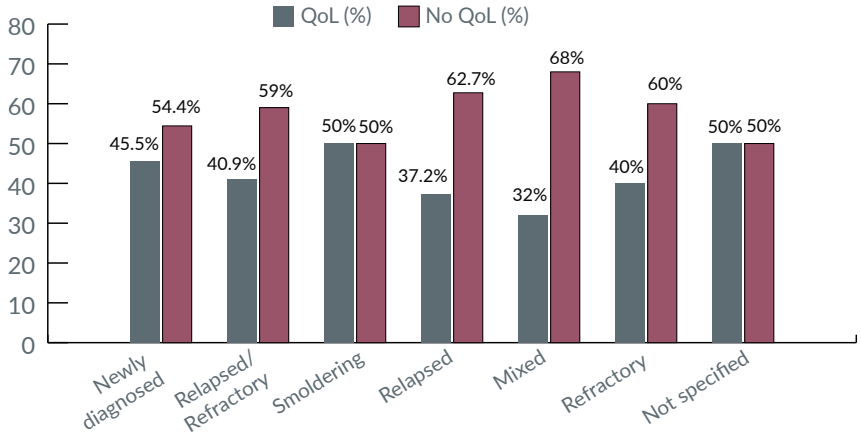
Percentage of registered European myeloma trials by sponsor which collected QoL data

Study type

A vast majority (81%, n=427) of the trials were interventional in nature, and 43% (n=185) of these captured QoL data. There were far fewer observational studies (19%, n=98) with less than a third (30%, n=30) collecting QoL data.

Population

Most myeloma clinical trials were run in relapsed/refractory patients (42%, n=222) followed by newly diagnosed patients (30%, n=158), a mixed population (14%, n=75) and relapsed individuals (10%, n=51). A small percentage of trials enrolled participants with smoldering myeloma (2%, n=12). Overall, QoL data was collected from all population groups less than half of the time, except smoldering myeloma, where QoL data was collected from 50% (n=6) of the trials. The other population group collection rate ranged between 32% (n=24) and 46% (n=72), with the highest percentage seen in trials that enrolled newly diagnosed patients and the lowest percentage seen in the mixed population.



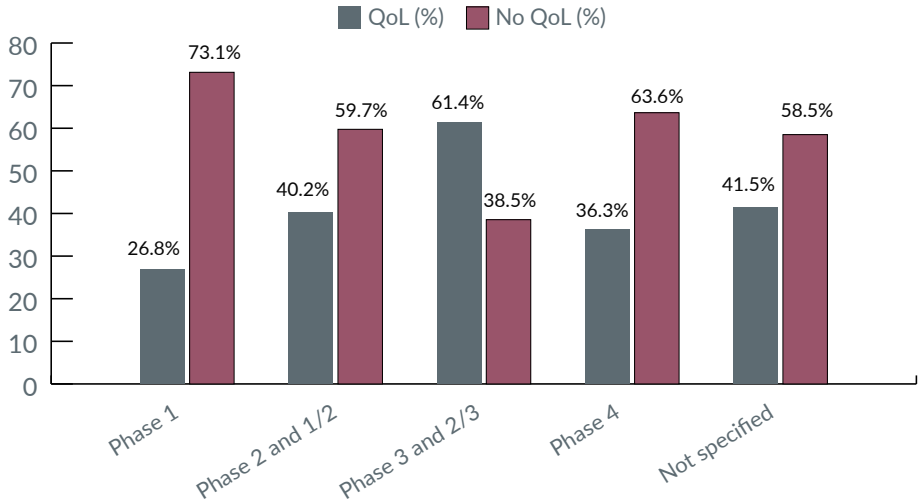
Percentage of registered European myeloma trials by population which collected QoL data

Objectives

In a considerable number of trials (71%, n=373), the objective was to assess treatment regimens, although less than half of them provided data on QoL (45%, n=166). Almost two-thirds of these trials (n=230, 62%) were in phase 2, phase 3 and phase 4 (phase 2, n=141, 38%; phase 2/3 n=5, 1%; phase 3 n=78, 21%; and phase 4, n=6, 2%). The remainder of the trials either did not explicitly declare their objective (19%, n=100) or were of a mixed character (10%, n=52). Neither of the former categories gathered much data on QoL.

Phases

As with the global trials, fewer than half of the European trials evaluated (45%, n=236) were phase 2 and 1/2, with slightly under a fifth (18%, n=96) being phase 3 and 2/3 trials. Phase 1 trials (13%, n=67) were also analysed, as were phase 4 studies with a small sample size (2%, n=11). One-fifth of trials were observational in nature and the phase was not assigned. Phase 3 and 2/3 trials collected the most significant proportion of QoL data in the trials (62%, n=59), whereas phase 1 trials collected the least QoL data (26.87%, n=18). Phase 2 and 1/2 trials (40.25%, n=95), and phase 4 trials (36%, n=4), collected over a third of the QoL data. The trials that did not specify the phase also collected a third of the QoL data (33%, n=36). Overall, the average collection of QoL data across all the phases was 41%.



Percentage of registered European myeloma trials by phase which collected QoL data

Type of PROM and endpoints

QoL outcomes are usually collected as secondary endpoints and this was confirmed by our study. Our findings showed that over two-fifths of the trials (n= 215, 41%) included QoL as an outcome measure. Among these 215 trials, 43 (20%) designated QoL as a primary endpoint, 184 trials (86%) as a secondary endpoint and five (2%) defined QoL as other (exploratory) endpoints. It is important to note that QoL in some trials is an outcome measure in more than one endpoint.

Altogether, 25 different PROMs (generic tools, n=15, 60%; cancer-specific, n=5, 20%; myeloma-specific, n=4, 16%; issue-specific tools, n=1, 4%) were identified in all three endpoints. It is important to note that the majority of trials included a variety of PROMs. The PROMs were utilised 552 times in total, most frequently with secondary endpoints (n=474, 86%), and least frequently with other endpoints (n=12, 2%). In trials using QoL as a primary endpoint, these tools are used 66 times (12%).

The most popular choice of instruments used in the primary endpoint trials were PRO-CTCAE (n=25, 38%), followed by EORTC QLQ-C30 (n=13, 20%) and EORTC QLQ-MY20 (n=9, 14%). The most popular choice of PROMs used in the secondary endpoint trials were EORTC QLQ-C30 (n=159, 34%) and PRO-CTCAE (n=99, 21%), followed by EORTC QLQ-MY20 (n=75, 16%), EQ-5D-3L (n=50, 11%) and EQ-5D-5L (n=31, 7%). The most popular choice of PROMs used in the other endpoint trials were EORTC QLQ-C30 (n=2, 17%) EORTC QLQ-MY20 (n=2, 17%) and HADS (n=2, 17%).

6.2 COMPREHENSIVE LITERATURE OVERVIEW OF QOL PUBLICATIONS IN MYELOMA

6.2.1 Identification of publications

The literature search identified 5,240 articles from the three databases (Ovid Medline, Embase and Web of Science). Details of the articles identified are presented in figure 1 (PRISMA chart) presented in the annex of this report. Prior to the screening, 1,564 duplicate articles were removed, and nine papers were removed for miscellaneous reasons. The remaining 3,667 articles were screened and 3,082 were discarded because the articles did not mention a QoL measure, or any hematologic cancer (n=585). A further 31 articles were removed from the screened articles because they could not be retrieved. In addition, 554 papers were assessed further for eligibility, and 288 articles were excluded (duplicates n=77, no QoL measures mentioned n=63, no mention of myeloma n=120, others n=18). Therefore, 266 articles were included in the final analysis as these articles focused on myeloma and measurement of QoL.

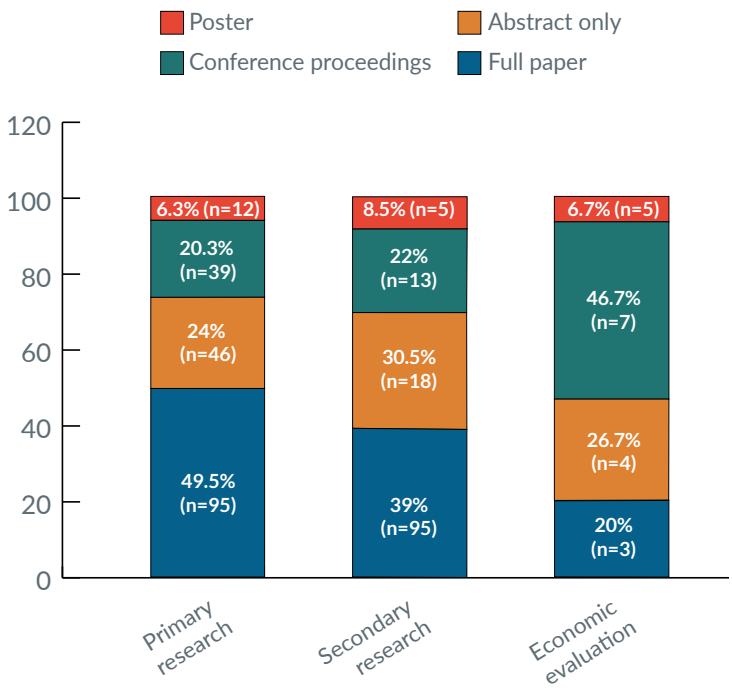
6.2.2 Overview

Of the 266 articles in the final analysis, 192 were primary research (PR) articles (72%), 59 were secondary research (SR) articles (22%), and 15 articles were economic evaluation (EE) studies (6%). Overall, the three different types of research (PR, SR, and EE) showed a rising trend in publication per year from 2011-2021, peaking in 2021 for PR and SR and 2018 for EE.

Just under half (50%) of the PR articles were full papers, and the rest of the literature identified were either abstracts (24%), conference proceedings (20%) or poster presentations (6%). Just under two-fifths of the SR articles analysed were full papers (39%), and over three-fifths were either abstracts (31%), conference proceedings (22%) or poster presentations (9%). Only a fifth of the EE articles were presented

as full papers (20%), and the majority were either conference proceedings (47%), abstracts (27%) or poster presentations (7%).

The myeloma population that the different articles focused on varied. The majority of the PR articles enrolled a mixed myeloma population (n=82, 43%), that is, newly diagnosed, relapsed and relapsed/refractory. In contrast, SR had almost an equal proportion of articles that focused on newly diagnosed (19%, n=11), relapsed/refractory (17%, n=10) and mixed population (19%, n=11). The remaining SR articles did not state specifically the population of myeloma included in the article (45%, n=27). More than half of the EE articles were based on relapsed/refractory (53%, n=8) and over a quarter focused on the newly diagnosed myeloma population (27%, N=4).



Percentage availability of myeloma QoL publications

QoL and PROM data

QoL measurement used as an endpoint in the literature review varied between article types. QoL was a primary endpoint in 54% (n=103) of the PR articles, whereas secondary and exploratory endpoints were 43% (n=83) and 3% (n=5) respectively. None of the EE articles identified specifically whether the QoL measure was a primary, secondary, or exploratory endpoint.

The literature search identified 93 different PROMs. Just under two-thirds of these instruments were generic (64%, n=59), approximately one-sixth were cancer-specific (16%, n=15), over one-tenth were issue-specific (13%, n=12) and the smallest proportion were myeloma-specific tools (8%, n=7). The most commonly used instruments in all three types of research were generic tools only (24%, n=64), followed by a combination of cancer- and issue-specific (18.4%, n=49), generic, cancer-, myeloma- and issue-specific (17%, n=46), and generic, cancer- and issue-specific (15%, n=40). Cancer- and myeloma-specific (12%, n=32) and myeloma-specific tools only (5%, n=14) were used less frequently.

THE QoL/PRO INSTRUMENTS IDENTIFIED

93 QoL/PRO instruments were identified. A full list of all the tools identified in this research is presented in a separate document.

Type of QoL Instrument	Example	Count
Generic	EQ-5D, SF-36, HAD, VAS	59
Cancer Specific	EORTC QLQ-30, FACT-GOG-Ntx	15
*Issue Specific	DN-4, MoCA, TUGT	12
Myeloma Specific	EORTC QLQ-MY20, FACT-MM, MyPOS	7

*Instruments that are designed to measure particular aspects of QoL, such as neuropathic cognitive assessment.

6.2.3 Primary research articles

Overview

A total of 192 articles were identified as PR and of these 52% were interventional trials (n=100), 39% were observational (n=75), 8% were follow-up trials (n=16) and 1% were reporting on registry data (n=1). Over two-thirds of the trials were non-randomised (70%, n=135) and almost one-third was randomised trials (30%, n=57).

QoL and PROM data

A considerable number of PR articles reported that QoL was measured at baseline (n=122), with the remainder either not mentioning if QoL was measured at baseline (n=17) or QoL assessment at baseline was not applicable, as these articles were cross-sectional studies (n=52). Excluding baseline QoL measures, 63 trials measured QoL four times or more after baseline, 29 trials measured 2-3 times after baseline, 32 trials measured one time only and 52 trials did not need additional measurements (cross-sectional studies).

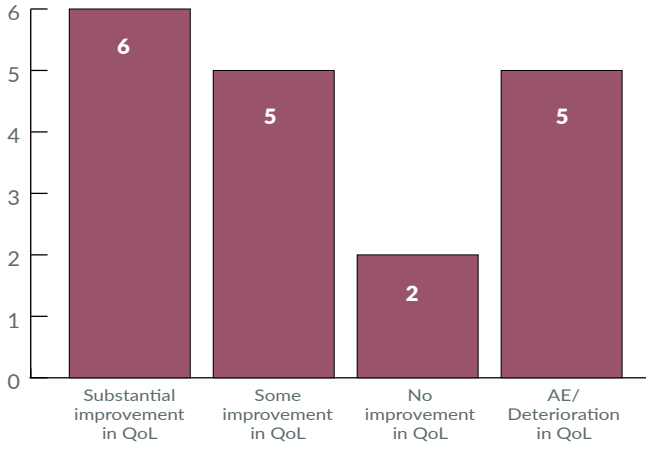
The following QoL outcomes were reported in myeloma PR articles: 122 articles measured and quantified the impact on QoL, 26 articles were ongoing trials with unpublished data, 18 articles were epidemiology studies, 16 articles assessed the validity or developed a QoL instrument, eight articles did not mention the impact on QoL, and two articles guided healthcare professionals on myeloma and the importance of QoL. In the 122 articles that measured and quantified the effect on QoL, 39% of the interventions substantially improved QoL outcomes (n=47), 30% of the intervention showed some improvement in QoL (n=36), 16% of the intervention had no impact on the QoL (n=20) and 16% of the intervention either caused a deterioration in QoL or an adverse event.

6.2.4 Secondary research articles

A total of 59 articles were identified as SR and of these, 36% were literature review (n=21), 32% were systematic reviews (n=19), 27% were miscellaneous articles (n=16) and 5% were case studies (n=3).

Impact of QoL

The following QoL outcomes were reported in myeloma SR: 18 articles measured and quantified the impact on QoL, 18 were a review of secondary research in epidemiology studies, 14 articles were a review of PROMs and nine articles were miscellaneous (guidance for healthcare professionals on myeloma and QoL, mapping study, systematic review on QoL data and review of caregivers). In the 18 articles that measured and quantified the impact on QoL, 33% of the evaluations found that the intervention substantially improved QoL outcomes (n=6), 28%



Reporting QoL outcomes in myeloma secondary research (QoL measured and quantified)

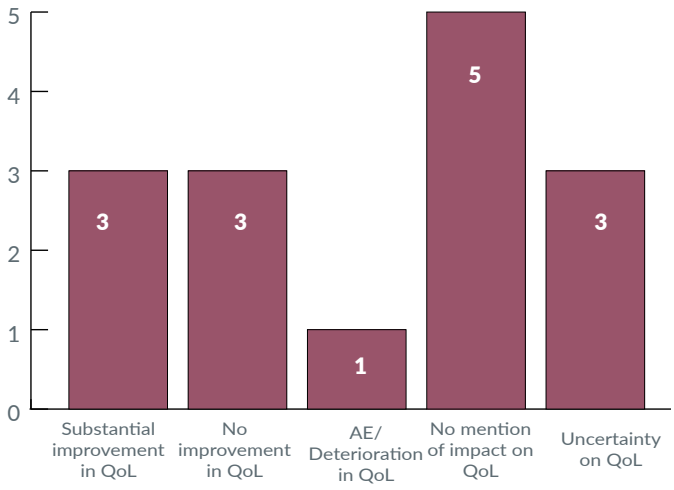
of the review found that the intervention showed some improvement in QoL (n=5), 11% found that the intervention had no impact on the QoL (n=2) and 28% of the review found that the intervention either caused a deterioration in QoL or an adverse event (n=5).

6.2.5 Economic evaluation articles

Impact on QoL

The following QoL outcomes were reported in myeloma economic evaluation: 10 articles measured and quantified the impact on QoL, and five articles did not address the effect of the intervention on participants' QoL. In the 10 articles that measured and quantified the impact on QoL, 20% of the articles found that the intervention substantially improved QoL outcomes (n=3), 20% found that the intervention had no impact on QoL outcomes (n=3) and 7% found that the intervention caused a deterioration in QoL (n=1). 20% of the articles were inconclusive about the intervention effect on the QoL outcome (n=3).

Almost three-quarters (73%, n=11) of the EE articles regarded the treatments as cost-effective, 7% as not cost-effective (n=1) and exactly one fifth did not disclose the intervention's cost-effectiveness.



Reporting QoL outcomes in myeloma economic evaluation research

6.2.6 Articles identified with registered clinical trials

Overview

There were 75 articles identified as being associated with 64 clinical trials. Two-thirds of the articles (67%, N=50) were linked to 43 clinical trials that met the inclusion criteria of this research (within the scoping period of 2011-2021 and MM-only trials). Whereas one-third of the articles (33%, N=25) were associated with 21 clinical trials that were conducted either outside the scoping period of 2011-2021 (N=20) or were not pure myeloma trials (N=5).

6.2.7 Articles identified with clinical trials within the inclusion criteria

Phase

More than half of the trials were phase 3 trials (56%, n=24), almost a third were phase 2 trials (30%, n=13), and a small proportion were miscellaneous in nature (14%, n=6).

QoL as an endpoint

The majority of these trials measured QoL as a secondary endpoint (77%, N=33), followed by the primary endpoint (16%, N=7) and the exploratory endpoint (5%, N=2), while one did not report QoL as the trial was terminated (2%, N=1).

Article type and publication period

In total, 38 trials were associated with one publication within the inclusion criteria, three trials (NCT03180736, NCT03308474, NCT03548207) were associated with two articles each and two trials (NCT02990338, NCT03173092) were associated with three publications each within the inclusion criteria. Almost half of the articles were published as full papers (44%, N=22), less than a third were in abstract form (32%, N=16) and the remainder were either in the form of conference proceeding (14%, N=7) or poster presentation (10%, N=5).

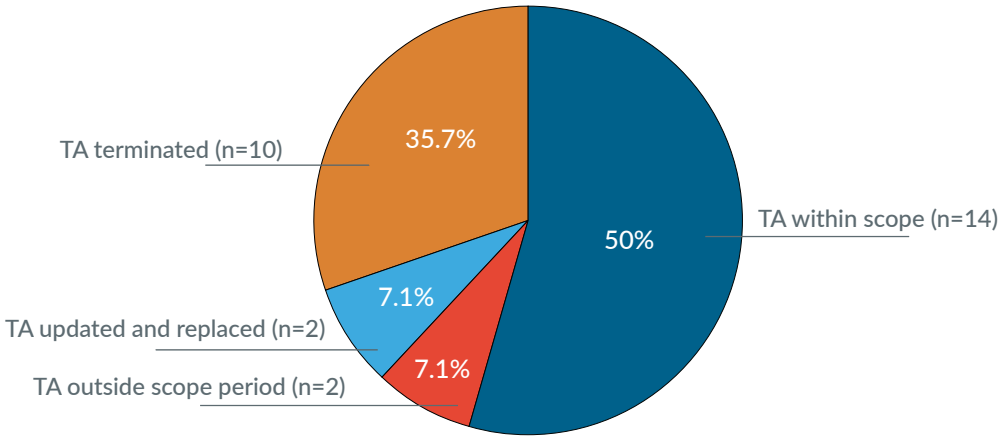
An overwhelming number of articles reported on interim results and were published before the clinical trial ended (86%, N=44). Most of the articles that reported on interim results were either in an abstract form (32%, N=16) or full paper (30%, N=15). It must be noted that one article was published in full, but QoL data was not reported as the trial (NCT02579863) terminated early; a detailed explanation of this trial is present in section 6.2.3 of this report. There was a substantial number of conference proceedings (14%, N=7) and poster presentations (10%, N=5) published before the trial was complete.

It is important to note that of the 43 clinical trials related to the 50 articles, 29 of these trials (67%) are still ongoing and 36 articles (82%) are an outcome of these trials. One trial (3%) did not state its end date, and only 13 trials were complete, producing seven interim results articles and six full result articles. These six full result articles were generated from six clinical trials; one published its findings within a month of the trials ending (NTR6297), one trial (NCT03170882) reported the results within two months, one trial (NCT02046070) reported the results within five months and three trials (NCT02573935, NCT02336815, ISRCTN38480455) published their findings between 22 and 29 months after trial completion.

6.3 MYELOMA NICE APPRAISAL FOR QOL DATA

We identified 28 NICE TAs in myeloma. A total of 14 appraisals were removed: two TAs were outside the scoping period, two TAs were updated and replaced, and 10 appraisals were terminated due to lack of evidence submitted by the company.

As a result, we reviewed 14 appraisals: one was an MTA and 13 were STAs. Between 2011 and 2016, one appraisal per year was published by NICE, whereas 2019 and 2020 saw two appraisals each year, and 2018 and 2021 had three appraisals each year.



NICE technical appraisal (TAs) in myeloma (2011-2021). Percentages based on 28TAs

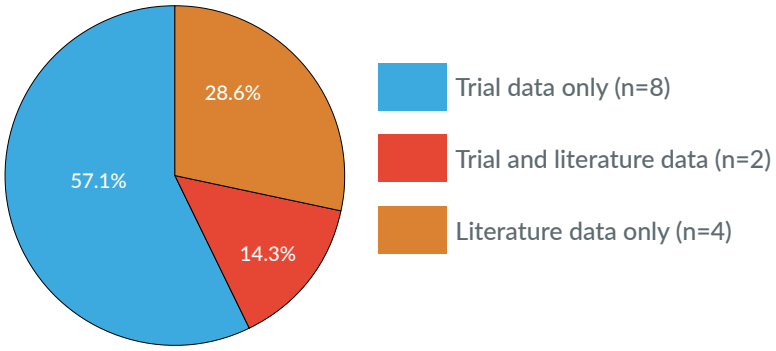
6.3.1 Clinical trials data

The 14 TAs analysed data from 26 clinical trials, of which 25 were phase 3, and one was phase 1/2. The AG/ERG considered the quality of 14 of the trials to be good, five as moderate, six as poor and one study was not assessed for its quality. The number of participants enrolled in these trials ranged from 104-4420, with a mean age range of 55.6-80 years. Over 90% (n=24) of the trials were conducted in Europe; 12 studies were conducted exclusively in Europe, 10 in more than three continents, including European countries, two in Europe and North America, and two in North America only.

6.3.2 Quality of life data

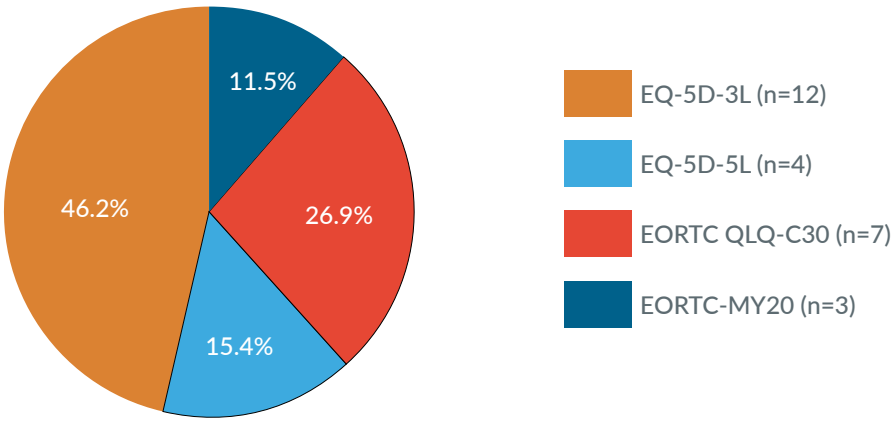
Source of the data

Of the 14 TAs analysed, 10 used QoL data collected in the main clinical trial(s) and four used data collected in dedicated QoL studies. A dedicated study is research that is conducted only for the purpose of advancing knowledge in a particular area of interest. For instance, a clinical trial may examine several outcomes, resulting in multiple publications, with some of these focusing exclusively on QoL data.



Source of the QoL data in myeloma NICE TAs

Almost all TAs that collected QoL data in the trials (8/10) used this evidence to calculate the utility values and two TAs used data from the clinical trial and a dedicated study (TA380, TA763). Four TAs (TA 311, TA 510, TA586, TA680) used dedicated studies [van Agthoven et al. (2004), Acaster et al. (2013) and Palumbo et al. (2013)] to calculate utility values. Almost two-thirds of the TAs had submitted QoL evidence that was of acceptable quality (9/14), and about one-third was of poor quality (5/14). According to the NICE Committees, six TAs submitted QoL evidence that caused uncertainty in the decision-making process.



QoL instruments identifed in myeloma NICE TAs. Percentages based on 14 TAs

Instruments

The most common PROM used was EQ-5D-3L (n=12), followed by EORTC QLQ-C30 (n=7), EQ-5D-5L (n= 4) and EORTC -MY20 (n=3). To calculate utility values, most of the QoL data (8/14) was mapped from EORTC QLQ-C30 and EORTC-MY20 to EQ-5D.

Endpoints

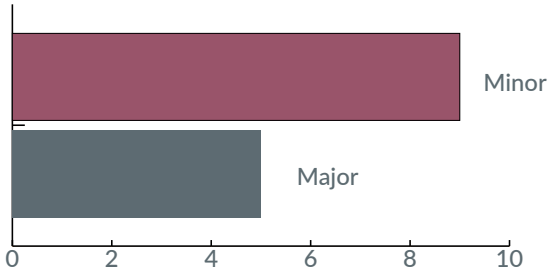
Out of the 26 clinical trials featured in the TAs, only nine clinical trials (35%) had collected QoL data as their objectives. These were all secondary endpoints.

Issues with the QoL data

The Committees found the QoL data presented in nine TAs to be adequate, and while minor issues were raised in some (5/9) of the TAs, the evidence submitted was deemed appropriate for the decision-making process. Minor issues centred around discrepancies in utility estimations but not such that the Committee could not incorporate these or utilities from another mentioned trial for the decision-making process (TA505, TA510, TA573). In one TA (TA658), the Committee stated that it was unclear to 'what extent increased hope may be captured within the anxiety and depression dimension of the EQ-

5D', and in TA763, the Committee indicated that the company did not use QoL tools that were 'specific to myeloma or its symptoms'.

Finally, the QoL data presented in the other five TAs (TA228, T586, A587, TA680, TA695) raised significant issues and complicated the decision-making process. Most of the problems stemmed from limited, missing, or inadequate QoL evidence that resulted in uncertainty in the decision-making process. The AG or the ERG conducted a sensitivity analysis in all these TAs to resolve the uncertainty. This meant that the Committee was able to recommend all these pharmaceutical agents for use in the NHS because they were all considered to be cost-effective. Hence, patients should have access to these medications within 90 days of recommendation.



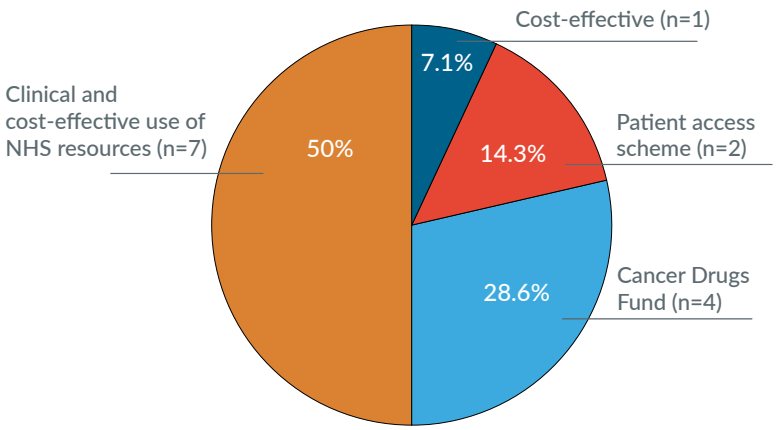
Issue with the QoL data in NICE TAs. Total number of NICE TAs=14

Overall outcomes – decisions

NICE gave 7 TAs (TA228, TA311, TA586, TA587, TA680, TA695, TA763) a positive recommendation for reimbursement in the NHS because they were considered a clinically and economically appropriate use of NHS resources. Furthermore, two TAs (TA586, TA587) were considered to offer treatment pathways that would reduce unmet needs in newly diagnosed patients and offer an alternative in treatment options for people who cannot take thalidomide. Also, TA680 was recommended because there was no maintenance treatment for newly diagnosed myeloma patients, thereby increasing their survival chances and delaying the reoccurrence of cancer. Lastly, clinical evidence from TA695 showed that even though the length of the remission period was uncertain due to immature data, the period was longer than the current practice.

The Committee considered one TA (TA658) cost-effective as a second-line treatment, but as a third-line treatment, it was not considered to be cost-effective or an appropriate use of NHS resources. TA380 and TA427 were recommended within its marketing authorisation as the manufacturer has agreed on a PPRS with the Department of Health (DoH). The level of the discount is commercial-in-confidence; that is, the agreed discount is known only to the DoH and the manufacturer and this information is not revealed to any third party. Three TAs (TA505, TA510, TA573) were not considered a cost-effective use of NHS resources and were recommended for use only within the Cancer Drugs Fund. The Committee considered the evidence submitted in TA658 for the clinical data to be "not suitable for decision-making because of limitations". It therefore approved the regimen for use in the Cancer Drugs Fund.

The Committee's primary concern in making its decision was the quality of evidence submitted: if deemed insufficient, limited, or absent, the Committee recommended that the pharmaceutical industry produce more mature and robust data for that treatment regime. This was particularly evident in TA228, TA311, TA427, TA505, TA510, TA573, TA586 and TA658.



Why was the pharmaceutical product approved by nice? (Percentages based on 14 TAs)

7. DISCUSSION

In both clinical research and routine care, PROMs give information on QoL, including the physical, functional and psychological aspects of disease and therapy from the patients' perspective. PROMs not only provide individualised therapy, auditing/benchmarking and symptom monitoring, but they facilitate health care decisions, regulatory decisions, health care policy and cost-effectiveness analysis (Black, 2013; Bull and Callander, 2022).

The following issues emerged from our evaluation of QoL reporting in clinical trials and literature reviews of myeloma patients. We found that PROMs were either not part of the clinical trial protocol, or QoL outcomes were poorly reported. Our findings are consistent with a 2019 review of 160 cancer trials by Kyte and colleagues, who found that 61 (38%) of the trials that enrolled approximately 50,000 patients failed to report on their PRO data. Furthermore, in the majority of the articles that did present PRO results, the reporting was often inadequate because most publications are not available in full-text format.

A lack of reporting may compromise QoL and PRO-specific trial conduct, diminish data quality and endanger clinical applicability of trial results. As patients, clinicians and researchers may not have access to vital information, this could significantly influence treatment decision-making and outcomes. This wastes valuable healthcare and research resources, and may hinder the proper implementation of QoL findings in trials. In addition, it devalues the significant contribution of trial participants who devote time and effort to supplying PROMs information with the expectation that the data will be used for the benefit of future patients.

QoL measurement, adoption and patient benefit have been hampered by several hurdles, with PRO research design, implementation, reporting and interpretation posing the greatest obstacles (Calvert et al., 2019). PRO data collection is scattered, with little coordination across research and clinical care teams. Although research demonstrates that clinicians recognise that PRO data enhances clinical treatment and is valuable, doctors also feel PROs are subjective and hence skewed or insignificant when compared to laboratory results (Black, 2013; Calvert et al., 2019). Frequently, there is an absence of a standardised evaluation method, and patients may be required to complete various questionnaires with overlapping questions that are cumbersome and complicated. Underreporting, or not reporting all PROs data, restricts their impact on patient treatment and is unethical (Calvert et al., 2019; Bull and Callander, 2022).

Our research of myeloma clinical trials and published literature revealed that the QoL data collection remained inadequate from 2011 to 2021. Much more work is needed to enhance the existing practices significantly. To guarantee QoL data collection, accurate and timely reporting, and the commissioning of appropriate methodological work to standardise the set of instruments for QoL in myeloma, a coordinated, collaborative effort among myeloma organisations, multidisciplinary consortiums such as Setting International Standards of Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical trials (SISAQOL) and SISAQOL-IMI (SISAQOL- Innovative Medicines Initiative) and research funders is required. These measures will ensure that research efforts are comparable and accessible, as well as permit the prospective sharing of data.

8. LIMITATIONS

There were several limitations to our work:

1. We analysed trials registered in 17 databases (https://www.who.int/clinical-trials-registry-platform/network/data-providers) which may have resulted in the omission of trials that were not registered in these databases.
2. We did not specifically identify trials that had violated EUCTR reporting guidelines or FDAAA reporting legal requirements.
3. We identified articles that stemmed from clinical trials that took place outside the scoping period, but the article's publication date was not. As a result, practices that are no longer current and generalisable may have been captured.
4. The bulk (n=149, 56%) of the articles identified were abstracts, conference proceedings or poster presentations. Therefore, extraction of QoL data was not always straightforward because of insufficient or unclear reporting of methods and results.
5. While the sample size of NICE TA was complete, it was small and may not accurately reflect NICE's assessment methodology.

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10. ANNEXES

10.1 PROMS COMMONLY USED IN MYELOMA STUDIES

Click here to read this annex.

- EORTC-QLQ-C30
- EORTC QLQ-MY24 and QLQ-MY20
- FACT-G
- FACT-GOG – Ntx
- MyPOS
- EQ-5D (EQ-5D-3L) and EQ-5D-5L
- Mapping
- Figure 1: QoL Myeloma Literature Search PRISMA flow diagram
- Table 1: Summary of Instruments identified in Literature research
- Table 2: Summary of QoL Data submitted in MM NICE TA
- Table 3: Summary of Clinical Trials identified in MM NICE TAs

10.2 HEALTH ON TRIAL METHODOLOGY FOR DATA COLLECTION AND ARTICLE SEARCH STRATEGY

Click here to read this annex.

- Search strategy
- Ovid
- Web of science

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