Humanistic burden in relapsed or refractory follicular lymphoma: a systematic literature review

Carol Forbes, PhD,[1] Iwona Pustulka, MSc,[2] Solange Nunez-Gonzalez, MD, MSc,[3] Jinender Kumar, MS[4]

[1]Evidera PPD, London, UK; [2]Evidera PPD, Warsaw, Poland; [3]Evidera PPD, Waltham, MA, USA; [4]Bristol Myers Squibb, Princeton, NJ, USA

Introduction

- Relapsed or refractory (R/R) follicular lymphoma (FL) has a significant impact on patients' health-related quality of life (HRQOL) such as worry about future health, fatigue, and lethargy[1]
- The objective of this project was to conduct a systematic literature review (SLR) to gather evidence on HRQOL, patient-reported outcomes (PROs), and utility/disutility values for patients with R/R FL, including those in third-line and later (3L+) settings

Methods

- An SLR was conducted and findings reported in accordance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting requirements
- Search strategies were developed to identify observational studies, clinical trials, and economic evaluations in English and reporting on HRQOL, PROs, and utility/disutility values in patients with R/R FL
- Literature searches were conducted in September 2022 via Ovid SP in the following databases: Embase, MEDLINE and MEDLINE In-Process, Cochrane Central Register of Controlled Trials (CENTRAL), PsycInfo, Health Economics Research Centre Mapping Database, and Centers for Disease Control and Prevention HRQOL publication
- Grey literature searches were performed across several health technology assessment (HTA) websites and in conference proceedings published from 2020—2022. Additionally, the reference list of a published SLR in marginal zone lymphoma and FL regardless of therapy line was screened for relevant studies[2]

Table 1. PICOS selection criteria

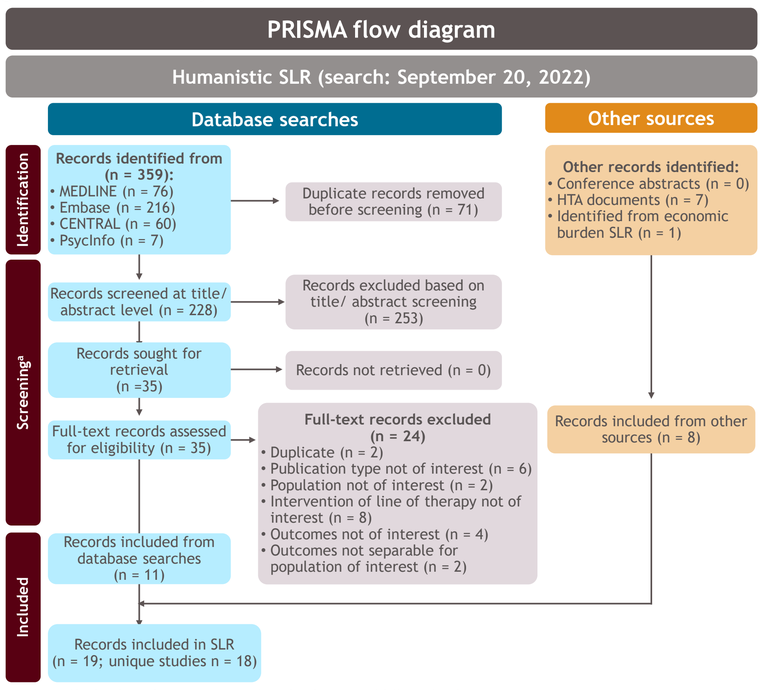
Criteria	Inclusion criteria
Population	• Adults (≥ 18 years) diagnosed with R/R FL • Where studies include mixed populations of patients, separate data must be available for patients with FL or ≥ 80% of included patients should have FL
Interventions	• Any interventions for treatment of R/R FL
Comparators	• Any comparator or no comparator
Outcomes	• HRQOL/PRO outcomes for patients, family, and/or caregivers assessed using any tool (eg, EQ-5D, EQ-5D VAS, EORTC QLQ-C30, EORTC QLQ-NHL-LG20, EORTC QLQ-NHL-HG29, SF-36, SF-12, FACT-Lym, and FACT-G) • Utility and disutility outcomes were assessed using direct (ie, standard gamble, time trade-off VAS) and indirect (ie, EQ-5D index score, SF-6D, HUI2, HUI3) methods
Study design	• Observational studies (prospective or retrospective, including surveys and questionnaires, cross-sectional studies) • Economic models (utility and disutility values only)
Limits	• Limit to English[a]

[a]Articles in languages other than English were not included in the review but they have been flagged.
EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Items; EORTC QLQ-NHL-HG29, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Non-Hodgkin Lymphoma-High Grade 29 Items; EORTC QLQ-NHL-LG20, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Non-Hodgkin Lymphoma-Low Grade 20 Items; FACT-G, Functional Assessment of Cancer Therapy - General; FACT-Lym, Functional Assessment of Cancer Therapy - Lymphoma; HUI2, Health Utility Index 2; HUI3, Health Utility Index 3; PICOS, Population, Intervention, Comparison, Outcomes, and Study design; SF-6D, 6-Dimension Short Form Health Survey; SF-12, 12-Item Short Form Health Survey; SF-36, 36-Item Short Form Health Survey.

- Predetermined PICOS selection criteria are shown in **Table 1**
- Data were extracted from the included studies by a single reviewer and validated by a second independent reviewer. The quality of included randomized clinical trials (RCT) was assessed using the Cochrane Risk of Bias Assessment Tool by 1 reviewer and validated by a senior reviewer

Results

Figure 1. PRISMA study flow



[a]Performed by 2 independent reviewers at the title/abstract and full-text levels.

Table 2. Study characteristics

Author and year (country)	Study type (LOT)	Outcomes reported (tool used)
Guzauskas 2018 (US)[7]	Economic model (2L)	Utility (EQ-5D)
Blommestein 2014 (the Netherlands)[8]	Economic model (2L)	Utility (NR)
Tang 2022 (US)[9]	Economic model (3L)	Utility (EQ-5D)
Vijenthira 2021 (Canada)[10]	Economic model (2L+)	Utility (NR)
Hayslip 2008 (US)[11]	Economic model (2L+)	Utility (NR)
Kasteng 2008 (Sweden)[12]	Economic model (3L+)	Utility (EQ-5D)
CADTH idelalisib 2016 (Canada)[4]	HTA report (3L+)	HRQOL, utility (FACT-Lym)
Pettengell 2008 (UK)[5]	Observational study (R/R)	HRQOL (FACT-Lym, WPAI)
Cheson 2017 (multinational)[3]	RCT (R/R)	HRQOL (FACT-Lym)
Fowler 2021 (multinational)[6]	Single-arm study (3L+)	HRQOL (FACT-G, FACT-Lym, SF-36)
Haukaas 2018 (Norway)[13]	Economic model (R/R)	Utility (EQ-5D)
Soini 2011 (Finland)[14]	Economic model (R/R)	Utility, disutility (EQ-5D)
Deconinck 2010 (France)[15]	Economic model (R/R)	Utility (EQ-5D)
TA627 lenalidomide + rituximab 2020 (UK)[16]	HTA report (R/R)	Utility, disutility (EQ-5D)
TA629 obinutuzumab + bendamustine 2020 (UK)[17]	HTA report (R/R)	Utility (NR)
SMC No. (1219/17) obinutuzumab + bendamustine 2017 (Scotland)[18]	HTA report (R/R)	Utility (EQ-5D)
SMC2281 lenalidomide + rituximab 2020 (Scotland)[19]	HTA report (R/R)	Utility (EQ-5D)
PBAC obinutuzumab + bendamustine 2016 (Australia)[20]	HTA report (R/R)	Utility (EQ-5D)

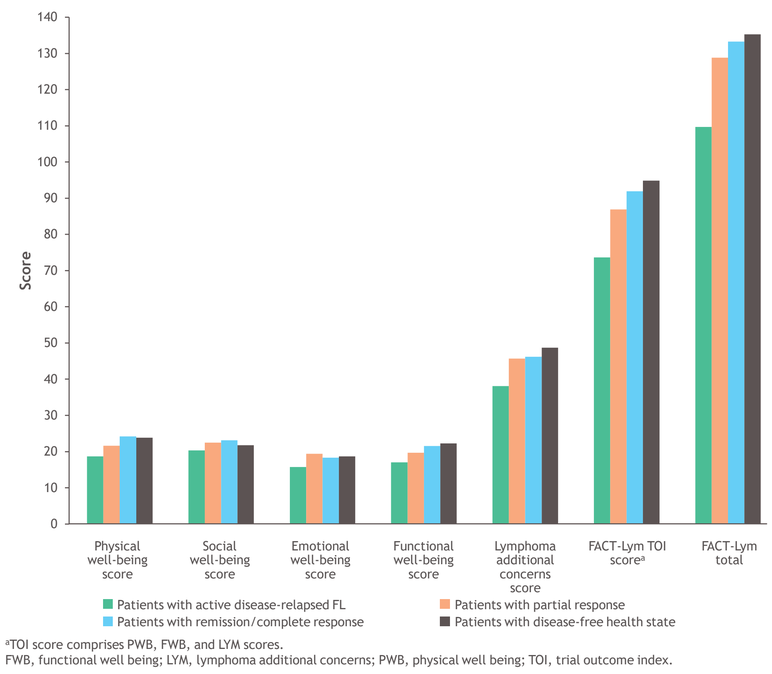
2L, second line; 2L+, second line or later; 3L, third line; CADTH, Canada's Drug and Health Technology Agency; LOT, line of therapy; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; SMC, Scottish Medicines Consortium; TA, technology appraisal; US, United States.

- Of 359 records identified, 19 publications representing 18 unique studies were included in the SLR; of those, 9 were economic models, 7 were HTA reports, 2 were clinical trials, and 1 was an observational study (**Figure 1, Table 2**)
- Four publications (2 in the R/R population and 2 in the 3L+ setting) reported on HRQOL/PROs and 15 publications (12 in the R/R population and 3 in the 3L+ setting) reported on utility/disutility values
- The quality of the single RCT[3] was assessed using the Cochrane Risk of Bias Assessment Tool, and the lack of blinding suggested a potential risk of performance and measurement bias

HRQOL/PRO

- In all 4 HRQOL/PRO publications, the primary instrument used was the FACT-Lym, with 1 study each using SF-36 and Work Productivity and Activity Impairment (WPAI)[3–6]
  - All 4 studies suggested that treatment responses were associated with significant improvements in HRQOL

Figure 2. FACT-Lym scores by response to treatment[5]



[a]TOI score comprises PWB, FWB, and LYM scores.
FWB, functional well being; LYM, lymphoma additional concerns; PWB, physical well being; TOI, trial outcome index.

- In an observational study conducted in the United Kingdom (UK), patients with R/R FL that responded to treatment and were free of disease had the highest FACT-Lym scores, indicating greater HRQOL compared with active disease or partial response to chemotherapy[5] (**Figure 2**)
  - This study also reported that patients with active disease-relapsed FL had the highest mean total WPAI score (46.18), followed by those with partial response (37.00), remission/complete response (28.22), and disease-free patients (14.80). Thus, patients with active disease-relapsed FL experienced the most significant impairment in work activity and lower productivity as demonstrated by higher WPAI scores[5]
- In the GADOLIN trial,[3] a higher percentage of patients with R/R FL who received bendamustine plus obinutuzumab (42.6%) reported a clinically significant improvement in HRQOL at the 8- to 12-month follow-up visit compared with those who received bendamustine alone (31.3%)
- In the 3L+ settings, treatment with idelalisib was associated with improvements in HRQOL as demonstrated by higher scores compared with baseline on various domains of the FACT-Lym questionnaire[4]
- The ELARA study[6] assessed tisagenlecleucel in 3L+ R/R FL and found that 41% and 45% of patients experienced a clinically meaningful improvement in HRQOL based on their FACT-Lym total scores at 3 and 6 months, respectively. After 6 months, 45% and 34% of patients showed a clinically meaningful improvement in HRQOL using the PCS and Mental Component Score of SF-36, respectively

Table 3. Utility values in R/R and 3L+ settings

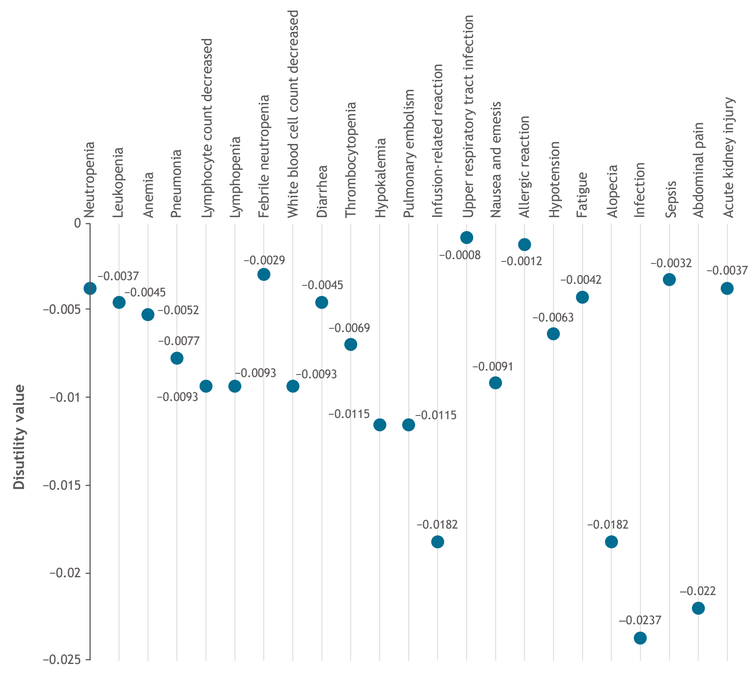
Author and year (country)	LOT (if specified), mean (SD) utility value for PF health state	LOT (if specified), mean (SD) utility value for PD health state	Primary source of utility value
R/R settings			
Guzauskas 2018 (US)[7]	2L: 0.805 (0.769—0.839)	2L: 0.618 (0.506—0.724)	Wild 2006[21]
Blommestein 2014 (the Netherlands)[8]	2L: 0.88 (NR)	2L: 0.78 (NR)	Wild 2006[21]
Vijenthira 2021[a] (Canada)[10]	2L+: NR	2L+: NR	NA
Hayslip 2008 (US)[11]	2L+: disease-free health state 0.73	2L+: NR	Brixner 2006[24]
Haukaas 2018 (Norway)[13]	PFS (on treatment): 0.807 (0.19) PFS (off treatment): 0.822 (0.175)	0.758 (0.249)	GADOLIN trial[3]
Soini 2011 (Finland)[14]	0.805 (0.018)	0.618 (0.056)	Pettengell 2008[5]
Deconinck 2010 (France)[15]	0.805 (0.018)	0.618 (0.056)	Wild 2006[21]
TA627 lenalidomide + rituximab 2020 (UK)[16]	PFS (R-CHOP/CVP): 0.863 PFS (obinutuzumab plus bendamustine): 0.814	NR	AUGMENT trial (Leonard 2019 and Dolan[b] 1997)[22,23]
TA629 obinutuzumab + bendamustine 2020 (UK)[17]	PFS (on treatment): NR (0.79—0.81) PFS (off treatment): NR (0.79—0.81)	NR (0.57—0.65)	GADOLIN trial[3]
SMC No. (1219/17) obinutuzumab + bendamustine 2017 (Scotland)[18]	0.81 (NR)	0.62 (NR)	Wild 2006[21]
PBAC obinutuzumab + bendamustine 2016 (Australia)[20]	PFS (on treatment): 0.82 PFS (off treatment): 0.81	0.77 (NR)	GADOLIN trial[3]
SMC2281 lenalidomide + rituximab 2020 (Scotland)[19]	Preprogressed disease: 0.81 (NR)	Progressed (off treatment): 0.78 (NR) Progressed (on treatment): 0.75 (NR)	AUGMENT trial (Leonard 2019 and Dolan[b] 1997)[22,23]
3L+ settings			
Tang 2022 (US)[9]	0.905 (range, 0.655—0.966)	0.618 (range, 0.494—0.742)	CHRONOS-3 trial[25]
Kasteng 2008 (Sweden)[12]	0.805 (NR)	0.618 (NR)	Utility values in FL 2005[26]
CADTH idelalisib 2016 (Canada)[4]	0.81 (NR)	NR	NR

[a]Reported utilities for health states other than PF and PD; [b]Described methods used to value utility values from the AUGMENT trial in the UK population using the time trade-off method.
CVP, cyclophosphamide, vincristine, prednisone; NA, not applicable; PFS, progression-free survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; SD, standard deviation.

Utility and disutility results

- Regardless of the treatment setting, better HRQOL was observed in the progression-free (PF) health state compared with the progressed disease (PD) health state across the studies (**Table 3**)
- Three main sources of utilities were used across all of the economic evaluations in R/R disease as follows: the GADOLIN trial,[3] AUGMENT trial,[22,23] and Wild 2006[21]
  - Utility values for the PF on-treatment health state ranged from 0.81[13] to 0.82[20] across different models, with values for the PF off-treatment health state ranging from 0.81[19] to 0.82.[13] Values for the PD health state were lower ranging from 0.62[14,15] to 0.78[8,19]

Figure 3. Disutility values due to AEs[16]



- Only 1 study reported disutility values for adverse events (AE). In total, 23 disutilities were reported for various AEs, ranging from −0.0237 for the disutility of AE infection to −0.008 for the disutility of AE upper respiratory tract infection[16] (**Figure 3**)

Discussion

- Only 18 studies reported on HRQOL/PRO and utility/disutility values in R/R FL, and evidence was predominantly reported in patients from Europe (n = 9) and North America (n = 5); the generalizability of these data to other geographical locations is unclear
- Across 4 publications reporting on HRQOL in R/R FL, evidence for patients who received 3L+ treatment was limited to an HTA report and a single-arm study; in general, studies failed to separate data between individual lines of therapy
- Only 2 of 4 studies reporting on changes in HRQOL after treatment indicated whether improvements were clinically meaningful, and these studies were limited in sample size (< 100 participants)
- Utility/disutility values were only reported in economic evaluations submitted for HTA assessment using data from older studies
- These models tended to cite values from the same core primary sources with unclear adjustments made to tailor values for each specific model and population; therefore, it was difficult to assess their validity
- Across all evaluations reporting utility values, the highest values were observed for the PF health state, whilst the lowest values were reported for the PD health state. These findings are in line with populations in real-world practice
- AEs were also associated with varying degrees of disutility (poorer HRQOL)

Strengths and limitations

- This SLR used robust methods in accordance with standard practices for conducting an SLR
- Comprehensive searches were conducted across both electronic databases and grey literature sources, including relevant HTA databases and conference proceedings
- Findings of the SLR are limited by the number of included studies, their methodologies, limited sample sizes, and poor reporting of the findings

Conclusions

- Data on HRQOL and utility/disutility values relevant to 3L+ treatment in R/R FL are scarce; data are often poorly reported and come from older studies or those with smaller sample sizes. No study reported data on individual line of therapy beyond the 3L setting
- Utility values are lower in patients with disease progression compared with those in a PF health state suggesting poorer HRQOL
- Further research is needed on HRQOL and utility/disutility values in R/R FL, specifically in 3L+ setting to better understand the HRQOL/PRO burden as well as to better inform the cost-effectiveness of new innovative treatment options

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