Supplementary File 2: Development of the BRIGHTLIGHT Severity of Illness Index (BRIGHTLIGHT SIX)

Rationale for developing a bespoke severity index

Within the BRIGHTLIGHT cohort, place of care was not randomly assigned but instead determined by local pathways of care, key influences including the type of cancer, age, proximity to principal treatment centres. As a consequence, differences exist between those who have all/some of their treatment in the teenage and young adult (TYA) Principal Treatment Centre (PTC) and those who have had no care in a TYA PTC. This fundamental difference between the populations of patients who receive no, some or all TYA PTC care was thought likely to be a major confounder in the interpretation of any observed differences in patient experience and outcome between these groups. The differences may not be reflected accurately if cases were grouped solely by, say, tumour type or disease stage due to the considerable variation between tumour types and between similar tumours of different stages in the intensity of treatment received and the likelihood of survival. To interpret the significance of any observed differences in our primary or secondary outcome measures across the populations with no, some or all TYA PTC care, we needed a measure that would allow comparison across patients with different tumours, but capable of discriminating between patient populations. Our primary outcome was quality of life (QOL) and a powerful determinant of QOL is 'the burden of cancer' patients had at diagnosis[1]. We wished to consistently and systematically describe the burden of cancer to assist analysis. The severity of illness index therefore needed to reflect prognosis, disease morbidity (symptoms, physical impact) and treatment morbidity (determined by treatment duration, intensity and anticipated late morbidity burden).

The BRIGHTLIGHT Severity of illness index (SIX)

Constructing the index

All cancer types were compared by symptom burden, treatment burden and prognosis using germ cell tumours as a reference: Stage 1 – very likely to survive, treatment either surgery alone or surgery plus a limited burden of chemotherapy, few if any anticipated late effects of treatment; Stage 2-3 – ~90% survival, many have intensive or multimodality treatment or larger operations, some late toxicity burden; Stage 4 – 50% survival and intensive treatment. Stage 4 we classed as 'most severe' and used this as a reference point to compare odds of survival and treatment burden for other cancers.

Germ cell tumours were chosen as a reference because they are relatively common in the TYA age group, have a range of prognoses from excellent to poor, and treatments have a range of morbidity from surgery alone through to very intensive chemotherapy with both acute and long-term sequelae.

[1] Husson O, Zebrack BJ, Block R, Embry L, Aguilar C, Hayes-Lattin B, Cole S. Health-Related Quality of Life in Adolescent and Young Adult Patients With Cancer: A Longitudinal Study. J Clin Oncol 2017;35:652-659

Three clinicians and two BRIGHTLIGHT researchers reviewed all cancer types to consider allocation to one of three severity levels. Survival estimates were based on examination of current or recently completed trial protocols where available and using a recently published comprehensive TYA-specific reference textbook[2]. We evaluated treatment burden using duration and expected toxicity from multiple sources, including clinical experience, trial protocols, a current TYA oncology text book and international guidelines (such as the National Comprehensive Cancer Network). In addition, other potentially comparable clinical severity scales were sought from the literature to determine comparability or utility in this context.

Content validity of the index

Once a preliminary scale had been constructed, its content was tested by expert review. At least two additional clinicians with specialist clinical expertise were approached to review each tumour type. The reviewers were sent a short document outlining the purpose of the scale and its development to that point as well as the scale itself. They were interviewed either face-to-face or by telephone by a senior clinician and BRIGHTLIGHT researcher (JSW) and asked to respond to two questions:

1. *Within the row(s) of the cancer types in which you have particular expertise (e.g. central nervous system tumours), do you agree with the allocation of grades of severity?*
2. *Looking at other tumour types, by comparison with other rows, do you agree with the allocation of grades of severity?*

Interviews were recorded and field notes taken. The scale was adjusted in response to expert comments to produce a final version (main paper, Table 2).

Applying the BRIGHTLIGHT SIX

BRIGHTLIGHT researchers (RMT, LAF, DS) independently allocated a severity level to each patient, conducting these assessments blind to responses to the survey, including QOL results. Comparisons between the three scores were made and, where there were differences, adjudication through a fourth researcher (JW) determined whether this was an error or due to ambiguity in the Index.

Other measures of severity

We found only one other example in which investigators had categorised TYA by cancer severity. Husson et al[1] used expected 5-year survival to divide patients into three groups, those with expected survival of greater than 80%, 50-80% and less than 50%.[3] Using the same source data[4], we also allocated each patient from the BRIGHTLIGHT cohort a second severity level based on 5-year survival.

We compared this method (Five year survival index, FYX) with BRIGHTLIGHT SIX. As anticipated, those judged to have the most severe cancer by BRIGHTLIGHT SIX are

[2] Bleyer, Barr, Ries, Whelan, Ferrari eds. Cancer in Adolescents and Young Adults. Springer International Publishing, Switzerland 2017

[3] Husson O, Zebrack BJ, Block R, Embry L, Aguilar C, Hayes-Lattin B, Cole S. Health-Related Quality of Life in Adolescent and Young Adult Patients With Cancer: A Longitudinal Study. J Clin Oncol 2017;35:652-659

[4] Bleyer, A. (2011). "Latest Estimates of Survival Rates of the 24 Most Common Cancers in Adolescent and Young Adult Americans." J Adolesc Young Adult Oncol 1(1): 37-42.

distributed across the three survival categories though weighted towards the two lower survival groups. Similarly, most but not all of those with the least severe cancer by BRIGHTLIGHT SIX had the best expected survival. Those with intermediate severity cancer are spread across the three FYX groups (Table 1).

Table 1: Comparison between the Five year survival Index (FYX) and BRIGHTLIGHT Severity of Illness Index (SIX)

	SIX level		
FYX	Least	Intermediate	Most
<50%	1	100	71
50-80%	56	98	171
>80%	546	56	7

We then analysed survival of the BRIGHTLIGHT cohort using the two indices. Figure 1 demonstrated a clear discrimination in survival by BRIGHTLIGHT SIX, consistent with anticipated survival being an important but not sole component of the index. The survival of the BRIGHTLIGHT cohort was then examined by allocated FYX category (Figure 2). FYX failed to distinguish three groups with distinct survival as that of those allocated to the two lower categories was superimposed.

Figure 1: Survival by BRIGHTLIGHT Severity of Illness Index

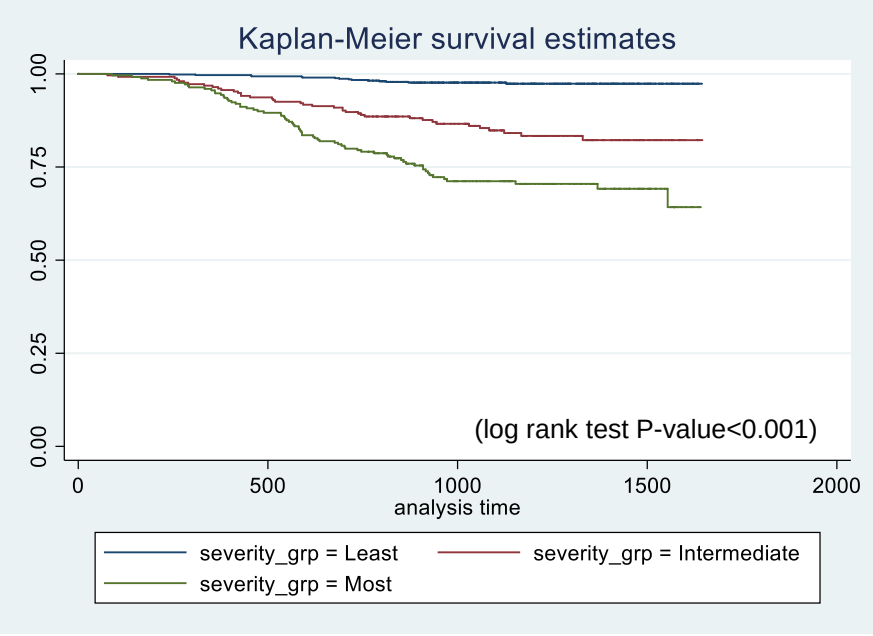

Figure 2: Survival of BRIGHTLIGHT cohort against allocated FYX group