APPENDIX 1

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1   cancer*.mp.

2   exp Neoplasms/

3   neoplasm*.mp.

4   exp Carcinoma/

5   carcinoma*.mp.

6   exp Sarcoma/

7   sarcoma*.mp.

8   exp Lymphoma/

9   lymphoma*.mp.

10   exp Leukemia/

11   leukemia*.mp.

12   myeloma.mp.

13   tumor*.mp.

14   tumour*.mp.

15   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16   exp "Quality of Life"/

17   quality of life.mp.

18   QOL.mp.

19   Health Related Quality of Life.mp.

20   HRQOL.mp.

21   HRQL.mp.

22   patient reported outcome*.mp. or exp "Outcome Assessment (Health Care)"/

23   ((pro or pros) and outcome*).ti,ab.

24   Patient Preference.mp. or exp Patient Preference/

25   16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26   drug*.ti,ab.

27   pharmaceutical preparations/ or controlled substances/ or exp dosage forms/ or exp drug combinations/ or exp drugs, essential/ or exp drugs, generic/ or exp drugs, investigational/ or exp materia medica/ or exp nonprescription drugs/ or exp pharmaceutic aids/ or exp placebos/ or exp prescription drugs/ or exp prodrugs/ or exp solutions/ or exp "vaginal creams, foams, and jellies"/ or exp xenobiotics/

28   drug therapy/ or antineoplastic protocols/ or exp chemoradiotherapy/ or chemotherapy, adjuvant/ or consolidation chemotherapy/ or exp administration, intravenous/ or exp administration, oral/ or exp chemotherapy, cancer, regional perfusion/ or exp infusions, parenteral/ or exp injections/ or exp drug carriers/ or exp drug prescriptions/ or drug therapy, combination/ or antineoplastic combined chemotherapy protocols/ or exp fluid therapy/ or home infusion therapy/ or induction chemotherapy/ or maintenance chemotherapy/ or molecular targeted therapy/

29   chemotherapy.mp.

30   growth substances/ or exp angiogenesis modulating agents/ or exp growth inhibitors/ or exp immunologic factors/ or exp adjuvants, immunologic/ or exp interferon inducers/

31   exp Tumor Necrosis Factor-alpha/ or biologic*.ti,ab. or exp Antibodies, Monoclonal/

32   Immunotherapy/

33   Immunotherapy.mp. or Immunotherapy/

34   Cytokines.mp. or exp Cytokines/

35   26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36   (Bevacizumab or avastin).mp.

37   (ixabepilone or ixempra).mp.

38   (lapatinib or Tykerb).mp.

39   (panitumumab or vectibix).mp.

40   (doxorubicin or doxil).mp.

41   (gemcitabine or gemzar).mp.

42   (trabectedin or yondelis).mp.

43   (sorafenib or nexavar).mp.

44   (pazopanib or votrient).mp.

45   (sunitinib or sutent).mp.

46   (erlotinib or tarceva).mp.

47   (docetaxel or doxetaxel or taxotere).mp.

48   36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47

49   35 or 48

50   15 and 25 and 49

51   randomized controlled trial$.mp.

52   randomized controlled trial.pt.

53   double-blind method/

54   single-blind method/

55   controlled clinical trial.pt.

56   ((double$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.

57   random$.mp.

58   51 or 52 or 53 or 54 or 55 or 56 or 57

59   50 and 58

60   animals/ not humans/

61   59 not 60

62   limit 61 to yr="2000 -Current"

APPENDIX 2

AUC for each group / arm, and the incremental AUC between groups for each study will be calculated using the trapezoidal rule. This rule from the family of formulas for numerical integration, or quadrature, is used for approximating the definite integral, and works by approximating the region under the graph of the function f(x) as a trapezoid and calculating its area. The trapezoid rule instructs to divide the curve into a series of trapezoids, each with area equaling average height (i.e. determined by the two adjacent HRQoL measures) multiplied by width, and to sum the areas of the strips.[1] Because area is a function of differences between means at different time points between curves, or intervention groups, incremental AUC (ΔAUC) is denoted by:

$$1)\ \Delta AUC = Area_I - Area_C = (A1_I + A2_I + \cdots) - (A1_C + A2_C + \cdots),$$

where the brackets containing the "I" subscript represent the total area of the treatment intervention group, and the brackets containing the "C" subscript represent the total area of the control group.

For the purposes of our analysis, this formula is expanded as follows:

$$2)\ \Delta AUC = \left[\frac{(Q1_I + Q2_I)}{2} \times (TD2_I - TD1_I) + \frac{(Q2_I + Q3_I)}{2} \times (TD3_I - TD2_I) + \cdots \right] - \left[\frac{(Q1_C + Q2_C)}{2} \times (TD2_C - TD1_C) + \frac{(Q2_C + Q3_C)}{2} \times (TD3_C - TD2_C) + \cdots \right],$$

where Q represents the mean HRQoL measurements provided for each treatment group, and half the sum between the Q's is the average height of the trapezoid, and where TD represents Time Duration as reported for each HRQoL measurement, and the difference between the TDs is the width of the trapezoid. Formula (2) can be used to find the incremental AUC point estimate difference between intervention and control groups, where we are given consecutive mean HRQoL measurements across time.

In order to perform our data analyses, we not only need the total incremental area point estimates, but also the total error estimates around these point values. We therefore need to calculate two separate variances to get the totals; one for within each treatment group, and the other for between the groups. We will start by calculating within group variances by taking each half of incremental area formula (2), first for the intervention group and then for control group, and once we simplify and rearrange for each group, our formula is as follows:

$$3)\ V(Area_{I\ or\ C}) = d_1^2 \times v(Q_1 + Q_2) + d_2^2 \times v(Q_2 + Q_3) + \cdots,$$

where d represents the constant of half the time duration difference, and where v($Q_1 + Q_2$) represents the pooled variance within a group.

Because variance within a group has repeated measures, we will account for covariance between measurements by applying the pooled standard deviation for dependent samples equation to formula (3) as follows:

$$4)\ V(Area_{I\ or\ C}) = d_1^2 \times (\sigma_1^2 + \sigma_2^2 + 2 \times \sigma_1 \times \sigma_2 \times p) + d_2^2 \times (\sigma_2^2 + \sigma_3^2 + 2 \times \sigma_2 \times \sigma_3 \times p) + \cdots,$$

where σ represents the standard deviation for each HRQoL measurement as extracted from the study, and where p will equal 0.5, an assumption of a positive midpoint correlation of +0.5. The rationale for this assumption originates from an expectation of increasing HRQoL over time for each particular group with subsequent HRQoL readings, due to treatment being provided in the RCT leading to increased

HRQoL over time compared to baseline. Formula (4) will be used to find the within group area variances for the intervention and control group.

In order to find total variance, which is the combination of within group plus between group variances, or variance of the incremental area, we will combine all within group variances calculated. For this we return to formula (1), but as opposed to mean incremental area being a function of differences between curves or groups, total variance is instead a function of the addition of all within group variances as follows:

$$5) \ V(\Delta Area) = V(Area_I) + V(Area_C)$$

Once total variance for incremental HRQoL area is calculated, we will use this in combination with the total sample size of all measurements to calculate the standard error (SE), since SE reflects the variability between means,[2] and we are calculating a difference between means for the incremental area. The SE will be used to derive the 95% confidence interval around the HRQoL incremental area for each study, and get a sense of the inherent uncertainty present in the dependent HRQoL variable.

REFERENCES

1. Mysovskikh IP. Trapezium formula: Encyclopedia of Mathematics; [updated 7 February 2011. Available from: http://www.encyclopediaofmath.org/index.php?title=Trapezium_formula&oldid=12696.
2. Streiner DL. Maintaining standards: differences between the standard deviation and standard error, and when to use each. Canadian journal of psychiatry Revue canadienne de psychiatrie 1996;**41**(8):498-502.