



CARE

Pre-operative intentional weight loss to support post-operative recovery in patients with overweight and colorectal cancer: the CARE feasibility randomised controlled trial

(Short title: Could supported weight loss reduce bowel cancer surgery complications?)

Statistical Analysis Plan supplementary

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Surgical Intervention Trials Unit (SITU)



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1. INTRODUCTION

The CARE SAP includes this text

3.7.2 Secondary and other outcomes

Further details regarding the secondary outcomes will be provided at a later date, (provisionally in a supplementary document) prior to database lock.

Excerpt from CARE_SAP_v1.0_14Mar2023.docx

This is that supplementary document.

2. OVERVIEW

The secondary outcomes will be summarised descriptively by trial group. If appropriate, the effect size and 95% confidence intervals will be estimated with regression models. Both absolute and relative effect sizes will be reported.

Complications will be summarised using one or more of the following:

- count/percentage of participants with any complication
- count/percentage of participants with any complication by grade
- count/percentage of participants with the highest grade of complication reported
- count/percentage of participants with any type of complication
- count of total complications.

3. DEFINITION OF POPULATION FOR ANALYSIS

Main analysis: All randomised participants that underwent surgery will be included in the main analysis on an intention-to-treat basis (ITT) regardless of withdrawal or non-adherence. An intention-to-treat basis assigns all randomised participants to their originally allocated group, whether they received their allocated randomised treatment arm approach or not, or dropped out or not. Participants who had their surgery less than 20 days since randomisation will be included in this analysis.

Per-protocol analysis: We will also conduct an analysis on a per-protocol basis. A per-protocol basis includes only those randomised participants who met all eligibility criteria, had no major deviations from the study procedures, and adhered to their assigned interventions. For the intervention group, this includes the participants who achieved $\geq 5\%$ weight loss from baseline to the day of surgery. For participants in the usual care group, this excludes those who lost $\geq 5\%$ weight loss from baseline to the day of surgery. Participants who had their surgery less than 20 days since randomisation will not be included in this analysis.

Adverse events: The adverse event analysis will include the participants in the control group and the participants commencing the intervention in the intervention group.

4. USE OF MODELS

4.1 Input variables

The SAP states that the mean and 95% confidence intervals for the secondary outcome variables will be estimated with adjusted regression models. Those adjustments will be our four input variables, specifically:

- treatment group. There are two treatment groups, the control and the intervention.
- baseline value (where applicable)
- time point (where applicable)
- stratification variables. The two stratification variables are performance status (0 vs 1-2) and age at diagnosis (≤ 70 years). These will be combined into one [1][2].

The extension from regression models to mixed models was not explicitly stated but is assumed. Such models will have fixed effects and may be further extended to include a random effect and/or an interaction. Details of those models include:

- The fixed effects are the adjustments
- The random effect is the participant/study ID
- The interaction is multiplicative. For example, an interaction between the treatment group and the time point (both of which are fixed) will be considered.

In models with interaction terms, the treatment effect will be the interaction term. In models without an interaction term, the treatment effect will be the treatment group.

4.2 Output variables

We expect to model all secondary outcome variables, except survival, recurrence, new primary/secondary cancer, re-admission rates, re-operation rates, costs and resource use, and adverse events. The final decision will depend on the available data. For example, if the counts for conversion to open surgery rates are very low, we will not model this outcome.

Therefore, we plan on analysing:

- Morbidity (five variables not including 2iii survival)
- Operative outcomes (seven variables not including re-operation and re-admission rates)
- Hospital stay (two variables)
- Anthropometry (two variables)
- Fitness (one variable)
- Health-related quality of life (HRQoL) (three variables)

That's twenty variables equating to at least 20 models, as some of those variables will be further subdivided (eg HRQoL variable "EQ-5D-5L" has two subdivisions, index and VAS).

4.3 Model selection for a given outcome variable

See Appendix “Use Of The Word “Linear” In Linear Models” for an explanation of the use of the word “linear” even if the underlying curve is a higher polynomial

The output variables may be continuous or categorical and the input variables may be categorical or continuous. This would imply a logistic model (logistic regression or discriminant analysis) or a linear model (linear regression or ANOVA or ANCOVA or mixed) or a generalized model (GLM) approach. As GLMs are the most capable, we will use GLMs for our models where possible.

5. LIST OF SECONDARY OUTCOMES

Table: secondary outcomes

Objectives	Outcome Measures	Timepoint(s)	Type	Distribution
To report between-group differences in				
2. Morbidity	i. Any morbidity	i.-ii. Discharge and 30-days post-op	Binary	Binomial
	ii. Morbidity by grade (I, II, IIIa, IIIb, IVa, IVb)	ditto	Binary	Binomial
	iii. Survival (grade V)	iii: Discharge, 30-days post-op, 3 yrs	N/A: not model	
	iv Morbidity by highest grade	i.-ii. Discharge and 30-days post-op	Binary	Binomial
	v. Number of people with no morbidity	iii: Discharge, 30-days post-op, 3 yrs	Binary	Binomial
	vi. Morbidity by type (e.g., arrythmia, wound infection, etc)	i.-ii. Discharge and 30-days post-op	Binary	Binomial
3. Oncological outcomes	iv. Resection margins (involved Y/N)	iv. Discharge	Binary	Binomial
	v. Recurrence	v-vi: 3 years	N/A: not model	
	vi. New primary/ secondary cancer	ditto	N/A: not model	
4. Operative outcomes	vii. Intraoperative blood loss			
	Count/rate (transfused Y/N)	vii-ix: Discharge	Binary	Binomial
	units transfused (including untransfused)	ditto	Continuous	See lookup
	viii. Operative time	ditto	Continuous	See lookup
	ix. Conversion to open surgery	ditto	Binary	Binomial
	x. Surgical site infection	x-xiii: Discharge and 30-days post-op	Binary	Binomial
	xi. Stoma rates	ditto	Binary	Binomial
	xi. Stoma complications	ditto	Binary	Binomial
	xii. Radiologically -defined anastomotic leaks	ditto	Binary	Binomial
	xiii. Length of time in intensive care unit	ditto	Continuous	See lookup
	xiii. Length of time in high dependency unit	ditto	Continuous	See lookup
	xiv. Re-operation rates	xiv-xv: 30-days post-op and 3 years	N/A: not model	
	xv. Re-admission rates	ditto	N/A: not model	
	5. Hospital stay	xvi. Length of hospital stay (fitness to discharge)	xvi: Discharge	Time-to-event
xvii. Days alive and out of hospital		xvii: 30-days post- operatively	Time-to-event	See lookup
6. Anthropometry	xviii. Weight	xviii-xix: Baseline, pre-operative assessment 4, and 30 days post-op	Continuous	See lookup
	xix. Fat-free mass (absolute kg)	ditto	Continuous	See lookup
	xix. Fat-free mass (relative %)	ditto	Continuous	See lookup
7. Fitness	xx. Time for sit-to-stand test	xx: Baseline, 30 days post-op	Continuous	See lookup
8. HRQoL	xxi. EQ-5D-5L (Index score)	xxi-xxii: Baseline, pre-operative assessment 3 and 30 days post-op	Continuous	See lookup
	xxi. EQ-5D-5L (VAS)	ditto	Continuous	See lookup
	xxii. HADS (anxiety) continuous	ditto	Continuous	See lookup
	xxii. HADS (depression) continuous	ditto	Continuous	See lookup
	xxiii. EORTC-QLQ-CR29			
	29 individual items	ditto	N/A: not model	
9. Costs & resource use	N/A - dealt with by health economics			
10. Adverse events	xxvii. Adverse events (excluding morbidity i-vi)	xxvii: Baseline, pre-operative assessment and 30 days post-op	N/A: not model	

Details of each variable are provided below.

6. MORBIDITY

Morbidity

#	Outcome Measures	Control	Intervention	Delta
2a	i. Any morbidity			
	At or prior to discharge	X	X	X
	Between discharge and 30 days	X	X	X
	Other	X	X	X
	Total	X	X	X
	At or prior to discharge OR between discharge and 30 days	X	X	X
2b	ii. Morbidity by grade (I, II, IIIa, IIIb, IVa, IVb)			
	at least one Grade I	X	X	X
	.	X	X	X
	at least one Grade IVb	X	X	X
	Other	X	X	X
	Total	X	X	X
2c	iii. Survival (grade V)	X	X	X
2d	iv Morbidity by highest grade	X	X	X
2e	v. Number of people with no morbidity	X	X	X
2f	vi. Morbidity by type (eg arrhythmia, wound infection, etc)			
	Type	X	X	X
	.	X	X	X
	Type	X	X	X
	Other	X	X	X
	Total	X	X	X

Note: the "other" categories are included for completeness and will be omitted if absent

Note: this is a list of patients, not complications. Because a patient can have more than one complication of different times/grades, an arm may not add to 100%. See appendices for worked examples

6.1 i. Any morbidity

This secondary outcome is reported regardless of timepoint. The information to calculate it is derived from the morbidity grade as specified on the CRFs Complications Grading 1 and Complications Grading 2. It is a binary variable and collectively a count/rate (0-n/%). The entry is defined as the number of patients with at least one complication divided by the number of patients.

For worked examples of this please see the appendices.

6.2 ii. Morbidity by grade (I, II, IIIa, IIIb, IVa, IVb)

This secondary outcome is reported by grade regardless of timepoint (i.e., a complication can occur at either discharge or 30-days follow-up). The information to calculate it is derived from the morbidity grade as specified on the CRFs Complications Grading 1 and Complications Grading 2. The entry for each grade X is defined as the number of patients with at least one complication of grade X divided by the number of patients. It is a categorical variable. Each category is a count/rate (0-n/%) and will be modelled as a binary variable.

For worked examples of this please see the appendices.

6.3 iii. Survival (grade V)

This secondary outcome is reported for a single grade regardless of timepoint. The information to calculate it is derived from the morbidity grade as specified on the CRFs Complications Grading 1 and Complications Grading 2. It is a binary variable and collectively a count/rate (0-n/%). Given the expected low count, it is unlikely that this will be analysed statistically.

6.4 iv Morbidity by highest grade

As ii above. This secondary outcome is reported for a single grade regardless of timepoint. If a participant has one coded complication, the grade of that complication will count as the highest graded morbidity. If a participant has at least two complications, the highest grade will be counted for this variable. It is a categorical variable & each category is a count/rate (0-n/%). Each category will be modelled as a binary variable.

For worked examples of this please see the appendices.

6.5 v. Number of people with no morbidity

As i above.

6.6 vi. Morbidity by type (eg arrhythmia, wound infection, etc)

This secondary outcome is reported regardless of timepoint. The information to calculate it is derived from the complication type as specified on the CRFs Complications Grading 1 and Complications Grading 2 (as derived from previous CRFs eg Hospital Stay and Discharge). It is a categorical variable & each category is a count/rate (0-n/%). Each category will be modelled as a binary variable.

7. ONCOLOGICAL OUTCOMES

Oncological Outcomes

#	Outcome Measures	Control	Intervention	Delta
3a	iv. Resection margins	X	X	X
3b	v. Recurrence	X	X	X
3c	vi. New primary/ secondary cancer	X	X	X

7.1 iv. Resection margins

This secondary outcome is reported at discharge. The information to calculate it is derived from the resection margins as recorded on the CRF Hospital Stay and Discharge. It is recorded as a continuous variable and a measurement of distance. It will be reduced to a binary measure (involved/not involved) and collectively a count/rate (0-n/%).

7.2 v. Recurrence

This secondary outcome is reported at 3 years. The information to calculate it is derived from the recurrence or metastatic type data on the CRF NBOCA. It is a binary variable and collectively a

count/rate (0-n/%). Due to low expected numbers, we do not plan an analysis for this. It will be depicted using survival curves.

7.3 vi. New primary/ secondary cancer

This secondary outcome will be collected at the 3-year follow-up. It is a binary variable and collectively a count/rate (0-n/%). Due to low expected numbers, we do not plan an analysis for this. It will be depicted using survival curves.

8. OPERATIVE OUTCOMES

Operative Outcomes

#	Outcome Measures	Control	Intervention	Delta
4a	vii. Intraoperative blood loss			
	Count/rate (transfused Y/N)	X	X	X
	number of units transfused (including untransfused)	X	X	X
4b	viii. Operative time	X	X	X
4c	ix. Conversion to open surgery	X	X	X
4d	x. Surgical site infection	X	X	X
4e	xi. Stoma rates & complications	X	X	X
4f	xii. Radiologically-defined anastomotic leaks	X	X	X
4g	xiii. Time in intensive care unit	X	X	X
4g	xiii. Time in high dependency unit	X	X	X
4h	xiv. Re-operation rates	X	X	X
4i	xv. Re-admission rates	X	X	X

8.1 vii. Intraoperative blood loss

This outcome is reported using two variables: by the presence of intraoperative blood transfusion and by the number of units transfused (including the untransfused). The information to calculate it is derived from the fact of an intraoperative blood transfusion and the number of blood units used. These variables are recorded on the CRF Hospital Stay and Discharge.

The first variable is a binary variable and collectively a count/rate (0-n/%). The second variables are continuous variables and measurements of amount.

8.2 viii. Operative time

The information to calculate this outcome is derived from the total time taken for the procedure on the CRF Hospital Stay and Discharge. It is a continuous variable and a measurement of time.

8.3 ix. Conversion to open surgery

The information to calculate this outcome is derived from the operation performed as recorded on the CRF Hospital Stay and Discharge. It is a binary variable and collectively a count/rate (0-n/%).

8.4 x. Surgical site infection

The information to calculate this outcome is derived from the complications data on CRF Complications Grading 1 (as derived from previous CRFs eg Hospital Stay and Discharge). It is a binary variable and collectively a count/rate (0-n/%).

8.5 xi. Stoma rates & complications

The information to calculate each of the two subsets of this outcome is derived from the stoma/anastomosis data on the CRFs Hospital Stay and Discharge and Complications Grading 1. The existence of a stoma/anastomosis (Y/N) is derived from the “Stoma/anastomosis formed” CRF elements. The existence of complications (Y/N) is derived from the “Were there any stoma-specific complications?” CRF elements. Each one is a binary variable and collectively a count/rate (0-n/%).

8.6 xii. Radiologically-defined anastomotic leaks

The information to calculate this outcome is derived from the complications data on CRF Complications Grading 1 (as derived from previous CRFs eg Hospital Stay and Discharge). It is a binary variable and collectively a count/rate (0-n/%).

8.7 xiii. Time in intensive care unit and time in high dependency unit

The information to calculate these two lengths of time is derived from the ward and time details on the CRF Hospital Stay and Discharge. Each one is a continuous variable and a measurement of time.

8.8 xiv. Re-operation rates

The information to calculate this outcome is derived from the return to theatre data on the CRFs NBOCA data and Hospital Stay and Discharge. It is a binary variable and collectively a count/rate (0-n/%).

8.9 xv. Re-admission rates

The information to calculate this outcome is derived from the readmission data on the CRF Hospital Stay and Discharge. It is a binary variable and collectively a count/rate (0-n/%).

9. HOSPITAL STAY

#	Outcome Measures	Control	Intervention	Delta
5a	xvi. Length of hospital stay (fitness to discharge)	X	X	X
5b	xvii. Days alive and out of hospital	X	X	X

9.1 xvi. Length of hospital stay (fitness to discharge)

We will calculate the numbers of days of hospital stay using the date of admission and the date of discharge. The information to calculate it is derived from the admission and discharge data on the CRFs Admission and Hospital Stay and Discharge. It is a time-to-event variable and a measurement of time. Instructions for modelling time-to-event variables are given in the appendices.

9.2 xvii. Days alive and out of hospital

This secondary outcome is displayed by timepoint. We will calculate the number of days based on the dates of admission, discharge, and 30-day follow-up. The information to calculate it is derived from the discharge and other data on the CRFs Hospital Stay and Discharge and Anthropometry. It is a time-to-event variable and a measurement of time. Instructions for modelling time-to-event variables are given in the appendices.

The possibility of censorship must be noted here.

- If somebody has surgery on the 1st, discharged on the 10th and followed-up on the 30th, then on the 30th the state is known: at that date the days alive and out of hospital is known to be 20 days.
- But if somebody has surgery on the 1st, discharged on the 10th and followed-up on the 27th, then on the 30th the state is not known with certainty as they may have died in the meantime.

To prevent this censorship, we will seek confirmation from the local research teams that the person is still alive on the 30th.

10. ANTHROPOMETRY

#	Outcome Measures	Control	Intervention	Delta
6a	xviii. Weight	X	X	X
6b	xix. Fat-free mass	X	X	X

10.1 xviii. Weight

This secondary outcome is displayed by timepoint. The information to calculate it is derived from the weight data on the CRFs Anthropometry and Screening Visit. It is a continuous variable and a measurement of mass.

10.2 xix. Fat-free mass

This secondary outcome is displayed by timepoint. The information to calculate it is derived from the weight and body fat data on the CRFs Anthropometry and Screening Visit. It is a continuous variable and a measurement of mass. It is reported both as an absolute value (the fat-free mass in kg) and a relative value (the fat-free mass divided by the weight and depicted as a % of body mass).

11. FITNESS

#	Outcome Measures	Control	Intervention	Delta
7a	xx. Time for sit-to-stand test	X	X	X

11.1 xx. Time for sit-to-stand test

This secondary outcome is displayed by timepoint. The information to calculate it is derived from the sit-to-stand data on the CRF Sit To Stand Test. It is a continuous variable and a measurement of time.

12. HRQOL (HEALTH-RELATED QUALITY OF LIFE)

#	Outcome Measures	Control	Intervention	Delta
8a	xxi. EQ-5D-5L			
	Index score	X	X	X
	VAS	X	X	X
8b	xxii. HADS			
	• Anxiety (continuous)	X	X	X
	• Depression (continuous)	X	X	X
8c	xxiii. EORTC-QLQ-CR29			
	29 individual items	X	X	X

12.1 xxi. EQ-5D-5L

This secondary outcome is displayed by timepoint. The information to calculate it is derived from the CRF EQ-5D-5L. It is in two parts: a summary index value derived from the code, and a visual analogue scale score (VAS). Instructions for calculating these values are given in the appendices.

- The EQ-5D-5L summary index value ranges from less than 0 (indicating a health state worse than death) to 1 (indicating full health). Higher scores represent better health states.
- The EQ-5D-5L Visual Analogue Scale (VAS) ranges from 0 to 100. The maximum value is 100 and represents the best health you can imagine. The minimum value is 0 and represented the worst health you can imagine.

We will treat both variables as scores and continuous variables. The scoring rules are in the appendices.

12.2 xxii. HADS (anxiety)

This secondary outcome is displayed as both a continuous and categorical variable. The information to calculate it is derived from the CRF HADS and Pre-Surgery Questionnaire. It is a score. The scoring rules are in the appendices. The continuous version is detailed here. The other variants are detailed in the subgroup analysis.

- Continuous. The continuous version of this variable will be a number derived from that score. It will be modelled as a continuous variable

12.3 xxii. HADS (depression)

This secondary outcome is displayed as both a continuous and categorical variable. The information to calculate it is derived from the CRF HADS and Pre-Surgery Questionnaire. It is a score. The scoring rules are in the appendices. The continuous version is detailed here. The other variants are detailed in the subgroup analysis.

- Continuous. The continuous version of this variable will be a number derived from that score. It will be modelled as a continuous variable

12.4 xxiii. EORTC-QLQ-CR29

This secondary outcome is displayed by timepoint. The information to calculate it is derived from the CRF EORTC QLQ - CR29. It is a continuous variable and a score. The scoring rules are in the appendices. The score will be calculated for the 29 individual items. The 29 individual items will be descriptive only

13. COSTS AND RESOURCE USE

These outcomes will be calculated as part of the health economics section of the trial and are, therefore, not covered in this document.

14. ADVERSE EVENTS

#	Outcome Measures	Control	Intervention	Delta
10a	xxvii. Adverse events	X	X	X

14.1 xxvii. Adverse events

The information to calculate it is derived from CRF Adverse Events (any time). It is a categorical variable & each category is a count/rate (0-n/%).

#	Outcome Measures	Control	Intervention	Delta
10b	xxvii. Adverse events (by severity)			
	N of AEs in category Mild	X	X	X
	N of AEs in category Moderate	X	X	X
	N of AEs in category Serious	X	X	X
10c	xxvii. Adverse events (by seriousness)			
	N of AEs in category Serious	X	X	X
	N of AEs in category Non-serious	X	X	X
10d	xxvii. Adverse events (misc)			
	N of people with at least one AE	X	X	X
	N of people with at least one moderate AE	X	X	X
	N of people with at least one serious AE	X	X	X
	N of people with at least one SAE	X	X	X
	N of people with at least one moderate AE and/or SAE	X	X	X

15. FURTHER CONSIDERATIONS ON THE ANALYTICAL APPROACH

15.1 Missing data

Missing data will be checked and either corrected if wrong or left if legitimate. Missing data will not be imputed (but see sensitivity analysis). The amount of missing data will be quantified and analyses for variables with missing data will be noted as such.

Mixed effects models usually do not require imputation as they are usually robust to missing data (although this depends if missing data is missing at random or not).

15.2 Outliers

Outliers will be checked and either corrected if wrong or left if legitimate. Outliers will not be removed. Analyses for variables with outliers will be noted as such. There are various methods of identifying an outlier, including the “3SD’s beyond the mean” heuristic. We will use the “1.5IQR rule”: outliers will be those points below $Q1 - 1.5IQR$, or above $Q3 + 1.5IQR$ [6].

15.3 Subgroup Analyses

As stated in the section named “Statistics and Analysis” in the protocol, no formal subgroup analyses are planned. However, subgroup analyses requested after the protocol was written are permissible on an exploratory and descriptive basis at the discretion of the Trial Statistician. These subgroup analyses are referred to as “informal”. With the exception of the stratification factors (see sensitivity analysis below) those informal analyses are descriptive and without the need to calculate or report p-values.

15.3.1 HADS (anxiety)

#	Outcome Measures	Control	Intervention	Delta
8b	xxii. HADS			
	• Anxiety (is +ve change since baseline \geq MCID, Y/N)	X*	X*	X†
	• Anxiety (is -ve change since baseline \geq MCID, Y/N)	X*	X*	X†

† = difference between arms: ie compare the control change since baseline to the intervention change since baseline.

* = this is a count and percentage of all the patients in that arm whose change since baseline exceeds the MCID.

- Anxiety (is +ve change since baseline \geq MCID, Y/N)
 - This is the proportion of participants with a positive change at the pre-op 3 assessment since baseline of at least 1.7 points as the minimum clinically important difference (Y/N). This is a binary variable.
- Anxiety (is -ve change since baseline \geq MCID, Y/N)
 - This is the proportion of participants with a negative change at the pre-op 3 assessment since baseline of at least 1.7 points as the minimum clinically important difference (Y/N). This is a binary variable.

The minimum clinically important difference for HADS is 1.7 points, see Lemay KR, et al [8]

15.3.2 HADS (depression)

#	Outcome Measures	Control	Intervention	Delta
8b	xxii. HADS			
	• Depression (is +ve change since baseline \geq MCID, Y/N)	X*	X*	X†
	• Depression (is -ve change since baseline \geq MCID, Y/N)	X*	X*	X†

† = difference between arms: ie compare the control change since baseline to the intervention change since baseline.

* = this is a count and percentage of all the patients in that arm whose change since baseline exceeds the MCID.

As HADS (anxiety) above.

15.4 Sensitivity Analyses

Sensitivity analyses will be done on at least the following:

- **Per-protocol analysis.** The per-protocol analysis will repeat the above models using the per protocol population as defined in section 3.
- **Stratification factors.** The two stratification factors are performance status (“0” vs “1-2”) and age at diagnosis (“< 70 years” and “≥70 years”). For sensitivity analysis we will do the following:
 - Repeat the models with an interaction term between age at diagnosis (“< 70 years” and “≥70 years”) and treatment. This will be expanded to “...and treatment and time” if time is an input variable, see below.
 - Repeat the models with an interaction term between performance status (“0” vs “1-2”) and treatment. This will be expanded to “...and treatment and time” if time is an input variable, see below.
 - Models measuring the state at one timepoint (eg discharge) or the state change between two timepoints will not need a time variable. Models measuring the state at two or more timepoints (eg baseline vs admission vs 30-days post-op) will need a time variable. In such cases, the interaction above will include the time variable. The paper at [7] is an example of this.
- **Other.** Other sensitivity analyses may be conducted if deemed necessary by the Trial Statistician.

16. REFERENCES

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- [3] “Intention-To-Treat (ITT) vs. Per-Protocol (PP) analysis: what to choose?”, Clinfo.eu, see <https://www.clinfo.eu/itt-vs-pp/>

- [4] ICH Topic E9, "Statistical Principles for Clinical Trials, step 5: Note For Guidance On Statistical Principles For Clinical Trials (CPMP/ICH/363/96)", European Medicines Agency, September 1998, see https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf
- [5] Green, J. A. (2021). Too many zeros and/or highly skewed? A tutorial on modelling health behaviour as count data with Poisson and negative binomial regression. *Health Psychology and Behavioral Medicine*, 9(1), 436–455. <https://doi.org/10.1080/21642850.2021.1920416>
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17. APPENDIX: SCORING RULES

Where available, scoring rules are given below. To reduce duplication, rules that are explicated in the tables above are not duplicated here.

17.1 EQ-5D-5L: HRQoL using Patient Reported Outcome Measure (PROMs) EQ-5D-5L

- Sources: <https://euroqol.org/wp-content/uploads/2021/01/EQ-5D-5LUserguide-08-0421.pdf>
- Online calculator: https://euroqol.org/wp-content/uploads/2020/12/ENG_value-set_STATA.txt

17.1.1 Summary index value

Each variable has a tick box, where each dimension has five response levels: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, 5=unable to /extreme problems.

The answers are concatenated into a code (eg “12213”) and converted to a utility code, either manually or via code such as STATA. The scoring rules to translate the code into a utility code can be gotten from the user guide “EQ-5D-5L User Guide” at the EQ-5D website at <https://euroqol.org/wp-content/uploads/2021/01/EQ-5D-5LUserguide-08-0421.pdf>

Conversely, the scoring rules for translating the code to an utility code can be deduced by looking at the STATA code available https://euroqol.org/wp-content/uploads/2020/12/ENG_value-set_STATA.txt. That dataset gives us this lookup table:

variable	value	weight
mobility	1	0
mobility	2	0.058
mobility	3	0.076
mobility	4	0.207
mobility	5	0.274
selfcare	1	0
selfcare	2	0.05
selfcare	3	0.08
selfcare	4	0.164
selfcare	5	0.203
activity	1	0
activity	2	0.05
activity	3	0.063
activity	4	0.162
activity	5	0.184
pain	1	0
pain	2	0.063
pain	3	0.084
pain	4	0.276

pain	5	0.335
anxiety	1	0
anxiety	2	0.078
anxiety	3	0.104
anxiety	4	0.285
anxiety	5	0.289

So a code of “12213” would translate as $1 \times 0 + 2 \times 0.05 + 2 \times 0.05 + 1 \times 0 + 3 \times 0.104 = 0 + 0.1 + 0.1 + 0 + 0.312 = 0.512$

The EQ-5D-5L summary index value ranges from less than 0 (indicating a health state worse than death) to 1 (indicating full health). Higher scores represent better health states.

17.1.2 Visual Analogue Scale (VAS)

The EQ-5D-5L Visual Analogue Scale (VAS) ranges from 0 to 100.

- Maximum Value: 100, representing the best health you can imagine.
- Minimum Value: 0, representing the worst health you can imagine.

17.2 EORTC-QLQ-CR29

- Sources: https://drive.google.com/file/d/16j3pr9bEVYBRa2tMp6B_2QLnxJ85kaDP/view
<https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-CR29-English-2.1.pdf>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6541702/>
- Online calculator: https://score.awellhealth.com/calculations/eortc_qlq_cr29

The EORTC QLQ-CR29 is a patient-reported outcome measure to evaluate health-related quality of life among colorectal cancer (CRC) patients in research and clinical practice. For the scoring rules see here: https://drive.google.com/file/d/16j3pr9bEVYBRa2tMp6B_2QLnxJ85kaDP/view.

The questionnaire includes 29 items, numbered 31 to 59. They are divided into two categories: items about symptoms (gastrointestinal, urinary, pain and others) and items about functions (sexual, body image and others) that are associated with CRC and its treatments. There are separate versions of items 49 to 54 for people with and without stomas, and item 55 is only for patients with a stoma. Items 56 and 57 are for men only, and items 58 and 59 are for women only.

All the QLQ-CR29 questions except one (item 48 requires a yes or no answer) have four possible answers. They are

- Not at all (1)
- A little (2)
- Quite a bit (3)
- Very much (4)

Those four levels are a Likert scale of four response categories and are linearly converted into a scale from 0 to 100 (ie 0,33,67,100 or 100,67,33,0). Patients are asked to indicate their symptoms during the past week except for the sexuality questions, which ask for the past four weeks.

Table: EORTC-QLQ-CR29 Functional Scales (0 is bad, 100 is good)

Scale	Scale name	Number of items	Item #	Question #	100 score at
Body_Image	BI	3	15,16,17	45,46,47	Not at all (1)
Anxiety	ANX	1	13	43	Not at all (1)
Weight	WEI	1	14	44	Not at all (1)
Sexual_interest_(men)	SEXM	1	26	56	Very much (4) [1]
Sexual_interest_(women)	SEXW	1	28	58	Very much (4) [1]

Table: EORTC-QLQ-CR29 Symptom scales (0 is good, 100 bad)

Scale	Scale name	Number of items	Item #	Question #	100 score at
Urinary_frequency	UF	2	1,2	31,32	Very much (4)
Blood_and_mucus_in_stool	BMS	2	8,9	38,39	Very much (4)
Stool_frequency*	SF	2	22,23	52,53	Very much (4)
Urinary_incontinence	UI	1	3	33	Very much (4)
Dysuria	DY	1	4	34	Very much (4)
Abdominal_pain	AP	1	5	35	Very much (4)
Buttock_pain	BP	1	6	36	Very much (4)
Bloating	BF	1	7	37	Very much (4)
Dry_mouth	DM	1	10	40	Very much (4)
Hair_loss	HL	1	11	41	Very much (4)
Taste	TA	1	12	42	Very much (4)
Flatulence*	FL	1	19	49	Very much (4)
Faecal_incontinence*	FI	1	20	50	Very much (4)
Sore_skin*	SS	1	21	51	Very much (4)
Embarrassment*	EMB	1	24	54	Very much (4)
Stoma_care_problems	STO	1	25	55	Very much (4)
Impotence	IMP	1	27	57	Very much (4)
Dyspareunia	DYS	1	29	59	Very much (4)

Table: EORTC-QLQ-CR29 Questions

#	#	Code	Question	Levels	Scale	Scale name	100 at	NB
31	1	EORTCQLQCR29_Q31	Did you urinate frequently during the day during the past week?	4	Symptom	Urinary frequency	Very much (4)	
32	2	EORTCQLQCR29_Q32	Did you urinate frequently during the night during the past week?	4	Symptom	Urinary frequency	Very much (4)	
33	3	EORTCQLQCR29_Q33	Have you had any unintentional release (leakage) of urine during the past week?	4	Symptom	Urinary incontinence	Very much (4)	
34	4	EORTCQLQCR29_Q34	Did you have pain when you urinated during the past week?	4	Symptom	Dysuria	Very much (4)	
35	5	EORTCQLQCR29_Q35	Did you have abdominal pain during the past week?	4	Symptom	Abdominal pain	Very much (4)	
36	6	EORTCQLQCR29_Q36	Did you have pain in your buttocks/anal area/rectum during the past week?	4	Symptom	Buttock pain	Very much (4)	
37	7	EORTCQLQCR29_Q37	Did you have a bloated feeling in your abdomen during the past week?	4	Symptom	Bloating	Very much (4)	
38	8	EORTCQLQCR29_Q38	Have you had blood in your stools during the past week??	4	Symptom	Blood and mucus in stool	Very much (4)	
39	9	EORTCQLQCR29_Q39	Have you had mucus in your stools during the past week??	4	Symptom	Blood and mucus in stool	Very much (4)	
40	10	EORTCQLQCR29_Q40	Did you have a dry mouth during the past week?	4	Symptom	Dry mouth	Very much (4)	
41	11	EORTCQLQCR29_Q41	Have you lost hair as a result of your treatment during the past week?	4	Symptom	Hair loss	Very much (4)	
42	12	EORTCQLQCR29_Q42	Have you had problems with your sense of taste during the past week?	4	Symptom	Taste	Very much (4)	
43	13	EORTCQLQCR29_Q43	Were you worried about your health in the future during the past week?	4	Functional	Anxiety	Not at all (1)	
44	14	EORTCQLQCR29_Q44	Have you worried about your weight during the past week?	4	Functional	Weight	Not at all (1)	

45	15	EORTCQLQCR29_Q45	Have you felt physically less attractive as a result of your disease or treatment during the past week?	4	Functional	Body Image	Not at all (1)	
46	16	EORTCQLQCR29_Q46	Have you been feeling less feminine/masculine as a result of your disease or treatment during the past week?	4	Functional	Body Image	Not at all (1)	
47	17	EORTCQLQCR29_Q47	Have you been dissatisfied with your body during the past week?	4	Functional	Body Image	Not at all (1)	
48	18	EORTCQLQCR29_Q48	Do you have a stoma bag (colostomy/ileostomy)?	2	n/a	n/a	Very much (4)	
49	19	EORTCQLQCR29_Q49_NO_STOMA	Have you had unintentional release of gas/flatulence from your back passage during the past week?	4	Symptom	Flatulence*	Very much (4)	[1]
49	19	EORTCQLQCR29_Q49_STOMA	Have you had unintentional release of gas/flatulence from your stoma bag during the past week?	4	Symptom	Flatulence*	Very much (4)	[2]
50	20	EORTCQLQCR29_Q50_NO_STOMA	Have you had leakage of stools from your back passage during the past week?	4	Symptom	Faecal incontinence*	Very much (4)	[1]
50	20	EORTCQLQCR29_Q50_STOMA	Have you had leakage of stools from your stoma bag during the past week?	4	Symptom	Faecal incontinence*	Very much (4)	[2]
51	21	EORTCQLQCR29_Q51_NO_STOMA	Have you had sore skin around your anal area during the past week?	4	Symptom	Sore skin*	Very much (4)	[1]
51	21	EORTCQLQCR29_Q51_STOMA	Have you had sore skin around your stoma during the past week?	4	Symptom	Sore skin*	Very much (4)	[2]
52	22	EORTCQLQCR29_Q52_NO_STOMA	Did frequent bowel movements occur during the day during the past week?	4	Symptom	Stool frequency*	Very much (4)	[1]
52	22	EORTCQLQCR29_Q52_STOMA	Did frequent bag changes occur during the day during the past week?	4	Symptom	Stool frequency*	Very much (4)	[2]
53	23	EORTCQLQCR29_Q53_NO_STOMA	Did frequent bowel movements occur during the night during the past week?	4	Symptom	Stool frequency*	Very much (4)	[1]
53	23	EORTCQLQCR29_Q53_STOMA	Did frequent bag changes occur during the night during the past week?	4	Symptom	Stool frequency*	Very much (4)	[2]
54	24	EORTCQLQCR29_Q54_NO_STOMA	Did you feel embarrassed because of your bowel movement during the past week?	4	Symptom	Embarrassment*	Very much (4)	[1]
54	24	EORTCQLQCR29_Q54_STOMA	Did you feel embarrassed because of your stoma during the past week?	4	Symptom	Embarrassment*	Very much (4)	[2]
55	25	EORTCQLQCR29_Q55_STOMA	Did you have problems caring for your stoma during the past week?	4	Symptom	Stoma care problems	Very much (4)	[2]
56	26	EORTCQLQCR29_Q56	To what extent were you interested in sex during the past four weeks?	4	Functional	Sexual interest (men)	Very much (4)	[3]
57	27	EORTCQLQCR29_Q57	Did you have difficulty getting or maintaining an erection during the past four weeks?	4	Symptom	Impotence	Very much (4)	[3]
58	28	EORTCQLQCR29_Q58	To what extent were you interested in sex during the past four weeks?	4	Functional	Sexual interest (women)	Very much (4)	[4]
59	29	EORTCQLQCR29_Q59	Did you have pain or discomfort during intercourse during the past four weeks?	4	Symptom	Dyspareunia	Very much (4)	[4]

[1] Answer this question only when you DO NOT have a stoma bag.

[2] Answer this question only when you have a stoma bag.

[3] For men only.

[4] For women only

17.3 HADS

- Sources: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5700594>, <https://academic.oup.com/occmed/article/64/5/393/1436876>, <https://score.awellhealth.com/calculations/hads/documentation>
- Online calculator: <https://score.awellhealth.com/calculations/hads>
- Note: HADS is a generated score in the SITU RedCap for this project.

The HADS questionnaire measures hospital anxiety or depression level.

It has fourteen questions divided into two subscales. There are seven questions for one subscale (depression) and seven questions for the other (anxiety). Scoring for each item ranges from zero to

three, with three denoting highest anxiety or depression level. So depression ranges from 0 (good) to 21 (bad), and anxiety ranges from 0 (good) to 21 (bad). A score of more than 8 means considerable symptoms of anxiety or depression.

Table: items on the questionnaire that relate to anxiety

QUESTIONS	ANSWERS	SCORE
I feel tense or wound up	Most of the time; A lot of the time; From time to time, occasionally; Not at all	3-0
I get a sort of frightened feeling as if something awful is about to happen	Very definitely and quite badly; Yes, but not too badly; A little, but it doesn't worry me; Not at all	3-0
Worrying thoughts go through my mind	A great deal of the time; A lot of the time; From time to time, but not too often; Only occasionally	3-0
I can sit at ease and feel relaxed	Definitely; Usually; Not often; Not at all	0-3
I get a sort of frightened feeling like 'butterflies' in the stomach	Not at all; occasionally; Quite often; Very often	0-3
I feel restless as I have to be on the move	Very much indeed; Quite a lot; Not very much; Not at all	3-0
I get sudden feelings of panic	Very often indeed; Quite often; Not very often; Not at all	3-0

Table: items on the questionnaire that relate to depression

QUESTIONS	ANSWERS	SCORE
I still enjoy the things I used to enjoy	Definitely as much; Not quite so much; Only a little; Hardly at all	0-3
I can laugh and see the funny side of things	As much as I always could; Not quite so much now; Definitely not so much now; Not at all	0-3
I feel cheerful	Not at all; Not often; Sometimes; Most of the time	3-0
I feel as if I am slowed down	Nearly all the time; Very often; Sometimes; Not at all	3-0
I have lost interest in my appearance	Definitely; I don't take as much care as I should; I may not take quite as much care ; I take just as much care as ever	3-0
I look forward with enjoyment to things	As much as I ever did; Rather less than I used to; Definitely less than I used to; Hardly at all	0-3
I can enjoy a good book or radio or TV program	Often; Sometimes; Not often; Very seldom	0-3

18. APPENDIX: SCREENSHOT OF EORTC-QLQ-CR29 QUESTIONNAIRE

Table: Image of questionnaire EORTC-QLQ-CR29

EORTC QLQ - CR29				
<p>Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.</p>				
<p>During the past week:</p>				
	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4
<p>During the past week:</p>				
	Not at All	A Little	Quite a Bit	Very Much
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

Please go on to the next page				
<p>During the past week:</p>				
	Not at All	A Little	Quite a Bit	Very Much
<p>Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:</p>				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4
<p>Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:</p>				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4
<p>During the past 4 weeks:</p>				
	Not at All	A Little	Quite a Bit	Very Much
<p>For men only:</p>				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4
<p>For women only:</p>				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

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<https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-CR29-English-2.1.pdf>

19. APPENDIX: SCREENSHOT OF HADS QUESTIONNAIRE

Table: Image of HADS questionnaire

Hospital Anxiety and Depression Scale (HADS)			
Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.			
D	A	D	A
I feel tense or 'wound up':		I feel as if I am slowed down:	
3	Most of the time	3	Nearly all the time
2	A lot of the time	2	Very often
1	From time to time, occasionally	1	Sometimes
0	Not at all	0	Not at all
I still enjoy the things I used to enjoy:		I get a sort of frightened feeling like 'butterflies' in the stomach:	
0	Definitely as much	0	Not at all
1	Not quite so much	1	Occasionally
2	Only a little	2	Quite Often
3	Hardly at all	3	Very Often
I get a sort of frightened feeling as if something awful is about to happen:		I have lost interest in my appearance:	
3	Very definitely and quite badly	3	Definitely
2	Yes, but not too badly	2	I don't take as much care as I should
1	A little, but it doesn't worry me	1	I may not take quite as much care
0	Not at all	0	I take just as much care as ever
I can laugh and see the funny side of things:		I feel restless as I have to be on the move:	
0	As much as I always could	3	Very much indeed
1	Not quite so much now	2	Quite a lot
2	Definitely not so much now	1	Not very much
3	Not at all	0	Not at all
Worrying thoughts go through my mind:		I look forward with enjoyment to things:	
3	A great deal of the time	0	As much as I ever did
2	A lot of the time	1	Rather less than I used to
1	From time to time, but not too often	2	Definitely less than I used to
0	Only occasionally	3	Hardly at all
I feel cheerful:		I get sudden feelings of panic:	
3	Not at all	3	Very often indeed
2	Not often	2	Quite often
1	Sometimes	1	Not very often
0	Most of the time	0	Not at all
I can sit at ease and feel relaxed:		I can enjoy a good book or radio or TV program:	
0	Definitely	0	Often
1	Usually	1	Sometimes
2	Not Often	2	Not often
3	Not at all	3	Very seldom

Please check you have answered all the questions

Scoring:
 Total score: Depression (D) _____ Anxiety (A) _____
 0-7 = Normal
 8-10 = Borderline abnormal (borderline case)
 11-21 = Abnormal (case)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5700594/>

20. APPENDIX: LINEAR MIXED MODEL THEORY

20.1 Linear mixed models: links

See <https://stats.oarc.ucla.edu/other/mult-pkg/introduction-to-linear-mixed-models/>

20.2 Linear mixed models: the theory

The formula is:

$$y=xb+zu+e$$

where

Symbol	Description	Type
ny	number of values of the outcome variable	Scalar
np	number of predictor variables	Scalar
nj	number of groups	Scalar
nq	number of random intercepts per group	Scalar
y	outcome variable	ny x 1 vector
x	predictor variables aka fixed-effects variables,	ny x np matrix
b	fixed-effects regression coefficients (parameters)	np x 1 vector
z	random effects variables	ny x nj matrix
u	random-effects regression coefficients	nj x 1 vector
e	residuals (error)	ny x 1 vector

20.3 Linear mixed models: worked example

Consider this scenario:

Arm (J=2) indexed by the j subscript each see nj patients. So our grouping variable is the arm. Each arm sees 36 patients. The total number of patients is the sum of the patients seen by each arm. In our example, N=72, so 72 patients were seen by two arms. Our outcome is a continuous variable, output weight. Furthermore we have 3 fixed effects predictors, baseline value, timepoint, and stratification variable, plus a fixed intercept and one random intercept (q=1) for each of the J=2 arms. For simplicity, we are only going to consider random intercepts. We will let every other effect be fixed for now. The reason we want any random effects is because we expect that output weights within arms may be correlated.

So the formula is

$$y=xb+zu+e$$

That gives us this table below:

Symbol	Description	Type
ny	number of values of the outcome variable	72
np	number of predictor variables	4
nj	number of groups	2
nq	number of random intercepts per group	1
y	outcome variable	72 x 1 vector
x	Four predictor variables aka fixed-effects variables, <ul style="list-style-type: none"> Fixed intercept baseline value, timepoint, stratification variable 	72 x 4 matrix
b	fixed-effects regression coefficients (parameters)	4 x 1 vector
z	One random effects variable <ul style="list-style-type: none"> Random intercept 	72 x (1x2) matrix
u	random-effects regression coefficients	2 x 1 vector
e	residuals (error)	72 x 1 vector

21. APPENDIX: USE OF THE WORD “LINEAR” IN LINEAR MODELS

The word “linear” in “linear models” refers to the parameters, not the variables: it can cope with quadratic equations

- <https://www.quora.com/Why-is-linear-regression-called-linear-if-we-can-use-quadratic-equations-in-our-model-which-gives-a-curved-line>
- <https://www.quora.com/Why-is-it-still-called-linear-regression-even-if-we-choose-a-polynomial-of-a-higher-degree-for-the-hypothesis>

22. APPENDIX: LOOKUP TABLE

The type of a variable can be used to deduce the variable distribution - for example a variable measuring strength may have a Gamma distribution and a frequency variable may have a Poisson. For the avoidance of doubt we shall graph it as well.

When the variable type and distribution is known, the lookup tables below can be used to deduce which model is needed and which code can be used to do that. Stata code is shown for convenience, although SAS or R code would also suffice. See the Stata help documentation for more details

22.1 GLMs

#	Variable Type	Distribution	Link Fn	Example Stata Code ^{†††}
1	Continuous (Normal)	Gaussian	Identity	glm depvar indepvars, family(gaussian) link(identity)
2	Continuous (SPC) [†]	Inverse Gaussian	Power -2	glm depvar indepvars, family(igaussian) link(power -2)
3	Binary	Binomial (multiple) or Bernoulli (single)	Logit	glm depvar indepvars, family(binomial) link(logit)
4	Count/Rate (Poisson)	Poisson	Log	glm depvar indepvars, family(poisson) link(log)
5	Count/Rate (NB)	Negative binomial	Log	glm depvar indepvars, family(nbinomial) link(log)
6	Continuous (SPC) [†]	Gamma	Power -1	glm depvar indepvars, family(gamma) link(power -1)
6	Continuous (Time)	Gamma?	Power -1?	glm depvar indepvars, family(gamma) link(power -1)
99	Time-to-event	Exponential ^{††}	Log	glm depvar indepvars, family(exponential) link(log)

[†] SPC = Skewed positive continuous variable.

^{††} Not available in Stata. Code shown is synthetic. GLMs in this case would require another language

^{†††} For a full list of families, link functions in Stata and their valid combinations, please see Stata help. Note that “inverse” is the same as “power -1”, “inverse squared” is the same as “power -2”, and so on

22.2 Non-GLMs if GLMs cannot cope or are inferior

Variable Type	Distribution	Link Function	Example Stata Code
Binary (Bernoulli)	Bernoulli	Logit (log-odds)	logit depvar indepvars, family(binomial) link(logit)
Binary (Probit)	Probit	Probit (CDF of standard normal)	probit depvar indepvars, family(binomial) link(probit)
Categorical (Nominal)	Multinomial	Logit	mlogit depvar indepvars, basecategory(1)
Categorical (Ordinal)	Categorical	Probit	ologit depvar indepvars
Categorical (Ordinal)	Cumulative logit	Logit (log-odds)	ologit depvar indepvars, family(ordinal) link(logit)
Categorical (Ordinal)	Proportional odds	Logit (log-odds)	ologit depvar indepvars, family(ordinal) link(logit)
Continuous (Normal)	Normal	Identity (linear)	reg depvar indepvars, family(gaussian) link(identity)
Count/Rate (NB)	Negative binomial	Log	nbreg depvar indepvars, family(nbinomial) link(log)
Count/Rate (Poisson)	Poisson	Log	poisson depvar indepvars, family(poisson) link(log)

22.3 Time-to-event models

Variable Type	Details	Example Stata Code
Time-to-event	Cox Proportional Hazards Model	stset depvar failure(eventvar==1) [†] stcox indepvars
Time-to-event	Parametric survival models, named distribution	stset depvar failure(eventvar==1) [†] streg indepvars, distribution(named distn) ^{††}

[†] depvar would be the time-to-event variable, eventvar=0 if censored, 1 if not

^{††} named distributions currently supported by Stata are exponential, Weibull, Gompertz, lognormal, loglogistic, and ggamma (short for generalized gamma). “Streg” can handle frailty and accelerated-failure-time models as well as proportional hazards models. See Stata help on “streg” for details

22.4 Green, JA (2021)

The paper Green, JA (2021) (see[5] for more details) also gave a guide for which variable types would need which families. This guide can be used in tandem with the tables above

Variable Type	Family
Count variables	Poisson
Count variables	Negative Binomial
Count variables with excess zeros	Zero-Inflated Poisson
Count variables with excess zeros	Zero-Inflated Negative Binomial
Count variables with excess zeros	Hurdle Models
Overdispersed count variables	Quasi-Poisson
Overdispersed count variables	Quasi-Negative Binomial
Overdispersed count variables	Quasi-Binomial
Continuous skewed variables	Gamma

23. APPENDIX: CATEGORICAL, BINARY, CONTINUOUS

Consider the following synthetic example designed for illustration purposes

Table: synthetic example

ID	Weight	EORTC QLQ-CR29 Category	Not at all	A bit	Quite a bit	StomaBagY/N
yyyyyyy1	4.4	AbdominalPain	1	0	0	1
yyyyyyy2	4.4	AbdominalPain	1	0	0	0
yyyyyyy3	4.2	BloodInStools	0	1	0	0
yyyyyyy4	2.1	DryMouth	0	0	1	1
yyyyyyy5	4.2	DryMouth	0	0	1	1

23.1 Continuous

This can be considered as a continuous variable that can be modelled with one model

Continuous variable

Continuous variable	Mean Weight
Weight	3.86

23.2 Categorical and binary

Or as a categorical variable with a count/rate that can be modelled with three models

Categorical and binary: a variable with three categories, each with a count/rate

Category	Count/rate
AbdominalPain	2/5
BloodInStools	1/5
DryMouth	2/5

23.3 Categorical and continuous

Or as a categorical variable with three categories, each holding a continuous variable. This can be modelled with one model

Categorical and continuous: a variable with three categories, each with a continuous variable

Category	Mean Weight
AbdominalPain	4.4
BloodInStools	4.2
DryMouth	3.15

23.4 Binary

Or as a binary variable that can be modelled with one model

Binary variable

Binary variable	Count/rate
StomaBagY/N	3/5

24. APPENDIX: ABSOLUTE VS RELATIVE

The results of the study are depicted as absolute and relative values, although not all variables will be depicted as both. As for the meaning of “absolute” and “relative”, we take our lead from the protocol. It says that *“Continuous variables will be summarised using means, standard deviations, and 95% confidence intervals. Medians with interquartile ranges will be presented where appropriate. Categorical variables will be summarised using counts and percentages.”*

For examples of the absolute vs relative distinction for effect size, please see “Appendix: Worked Examples Of Morbidity”

24.1 Continuous

As per protocol this is a mean and standard deviation (SD). Our synthetic example looks like this.

Continuous variable

Continuous variable	Mean Weight (SD)
Weight	3.86 (1.64)

24.2 Categorical and binary

As per protocol, this is a count and percentage. Our synthetic example looks like this.

Categorical and binary: a variable with three categories, each with a count/rate

Category	Count/rate
AbdominalPain	2 (40%)
BloodInStools	1 (10%)
DryMouth	2 (40%)
Total	5 (100%)

24.3 Categorical and continuous

As per protocol this is a mean and standard deviation (SD). Our synthetic example looks like this.

Categorical and continuous: a variable with three categories, each with a continuous variable

Category	Mean Weight (SD)
AbdominalPain	4.4 (1.6)
BloodInStools	4.2 (0)
DryMouth	3.15 (1.1)

24.4 Binary

As per protocol this is a mean and standard deviation (SD). Our synthetic example looks like this.

Binary variable

Binary variable	Count/rate
StomaBagY/N	3 (60%)
Total	5 (100%)

24.5 Discrete

As per protocol, this is a median and interquartile range. We do not have a synthetic example for this.

25. APPENDIX: GENERALIZED LINEAR MODEL THEORY

In statistics, a generalized linear model (GLM) is a flexible generalization of ordinary linear regression (LR).

A ordinary linear regression connects the input variables to the dependent variable via one function. But a GLM uses two functions: the variance function and the link function. This allows the linear model to be related to the response variable via a link function and allows the magnitude of the variance of each measurement to be a function of its predicted value.

Table: distributions and link functions for a GLM

Distribution	Variance Function	Typical Link Function
Normal	$V(\mu) = 1$	Identity: $g(\mu) = \mu$
Binomial	$V(\mu) = \mu(1-\mu)$	Logit: $g(\mu) = \log(\mu/(1-\mu))$
Poisson	$V(\mu) = \mu$	Log: $g(\mu) = \log(\mu)$
Gamma	$V(\mu) = \mu^2$	Inverse: $g(\mu) = 1/\mu$ or Log: $g(\mu) = \log(\mu)$
Inverse Gaussian	$V(\mu) = \mu^3$	Inverse squared: $g(\mu) = 1/\mu^2$
Negative Binomial	$V(\mu) = \mu + \alpha\mu^2$	Log: $g(\mu) = \log(\mu)$

26. APPENDIX: WORKED EXAMPLES OF MORBIDITY

The display of morbidity data can be difficult because problems arise when the morbidity has subdivisions or the data is displayed by patient not complications. To make things easier we provide worked examples below.

Firstly, let us build a synthetic example. This is an example designed for illustration purposes and it looks like this:

Synthetic example part 1: Control arm. three patients, four complications

Patient ID	Complication morbidity grade	Date of complication	Date of discharge	Date difference
xxxxxxx1	I	01Aug2024	15Aug2024	-14
xxxxxxx1	I	01Aug2024	15Aug2024	-14
xxxxxxx2	IIIa	01Aug2024	15Jul2024	17
xxxxxxx3	IV	01Aug2024	15Jun2024	47

Synthetic example part 2: Intervention arm. three patients, four complications

Patient ID	Complication morbidity grade	Date of complication	Date of discharge	Date difference
Xxxxxxx4	I	01Aug2024	15Jul2024	17
Xxxxxxx4	II	01Aug2024	15Jul2024	17
Xxxxxxx5	IIIa	01Aug2024	15Jul2024	17
Xxxxxxx6	IIIb	01Aug2024	15Jun2024	47

26.1 Worked example of “Any morbidity”

The synthetic example gives us this table. It is a list of patients, not complications

#	Outcome Measures	Control	Intervention	Delta
2a	i. Any morbidity			
	At or prior to discharge	1 (33%)	0 (0%)	-1 (-33%)
	Between discharge and 30 days	1 (33%)	2 (66%)	+1 (+33%)
	Other	1 (33%)	1 (33%)	-
	Total	3 (100%)	3 (100%)	-
	At or prior to discharge OR between discharge and 30 days	2 (66%)	2 (66%)	-

26.2 Worked example of “Morbidity by grade (I, II, IIIa, IIIb, IVa, IVb)”

The synthetic example gives us this table. It is a list of patients, not complications

#	Outcome Measures	Control	Intervention	Delta
2b	ii. Morbidity by grade (I, II, IIIa, IIIb, IVa, IVb)			
	At least one Grade I	1 (33%)	1 (33%)	-
	At least one Grade II	0 (0%)	1 (33%)	+1 (+33%)
	At least one Grade III	1 (33%)	2 (66%)	+1 (+33%)
	At least one Grade IV	1 (33%)	0 (0%)	-
	Other	0 (0%)	0 (0%)	-
	Total	3 (100%)	3 (100%)	-

Note: because a patient can have more than one complication, this example does not add to 100%

26.3 Worked example of “Morbidity by highest grade (I, II, IIIa, IIIb, IVa, IVb)”

The synthetic example gives us this table. It is a list of patients, not complications

#	Outcome Measures	Control	Intervention	Delta
2d	iv Morbidity by highest grade			
	Number of patients whose highest grade is Grade I	1 (33%)	0 (0%)	-1 (-33%)
	Number of patients whose highest grade is Grade II	0 (0%)	1 (33%)	+1 (+33%)
	Number of patients whose highest grade is Grade III	1 (33%)	2 (66%)	+1 (+33%)
	Number of patients whose highest grade is Grade IV	1 (33%)	0 (0%)	-
	Other	0 (0%)	0 (0%)	-
	Total	3 (100%)	3 (100%)	-

Note: because a patient can only have one highest grade, this example adds to 100%