A Cluster Double Crossover Trial of Early Versus Delayed Aperient Use in Mechanically Ventilated, Enterally Fed Patients

Statistical Analysis Plan

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INTRODUCTION

Bowel management in the intensive care unit (ICU) is a generally overlooked, and both constipation and diarrhoea appear common in critical care patients.[1,2] Their causes are multi-factorial and associated with adverse outcomes. Constipation, defined as infrequent stool passing, can lead to patient discomfort, nausea, vomiting, and feed intolerance.[3-5] In the critical care setting this may manifest as agitation and increased sedation requirements, and it can lead to abdominal distension, which causes atelectasis and increases the risk of pneumonia.[6,7] On the more severe end of the spectrum, prolonged faecal loading leads to pseudo obstruction which can result in ileus and bowel perforation, and as a result, constipation may prolong ICU stay, mechanical ventilation duration and increase mortality.[5-7]

Similarly, diarrhoea in the critical care patient population can be detrimental. It impairs patient dignity and, clinically, it may reflect or contribute to malabsorption, electrolyte depletion, skin breakdown and associated infection.[6] Furthermore, it may raise cost of care by increasing nursing workload, C. difficile testing and prolonging ICU length of stay.[6] Lastly, faecal management devices used to manage diarrhoea are not risk free and can cause bleeding, infection, rectal mucosal injury, sphincter tone loss and colonic perforation.[6]

Prophylactic bowel regimens are commonly used to prevent possible constipation.[1] However, this use is not current supported by evidence, as research findings have yielded conflicting results. For example, some studies have shown that bowel regimens are effective in preventing and treating constipation, and associated with a decreased SOFA score, and ICU length of ICU stay.[8-11] On the other hand, a recent systematic review failed to show a

statistically significant reduction in the risk of constipation.[6] A randomized control trial also failed to demonstrate a reduction in the rate of complications related to constipation or diarrhoea, including rate of rectal tube insertion, development of ileus, duration of ventilation, length of stay or mortality.[7] Moreover, there is evidence that there is no correlation between constipation and adverse hospital outcomes, thus challenging the necessity of laxatives in the ICU.[12]

Two recent systematic reviews have demonstrated a number of issues with research in this area, which may partly explain the discrepancy in findings.[6,13] Firstly, there is a lack of high-quality randomized control trials – for example the total sample size across three studies included in a recent metanalysis was less than 500.[6] Secondly, the definition of constipation is variable between studies and moreover often conflated with non-defecation for pragmatic reasons.[3,5,8,11,14] However, this approach has been criticized as simplistic and lacking in clinical relevance as non-defecation does not necessarily correlate with adverse effects of constipation, and may reflect either gastrointestinal dysmotility or complete absorption of liquid feed.[6,15]

The goal of this cluster crossover randomised clinical trial is to evaluate the impact of two bowel regimen on the incidence of diarrhoea during ICU stay in mechanically ventilated and enterally fed adult patients. These bowel regimens are currently reflective of practice variation in different ICU worldwide. This trial is registered with ANZCTR (ACTRN12623000112662).

METHODS

Study design

Single centre cluster double crossover, registry-embedded randomized clinical trial comparing two bowel regimens in ICU among adult patients requiring mechanical ventilation and enterally fed. The protocol was approved by the Austin Health Human Research Ethics Committee (HREC), and informed consent was waived or an opt out process was followed according to local jurisdictions. No interim analyses were planned.

Study population

Patients aged 18 years or older requiring mechanical ventilation at any time during ICU admission, and enterally fed via a feeding tube were eligible for inclusion in the study. The following exclusion criteria was used: 1) expected discharge form ICU in less than 24 hours; 2) life expectancy less than 24 hours; 3) receiving palliative care; 4) primary reason for ICU admission was a gastrointestinal pathology, gastrointestinal surgery, diarrhoea, constipation, or spinal injury; 5) patient has or was at risk of hepatic encephalopathy requiring lactulose; 6) patient has existing extensive abdominopelvic debridement, plastic or muscle flaps; or 7) patients at the time of screening for eligibility were receiving extra-corporeal membrane oxygenation (ECMO) therapy or prone ventilation. Patients who were admitted and eligible on more than one occasion had only their first admission included for analysis.

Randomization and masking

The study compared two standard bowel regimens among adults requiring mechanical ventilation and enterally fed. One approach was a ‘delayed aperient use’ and the other was an ‘early aperient use’. Each pod within the ICU (four pods of 10 beds) used one approach for a 3-month treatment period and then switched to the alternative approach for the next 3 months. As this is a double crossover design, the total duration of intervention is 12-months. The pods were randomised to the order of treatment (e.g., early-delayed-early-delayed or deleyed-early-delayed-early) (**Figure 1**). Clinicians, and investigators were aware of group assignments.

Intervention

Study treatments were administered open-label in this unblinded trial. Irrespective of the therapy assigned to the pod, aperients could be used for a particular patient at any point if the treating physician considered this preferable. In the event of development of diarrhoea, aperients may be ceased at the discretion of the treating clinician.

Patients who remained in the ICU through the crossover period continued to receive their originally assigned treatment. No washout occurred between crossover periods. Aperient administration was stopped if enteral feeding was no longer required or if the patient developed diarrhoea as per the study definition, or if the patient was discharged from the ICU.

<u>Early aperient use arm</u>

Aperient administration commences at day 1 of enteral feed starting. The treatment is for one oral Coloxyl with senna (Docusate sodium 50 mg / Sennosides 8 mg) tablet twice daily, starting the day that enteral nutrition was

commenced and continued daily while enteral nutrition continues or until the development of diarrhoea while in the patient is in the intensive care unit. If no bowel action occurred by day 5 lactulose will be commenced at 20 ml twice daily via the nasogastric tube while the patient is in the intensive care unit.

Delayed aperient use arm

Aperient administration commences at day 6 of enteral feed starting. The treatment is for no laxatives are to be administered until day 6 of enteral nutrition, when one Coloxyl with senna (Docusate sodium 50 mg / Sennosides 8 mg) tablet twice daily will be commenced and administered daily while enteral nutrition continues or until the development of diarrhoea while in the patient is in the intensive care unit.

Data collection

All baseline demographic data, illness severity, and outcome of included patients are being collected from data submitted to the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Adult Patient Database. These data are routinely collected by trained ICU staff for quality assurance purposes.

Individual patient-level data on aperients use and diarrhoea, and additional clinical and laboratory data are being collected for all included patients from electronic medical records, medication charts, and electronic prescribing and pharmacy dispensing data. Data collection of patients who are still inpatients was ceased at 28 days after ICU admission.

Study outcomes

Primary outcome

The primary outcome is the number of patients who develop diarrhoea during their ICU admission. Diarrhoea is defined as greater the three liquid stools per day as described by Bristol Stool Form Scale type 6 (**Figure 2**).

Secondary outcomes

Secondary outcomes include:

- Days until first episode of diarrhoea;
- Number of days with diarrhoea;
- Days until first defecation;
- Insertion of a bowel management device because of within-ICU diarrhoea;
- Development of a paralytic ileus or bowel obstruction during hospital admission;
- Constipation as a complication that occurs during hospital admission (ICD-10 coding);
- Testing for clostridium difficile and incidence of patients with positive testing;
- ICU length of stay (days);
- Hospital length of stay (days);
- ICU mortality;
- Hospital mortality;
- 30-day mortality.

Adverse event reporting

Since aperients have been in widespread use in ICUs for many years, and most of the adverse events are tolerated in this population, the more significant event assessed in the trial is if the trial drug needs to be stopped because of some significant adverse event.

Sample size

The sample size was calculated to evaluate the impact of the intervention on the primary outcome, assuming a cluster double crossover design. Based on preliminary data, we assumed an incidence of diarrhoea of 15% in patients randomised to 'early aperient' group[16,17] and an absolute risk reduction of 7.7% between the intervention and control. Using a significance level of 0.05 and a power of 80%, the initial calculation indicated a requirement of 525 patients for an individual randomized trial. To account for the clustered design with four clusters and an intraclass correlation coefficient (ICC) of 0.02, a design effect of 1 + (m - 1) * ICC, where m is the average number of patients per cluster per period, was applied. Further, we adjusted for the correlation between measurements across four periods (two intervention and two control) using (1 - rho_c / (total_periods - 1)), where rho_c = 0.1 and total_periods = 4. After these adjustments, the effective sample size required was 880. From previous ICU data, we estimated that a one-year period would be sufficient to include the proposed sample size.

Analysis plan

Bayesian methods allow estimation of the probability of different magnitudes of treatment effect, which clinical researchers may interpret more easily than

statements from conventional frequentist statistical models about rejection or not of a null hypothesis.

Statistical analyses

All statistical analyses will be conducted on an intention–to–treat basis, with patients analysed according to their assigned treatment arms, except for cases lost to follow up or withdrawal of informed consent. No or minimal losses to follow–up for the primary outcome is anticipated. Complete–case analysis will be carried out for all the outcomes. However, if more than 5% of missing data were found for the primary outcome, a sensitivity analysis using multiple imputations and estimating–equation methods will be carried out. Multiple imputation will consider imputation models based on prognostic baseline and post-baseline variables under a missing at random assumption. All analyses will be performed using R v.4.3.3 (R Core Team, 2016, Vienna, Austria).

A Bayesian framework will be used for all analyses. All analyses for outcomes will use individual patient-level data, and all models will consider the pod as the cluster unit (random effect) and will include as fixed effects the treatment group (delayed vs. early aperients), and the order of administration of the treatments (1^{st}, 2^{nd}, 3^{rd} or 4^{th} period), to account for the order and secular time effect. If due to the small number of clusters there is no sufficient data to differentiate the order effect from the treatment effect, the order of administration will be removed from the model. In addition, the intra-cluster correlation coefficient, the intra-period correlation coefficient, and the intra-cluster intra-period correlation coefficient will be calculated.

All Bayesian models will be fitted with the integrated nested Laplace approximation (INLA), allowing the calculation of posterior effect estimates with

their 95% credible intervals (CrI), and the probability of benefit with the use of delayed aperients. The criterion for declaring benefit will be a probability greater than 0.975. The threshold of 0.975 was chosen by convention (analogous to an alpha of 0.025 in a one-sided frequentist comparison).

Prior distributions for individual treatment effects for all analyses described above will be neutral (weakly informative) (**Figure 3**). The following prior will be used for the treatment arms: Normal(0, 1). The prior is centred at 0, reflecting no expected effect a priori, and the standard deviation of 1 provides weak regularization, allowing the data to dominate the posterior distribution. The Intercept and random effect priors will be weakly informative and defined as t(3, 0, 2.5).

Baseline characteristics

A description of the baseline characteristics of the trial participants will be presented by treatment group and by period (**Table 1** and **2**). Discrete variables will be summarized as numbers (%). Percentages will be calculated according to the number of trial participants for whom data are available. Where values are missing, the denominator will be stated in the table and no assumptions or imputations will be made. Continuous variables will be summarized by either means and standard deviations (SD) or medians and interquartile ranges (IQR), according to the observed distribution of the variable.

Bowel regimen characteristics

Bowel regimen characteristics including aperients used will be reported according to the **Table 3**, and in the figures proposed below. Absolute differences between the groups with the respective 95% CrI will be calculated and presented.

Primary outcome

The primary outcome of incidence of diarrhoea during ICU admission will be modelled considering a Bayesian logistic regression model, reported as odds ratio with its 95% CrI.

Secondary outcomes

Binary secondary outcomes will be modelled considering a Bayesian logistic regression model, reported as odds ratio with its 95% CrI. Continuous outcomes will be modelled considering a Bayesian linear regression model, reported as mean difference with its 95% CrI. The 30-day mortality will be compared using Bayesian Cox proportional hazard model reported as hazard ratio with its 95% CrI, and in Kaplan-Meier curves. Outcomes will be reported in a specific table (**Table 4**).

Subgroup analysis

The interaction between the allocation group and the following pre-specified subgroups will be assessed in the model described above for the primary outcome:

- Age (≤ 65 vs. > 65 years);
- APACHE III score (≤ median vs. > median);
- Admission type (medical vs. surgical);
- Sepsis (yes or no);
- Shock (yes or no).

Sensitivity analysis

An additional analysis for the primary outcome will be carried out adjusting for APACHE III and for any other imbalanced variable at baseline.

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Table 1 – Baseline Characteristics of the Included Patients

	Delayed Aperients (*n* =)	Early Aperients (*n* =)
Age, years		
Female gender - no. (%)		
APACHE III score		
Total SOFA		
Type of admission - no. (%)		
Surgical		
Medical		
Acute renal failure - no. (%)		
Cardiac arrest - no. (%)		
Sepsis - no. (%)		
Shock - no. (%)		
ICU source of admission - no. (%)		
Operating room		
Emergency room		
Ward		
Other		
Admission diagnosis category - no. (%)		
Cardiovascular		
Respiratory		
Gastrointestinal		
Neurological		
Sepsis		
Trauma		
Surgical		
Other		
Co-existing disorders - no. (%)		
Diabetes		
Chronic respiratory failure		
Chronic cardiovascular disease		
Chronic kidney disease		
Immunosuppression		
Metastatic cancer		
Organ support during ICU stay - no. (%)		
Use of inotrope and/or vasopressor		
Renal replacement therapy		
Vital signs and laboratory tests in the first 24 hours		
Mean arterial pressure, mmHg		
Highest hear rate, bpm		
Urine output, millilitres		
pH		
PaO_2 / FiO_2		
Highest creatinine, µmol/L		
Lactate, mmol/L		

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

Abbreviations: APACHE is Acute Physiology and Chronic Health Evaluation; ICU is intensive care unit; SOFA is sequential organ failure assessment.

Table 2 – Baseline Characteristics of the Included Patients

	Period 1 Delayed Aperients (*n* =)	Period 2 Early Aperients (*n* =)	Period 1 Early Aperients (*n* =)	Period 2 Delayed Aperients (*n* =)
Age, years				
Female gender - no. (%)				
APACHE III score				
Total SOFA				
Type of admission - no. (%)				
Surgical				
Medical				
Acute renal failure - no. (%)				
Cardiac arrest - no. (%)				
Sepsis - no. (%)				
Shock - no. (%)				
ICU source of admission - no. (%)				
Operating room				
Emergency room				
Ward				
Other				
Admission diagnosis category - no. (%)				
Cardiovascular				
Respiratory				
Gastrointestinal				
Neurological				
Sepsis				
Trauma				
Surgical				
Other				
Co-existing disorders - no. (%)				
Diabetes				
Chronic respiratory failure				
Chronic cardiovascular disease				
Chronic kidney disease				
Immunosuppression				
Metastatic cancer				
Organ support during ICU stay - no. (%)				
Use of inotrope and/or vasopressor				
Renal replacement therapy				
Vital signs and laboratory tests in the first 24 hours				
Mean arterial pressure, mmHg				
Highest hear rate, bpm				
Urine output, millilitres				
pH				
PaO_2 / FiO_2				
Highest creatinine, µmol/L				
Lactate, mmol/L				

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.

Abbreviations: APACHE is Acute Physiology and Chronic Health Evaluation; ICU is intensive care unit; SOFA is sequential organ failure assessment.

Table 3 – Bowel Regimen Characteristics and Medications Used

	Delayed Aperients (*n* =)	Early Aperients (*n* =)	Absolute Difference (95% CrI)
Aperients			
Days until first dose			
Use of docusate sodium and sennosides – no. (%)			
Use of lactulose – no. (%)			
Required additional aperients – no. (%)			
Other medications			
Use of opioids – no. (%)			
Morphine			
Fentanyl			
Use of metronidazole – no. (%)			
Use of vancomycin – no. (%)			

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.
Abbreviations: CrI is credible interval.

Table 4 - Clinical Outcomes According to the Groups

	Delayed Aperients (*n* =)	Early Aperients (*n* =)	Effect Estimate (95% CrI)	Probability of Benefit, %
Primary outcome				
Diarrhoea during ICU stay			Odds Ratio	
Secondary outcomes				
Days until first episode of diarrhoea			Mean Difference	
Number of episodes of diarrhoea			Mean Difference	
Days until first defecation			Mean Difference	
Insertion of a bowel management device			Odds Ratio	
Development of a paralytic ileus or bowel obstruction			Odds Ratio	
Constipation			Odds Ratio	
Testing for clostridium difficile			Odds Ratio	
Positive result			Odds Ratio	
ICU length of stay, days			Mean Difference	
Hospital length of stay. days			Mean Difference	
ICU mortality - no. (%)			Odds Ratio	
Hospital mortality - no. (%)			Odds Ratio	
30-day mortality - no. (%)			Hazard Ratio	

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding. Denominators are shown when the overall sample size was not available.
Abbreviations: ICU is intensive care unit; CrI is credible interval.

Figure 1 – Study Design

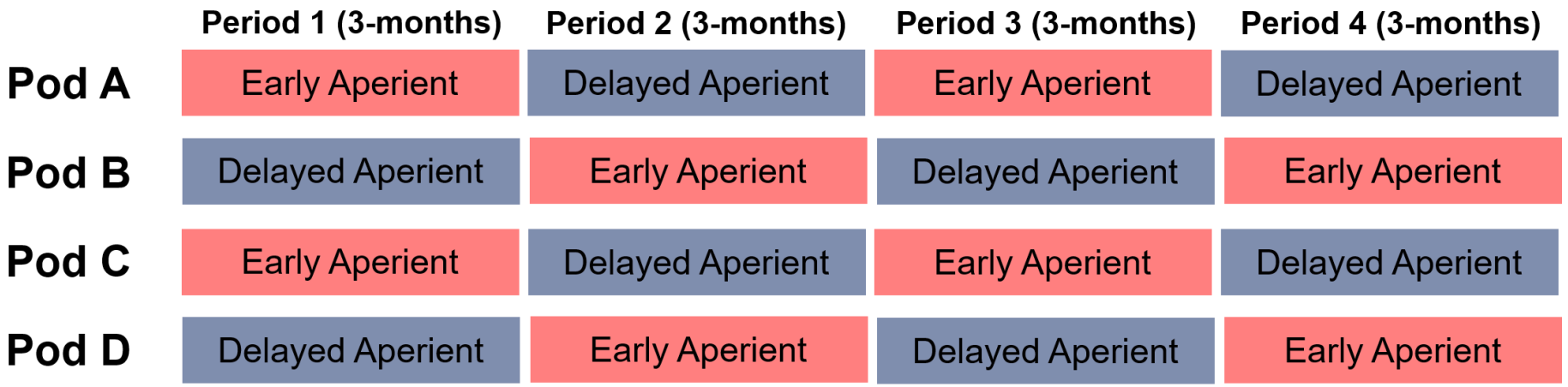
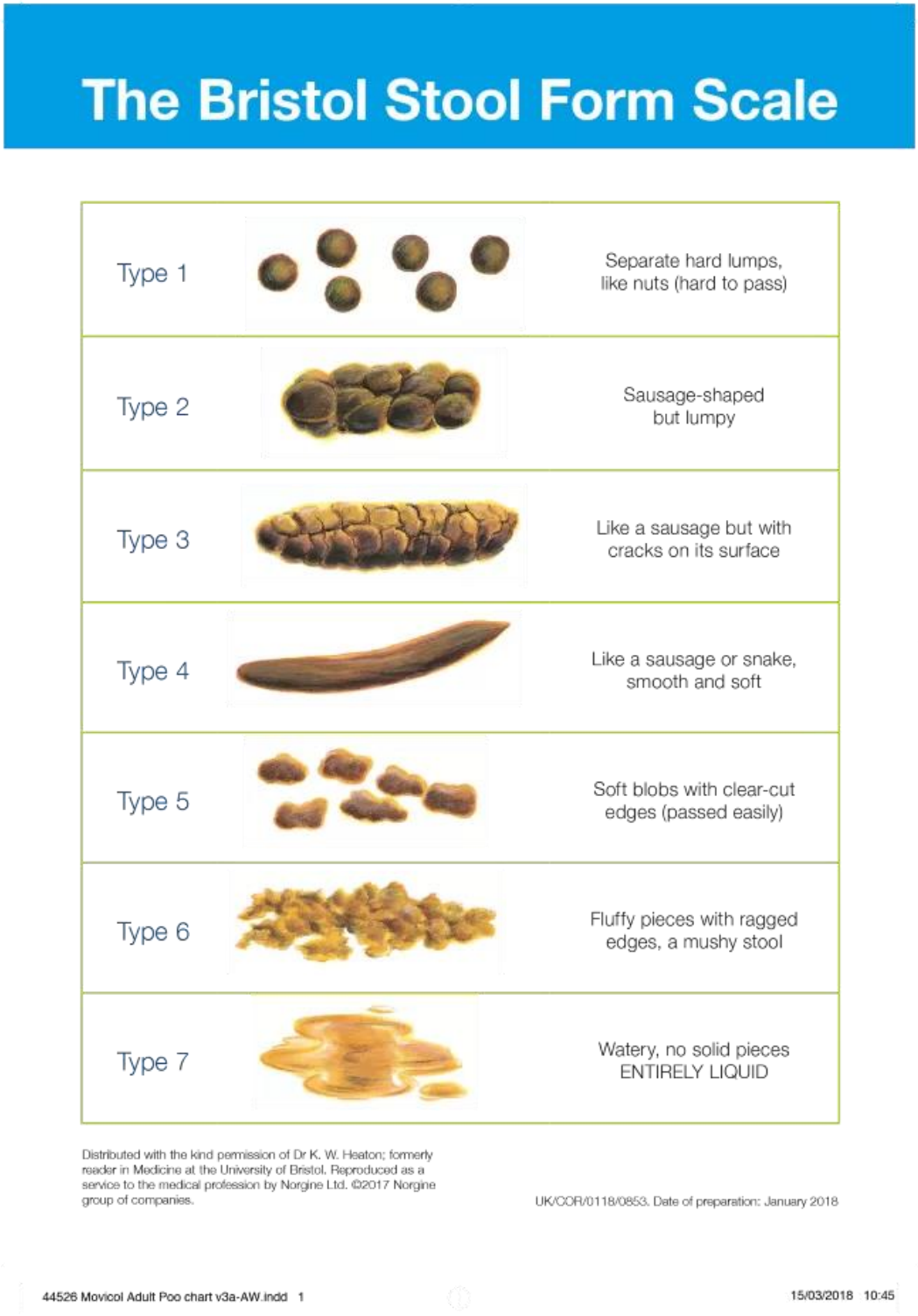


Figure 2 – Bristol Stool Form Scale



Diarrhoea is defined as greater the three liquid stools per day as described by Bristol Stool Form Scale type 6.

Figure 3 – Prior Distributions