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Routine monitoring of gastric residual for prevention of necrotising enterocolitis in preterm infants (Protocol)

Abiramalatha T, Thanigainathan S, Ninan B

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[Intervention Protocol]

Routine monitoring of gastric residual for prevention of necrotising enterocolitis in preterm infants

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

1. To assess the efficacy and safety of routine monitoring of gastric residual versus no monitoring of gastric residual on the incidence of necrotising enterocolitis (NEC) in preterm infants.

2. To assess the efficacy and safety of routine monitoring of gastric residual with two different criteria for interrupting feeds or decreasing feed volume on the incidence of NEC in preterm infants.

We will undertake subgroup analysis based on the gestational age (≤ 27 weeks, 28 weeks to 31 weeks, ≥ 32 weeks), birth weight (< 1000 g, 1000 g to 1499 g, ≥ 1500 g), small for gestational age versus appropriate for gestational age infants (classified using birth weight relative to the reference population), type of feeds the infant is receiving (human milk or formula milk), and frequency of monitoring of gastric residual (before every feed, before every third feed, etc) (Subgroup analysis and investigation of heterogeneity).

BACKGROUND

Description of the condition

Providing adequate nutrition is a key component of the health care of preterm neonates. There is increasing emphasis on early initiation and appropriate advancement of enteral feeds with the aim of achieving full volume enteral feeds at the earliest (Dutta 2015; Stevens 2016). The major hindrance to advancing feed volumes in preterm infants is feed intolerance and the risk of necrotising enterocolitis (NEC).

Feed intolerance is a common problem in preterm infants and is due to structural and functional immaturity of the gut of preterm infants. The preterm gut has decreased length, immature motility patterns and inadequate digestive and absorptive capacity, compared to term infants (Lucchini 2011). Feed intolerance causes frequent interruption and delayed advancement of enteral feeds resulting in protracted use of total parenteral nutrition (TPN) and central venous lines (CVL), increasing their complication rate (Hermansen 2005; Duro 2011; Kaur 2015). Delay in establishing

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full enteral feeds is a significant contributor to growth failure in preterm infants, resulting in neurodevelopmental impairment and long-term metabolic complications (Franz 2009; Embleton 2013; Stevens 2016).

Description of the intervention

Feed intolerance is variously defined by signs such as increased volume of gastric residual, altered gastric residual (bilious- or blood-stained), abdominal distension and/or emesis (Moore 2011). The use of gastric residual as an indicator of feed intolerance is controversial (Li 2014; Parker 2015).

Gastric residual is the measure of volume of milk along with gastro-intestinal secretions remaining in the stomach after a certain time interval. Increased gastric residual is common in preterm infants, due to the inherent immaturity of the gastro-intestinal system in the form of delayed gastric emptying, slower intestinal transit, inadequate secretion of gut hormones and enzymes and possible duodeno-gastric reflux (Ittmann 1992; Riezzo 2000). Apart from these intrinsic factors, some extrinsic factors such as formula feeds, certain drugs such as theophyllines, mydriatics and opioids, body position and sickness of the baby further delay gastric emptying, thus contributing to increased gastric residual (Malhotra 1992; Cohen 2004; Li 2014).

Routine monitoring of gastric residual (volume and/or colour) in preterm infants on gavage feeds is a common practice in many neonatal intensive care units (NICUs) and is used to guide advancement of gavage feeds (Gregory 2012). An increase in or altered gastric residual are putatively considered as signs of feed intolerance or early signs of NEC (Li 2014). Gastric residual becomes important when accompanied by other signs such as bilious vomiting, decreased bowel sounds, abdominal distension, abdominal wall erythema (redness of the skin), gross or occult blood in the stool, apnoea, bradycardia and temperature instability. The significance of increased gastric residual as an isolated finding is uncertain.

The volume and/or colour of the gastric residual that definitely indicates feed intolerance, or is predictive of NEC are unclear (Mihatsch 2002; Cobb 2004; Kenton 2004; Bertino 2009; Dutta 2015; Parker 2015). As a consequence, there is a wide variation in practice across NICUs. The various cut-offs used to define significant volume of gastric residual are $\geq$ 2 mL/kg of the infant's weight, > 2 mL or 3 mL depending on the infant's weight, > 30% of the previous feed volume or > 50% of the cumulative feed volume given during the time interval (Mihatsch 2002; Kaur 2015; Torrazza 2015; Grino 2016). Similarly, there is no standard recommendation for the frequency of assessment of gastric residual.

Increase in abdominal girth is the other commonly used sign of feed intolerance. An increase in abdominal girth of more than or equal to 2 cm is considered significant (Malhotra 1992; Lucchini 2011; Kaur 2015). However, the measurement of abdominal girth is highly prone to inter- and intra-observer variability. There is inadequate evidence to state abdominal girth as a reliable measure of feed tolerance (Dutta 2015).

How the intervention might work

There is some literature to suggest that an increase in/or an altered gastric residual may be predictive of NEC (Cobb 2004; Bertino 2009; Grino 2016). Withholding monitoring of gastric residual may take away the early indicator and thus may increase the risk of NEC and its complications, including mortality. Without aspiration at regular intervals, the gastric residual may accumulate in the stomach and cause gastric distension, increasing the risk of gastro-oesophageal reflux and aspiration pneumonia.

However, the use of gastric residual as a guide in the absence of uniform standards on its use, may lead to unnecessary delay in initiation and advancement of feeds or interruption of feeds in preterm infants (Shulman 2011; Kaur 2015). This may result in delay in reaching full enteral feeds, which in turn increase the duration of TPN and the risk of parenteral nutrition-associated liver disease (Duro 2011; Kaur 2015). It may also increase the number of days of CVL usage, thus increasing the risk of late-onset sepsis and other CVL-related complications (Hermansen 2005). The delay in achieving full enteral feeds increases the risk of extra-uterine growth restriction and neurodevelopmental impairment (Morris 1999; Franz 2009; Leppänen 2014). The negative pressure created by repeated aspirations, especially when the tip of the nasogastric (NG)/orogastric (OG) tube remains in the close contact with the gastric mucosa, has the potential to damage the gastric mucosa (Li 2014). Moreoever, the volume of the aspirated gastric residual may not be a reliable and accurate measure of residual gastric content and it varies with the baby's position, size of the nasogastric tube, aspiration technique and viscosity of feeds (Bartlett 2015; Parker 2015).

The other major confusion is whether to discard or to re-feed the aspirated gastric residual (Juvé-Udina 2009; Williams 2010; Dutta 2015). This question is being addressed in another Cochrane review (Abiramalatha 2017).

The gastric residual contains milk, gastro-intestinal enzymes and hormones that aid in digestion and promote gastro-intestinal motility and maturation, discarding which may have negative influence on the infant's gastro-intestinal system.

Why it is important to do this review

Given the potential use of gastric residual as an early indicator of NEC, as well the possible risks of its routine monitoring, we will undertake a systematic review that identifies and appraises data from randomised controlled trials, to provide a synthesis of evidence to inform practice and research. We have not found any existing systematic review of this topic.

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OBJECTIVES

1. To assess the efficacy and safety of routine monitoring of gastric residual versus no monitoring of gastric residual on the incidence of necrotising enterocolitis (NEC) in preterm infants.

2. To assess the efficacy and safety of routine monitoring of gastric residual with two different criteria for interrupting feeds or decreasing feed volume on the incidence of NEC in preterm infants.

We will undertake subgroup analysis based on the gestational age (≤ 27 weeks, 28 weeks to 31 weeks, ≥ 32 weeks), birth weight (< 1000 g, 1000 g to 1499 g, ≥ 1500 g), small for gestational age versus appropriate for gestational age infants (classified using birth weight relative to the reference population), type of feeds the infant is receiving (human milk or formula milk), and frequency of monitoring of gastric residual (before every feed, before every third feed, etc) (Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised trials and cluster-randomised trials will be included in the review.

Types of participants

Preterm (< 37 weeks' gestation) infants who do not have any overt sign of feed intolerance/NEC such as bilious vomiting, decreased bowel sounds, abdominal distension, abdominal wall erythema, gross or occult blood in the stool, apnoea, bradycardia or temperature instability.
The infant should be on gavage feeds (nasogastric (NG) tube). Randomisation should be done at the time of initiation of enteral feeds. Babies on respiratory support are also eligible, if they do not have any sign of feed intolerance/NEC.

Types of interventions

Comparison 1
Intervention: Routine monitoring of gastric residual to decide advancement of enteral feeds in infants who do not have any sign of feed intolerance/NEC.. Frequency of gastric residual monitoring could be at any time interval (for example, before every feed, before every third feed, etc) at the investigator's discretion.
Note: The investigator could have pre-defined criteria for the quantity and quality of gastric residual to decide feed interruption or for decreasing the feed volume.
Control: No routine monitoring of gastric residual in otherwise healthy babies until any sign of feed intolerance/NEC appears. The control group could be 'no routine monitoring for any sign of feed intolerance' or 'routine monitoring of other signs of feed intolerance such as increase in abdominal girth'.
Comparison 2
Monitoring of gastric residual is done in both the intervention and the control group and the decision on feeds (advancement/ continuation/ decrease/interruption) is based on two different pre-defined criteria of gastric residual. The criteria of gastric residual could be based on its quality and/or quantity.

Types of outcome measures

Primary outcomes

1. Number of infants with necrotising enterocolitis (NEC) stage 2 or 3 (Modified Bell's staging, Walsh 1986)
2. Time to establish full enteral feeds ≥ 150 mL/kg/day (days)

Secondary outcomes

1. Number of infants with surgical NEC
2. Time to regain birth weight (days) and subsequent rate of weight gain (g/kg/day), linear growth (cm/week) and increase in head circumference (cm/week) during the initial hospitalisation period
3. Number of infants with extra-uterine growth restriction at discharge (number of infants who remain below the 10th percentile for the index population for weight, length and head circumference)
4. Number of episodes of interruption of feeds (lasting ≥ 12 hours)
5. Number of days of total parenteral nutrition (TPN)
6. Number of infants with parenteral nutrition-associated liver disease
7. Number of days of central venous line (CVL) usage
8. Incidence of invasive infection as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, urine, or from a normally sterile body space
9. Number of infants with aspiration pneumonia or pneumonitis (clinical or radiological evidence of lower respiratory tract compromise that has been attributed to covert or evident aspiration of gastric contents).
10. Number of infants with gastro-oesophageal reflux diagnosed by (i) clinical features; post-feed (if bolus-fed) apnoea, desaturation, irritability, vomiting; or (ii) oesophageal pH monitoring, multiple intraluminal impedance or endoscopy.

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11. All-cause mortality before discharge or up to 44 weeks' postmenstrual age
12. Duration of hospital stay (days)
13. Growth measures following discharge from hospital to latest follow-up (weight, length and head circumference)
14. Neurodevelopmental outcomes assessed after 12 months corrected age: neurological evaluations; developmental scores; and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of one or more of the following: non-ambulant cerebral palsy; developmental quotient more than two standard deviations below the population mean; and blindness (visual acuity less than 6/60) or deafness (any hearing impairment requiring - or unimproved by - amplification).

Search methods for identification of studies

We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register).We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Electronic searches

We will conduct a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library; MEDLINE via PubMed (1996 to current); Embase (1980 to current); and CINAHL (1982 to current) using the following search terms: (gastric residual* OR aspirate*), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We will not apply language restrictions. We will search clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International Trials Registry and Platform, and the ISRCTN Registry).

Searching other resources

We will examine reference lists in the included studies. We will search the proceedings of the annual meetings of the Pediatric Academic Societies (1993 to present), the European Society for Paediatric Research (1995 to present), the Royal College of Paediatrics and Child Health (2000 to present), and the Perinatal Society of Australia and New Zealand (2000 to present). Trials reported only as abstracts will be eligible if sufficient information is available from the report, or from contact with the authors, to fulfil the inclusion criteria.
Additionally, we will review the reference lists of all identified articles for relevant articles not identified in the primary search.

Data collection and analysis

We will use the standard methods of Cochrane Neonatal and Cochrane (Higgins 2017).

Selection of studies

We will screen the title and abstract of all studies identified by the above search strategy and both review authors (TA and ST) will independently assess the full-text articles for all potentially relevant trials. We will exclude those studies that do not meet all of the inclusion criteria and we will state the reason for exclusion. We will discuss any disagreements until consensus is achieved.
We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009) and 'Characteristics of excluded studies' table.

Data extraction and management

Both review authors (TA and ST) will extract data independently using a data collection form to aid extraction of information on design, methodology, participants, interventions, outcomes and treatment effects from each included study. We will discuss any disagreements until we reach a consensus. If data from the trial reports are insufficient, we will contact the trialists for further information.

Assessment of risk of bias in included studies

Both review authors (TA and ST) will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2017) for the following domains.

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

Any disagreements will be resolved by discussion or by a third assessor. See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We will analyse the treatment effects in the individual trials using RevMan 2014 and report risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We will determine the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

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Unit of analysis issues

The unit of analysis will be the participating infant in individually-randomised trials. For cluster-randomised trials, we will undertake analysis at the level of the individual while accounting for the clustering in the data using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), or from another source (Higgins 2017). If ICCs from other sources are used, we plan to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we will synthesise the relevant information. We plan to combine the results where there is little heterogeneity between study designs and interactions between the effects of the intervention and the choice of randomisation unit is considered unlikely.

Dealing with missing data

We will request additional data from the trialists if data on important outcomes are missing or reported unclearly. Where data are still missing, we will examine the impact on effect size estimates in sensitivity analyses using the 'best-worst case scenario' technique.

Assessment of heterogeneity

We will examine the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We will calculate the I^2 statistic for each RR analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. Heterogeneity will be classified as none (< 25%); low (25% to 49%); moderate (50% to 74%); or high (≥ 75%). If we detect moderate or high heterogeneity ($I^2 \geq 50\%$), we will explore the possible causes (for example, differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

If 10 or more trials are included in a meta-analysis, we will examine a funnel plot for asymmetry.

Data synthesis

We will analyse all infants randomised on an intention-to-treat basis and treatment effects in the individual trials using a fixed-effect model to combine the data. For meta-analyses of categorical outcomes we plan to calculate typical estimates of RR and RD, each with 95% CIs; for continuous outcomes we plan to calculate the mean difference (MD) if outcomes are measured in the same way between trials, and standardised mean difference (SMD) to combine trials measuring the same outcome using different scales. We will determine the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD. Where meta-analysis is judged to be inappropriate, we will analyse and interpret individual trials separately.

Quality of evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: incidence of NEC and mortality.

Both review authors (TA and ST) will independently assess the quality of the evidence for each of the outcomes listed above. We will consider evidence from randomised controlled trials as high quality but downgrade the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We will use the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence. The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades.

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

1. Based on gestational age - ≤ 27 weeks, 28 weeks to 31 weeks, ≥ 32 weeks
2. Based on birth weight - < 1000 g, 1000 g to 1499 g, ≥ 1500 g
3. Small for gestational age versus appropriate for gestational age infants (classified using birth weight relative to the reference population)
4. Type of feeds the infant is receiving (human milk versus formula)
5. Frequency of monitoring of gastric residual (before every feed, before every third feed, etc)

Sensitivity analysis

We will undertake sensitivity analyses to determine if the findings are affected by including only studies of adequate methodology

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(low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up.

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The methods section of this protocol is based on a standard template used by Cochrane Neonatal.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Neonatal standard search strategy

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
Embase: ((exp infant) OR (infan* OR newborn or neonat* OR premature or very low birth weight or low birth weight or VLBW or LBW).mp AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp
CINAHL: (infan* OR newborn OR neonat* OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
CRS Web: (infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Risk of bias tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we will seek information regarding the method of randomisation, blinding and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Both review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the table 'Characteristics of included studies'. We will evaluate the following issues and enter the findings into the 'Risk of bias' table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?
For each included study, we will categorise the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?
For each included study, we will categorise the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk

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3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorise the methods as:

- low risk (< 20% missing data);
- high risk ($\geq$ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

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CONTRIBUTIONS OF AUTHORS

Both review authors contributed to the development of this protocol.

DECLARATIONS OF INTEREST

None known.

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