**Neonatal Stoma Refeeding Technique Protocol**

**Feasibility Study**

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**Date of Protocol:** 11/8/2020

**Protocol Number:** v2.0

**Study Sponsor:** TheInsides Company Limited.

**Investigation Site:** NICU - Neonatal Intensive Care Unit **-** Auckland City Hospital

 Other national NICU sites will be invited, including Christchurch Hospital

**Planned Commencement Date:**  July 2021

**Planned Conclusion Date:**  July 2023

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**Protocol History:**

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| **Version:** | **Reason for Amendment:** |
| **V0.21** | Protocol submitted to the ethics committee |
| **V1.0** | Re-submission of protocol after changes discussed in meeting with ethics committee on 26/01/21 |
| **V2.0** | Re-submission of protocol after changes discussed in meeting with ethics committee on 06/04/21 |

**Background**

Intestinal failure in neonatal and paediatric populations is an infrequent but burdensome condition associated with significant morbidity and mortality. Intestinal failure is defined as an impairment in gut function, creating an inability to absorb macronutrients, water, electrolytes, or a combination [1,2]. Short bowel syndrome secondary to massive intestinal resection is the most common cause of paediatric intestinal failure. Up to 50% of cases are due to necrotising enterocolitis, especially in premature neonates [3-6]. A small bowel double enterostomy is often performed in these cases at the time of resection, contributing to an insufficient functional gut length [3].

Small bowel double enterostomies often lead not only to intestinal failure but also high-output losses. Supportive therapy has two main goals: The first is to replace electrolytes and to minimise stoma output through restrictions in oral hypotonic fluids. The second goal is to suppress stoma output by using anti-secretory and anti-motility agents [1,2,7]. Due to the functional nutritional absorption impairment, parenteral nutrition may be required; however, the modality is associated with increased risks, including central line-associated bloodstream infections, cholestatic liver disease, metabolic complications, and thrombosis [5, 6, 8-18]. Also, this nutritional modality is exclusively administered in hospitals, leading to prolonged stays and increasing medical costs, currently estimated at US$100,000-$150,000 or more per patient per year [5,19]. The development of alternative therapy has the potential to benefit thousands of patients yearly, improve outcomes and reduce costs and risks.

Studies have shown that recycling chyme output from the proximal to distal double enterostomy limb is a beneficial therapeutic option in neonates, thus alleviating the burden from the above complications [3, 20-22]. Studies in adults have also demonstrated that the strategy is safe and beneficial [23]. The adoption of this practice is growing in popularity in the last years. However, this therapeutic option has been employed erratically in NICUs worldwide, with various indications, methods, and using repurposed materials.

This lack of uniformity creates practical challenges for the medical staff, most of whom do not consider the current options user-friendly. Recycling chyme requires nurses to dedicate some time to reinfuse the enteric material. The reinfusion is an easy process, but it requires manual effort and time from the staff. Furthermore, the literature currently presents a multitude of indication criteria, methods, supplies employed, and clinical outcomes. Creating a uniform protocol to optimise this therapeutic option will enable properly measuring the benefits associated with it. It will also make it more accessible and practical to be adopted by the medical staff.

Chyme reinfusion is often employed in Auckland, but using manual techniques that, as described above, are found to be time-consuming and inefficient for staff. In other New Zealand units, chyme reinfusion is undertaken in selected cases but faces similar obstacles and disincentives. New Zealand NICUs would benefit from improved methods and standard protocols for chyme reinfusion.

***Proposed Solution***

The development of a standardised protocol may encourage clinicians to employ the strategy according to objective indication criteria, using adequate methodology, utilising materials designed specifically for the purpose they were created for, and respecting safety guidelines.

Based on the literature, there are currently two therapeutic options: chyme recycling and prescribing parenteral nutrition while discarding the enteric material. Based on the literature review, it is found that chyme recycling has demonstrated numerous benefits compared with the therapeutic option more widely employed [3, 20-22]). The current challenge is to promote the chyme recycling option by making it more user friendly and less burdensome for the medical staff. Creating a standardised protocol will give further information on possible benefits associated with using a novel low-risk device developed explicitly for chyme reinfusion in the Neonatal Intensive Care Unit (NICU).

**Motives for Intervention:**

We aim to improve outcomes in neonates with enterostomies.

There are three main reasons to change therapeutic care currently being offered to neonates with high-output enterostomies and entero-atmospheric fistulas – 1. Reduce morbidity and mortality; 2. Reduce distal stoma atrophy and facilitate the intestinal anastomosis when the patient conditions improve; and 3. Reduce costs associated with lengthy hospital stays. Some of these difficulties can be reduced by using this therapeutic option, which is considered more physiological. A competing strategy – parenteral nutrition in conjunction with discarding the enteric material – is still employed today. It only exists due to some practical challenges associated with the chyme recycling option. The proposed protocol may reduce these challenges.

**Morbidity and Mortality**

These patients often suffer from dehydration, malnourishment, growth impairment, compromised immunity, and high infection rates. One study evaluated 175 premature neonates divided into two groups according to the presence of short bowel syndrome [6]. The group with short bowel syndrome suffered significantly higher morbidity than the group without it in all investigated variables (septic events, surgical complications, central venous line complications, cholestasis and liver failure, duration to adaptation and parenteral nutrition independence, and length of hospitalisation). The case fatality rate was 38% in patients with short bowel syndrome vs 13% in patients without it (p = .001). The two leading causes of death were liver failure and sepsis. These indicators refer to patients who underwent the traditional parenteral nutrition approach, as chyme recycling has only been proposed more recently.

**Distal stoma atrophy**

Due to the absence of chyme flow, which plays a significant role in the nutrition of the bowel’s inner layers, most patients develop distal gut atrophy, which imposes a technical challenge at reversal. A study with 68 neonates showed distal stoma stricture led to complications requiring further resection in 40% of the surviving individuals, alongside an additional 12% who required surgical anastomotic revision [21]. This complication is less frequent in patients who underwent chyme recycling than in recipients who had their enteral content discarded [20].

**Lengthy and expensive stays**

The prolonged use of parenteral (intravenous) nutrition prolongs the average stay and increases its costs. A study with 41 neonates in the U.S. found that the mean total cost of care for paediatric short bowel syndrome was US$505,250 for the first year of care alone [22]. Inpatient hospitalisation accounted for 82% of the total, and this was attributed to prolonged stays in intensive care units, numerous surgical interventions, and multiple readmissions during the first year of diagnosis. Hospital-based costs steadily declined in the following years, but, in contrast, home-care services, increased yearly for the first five years of diagnosis, reaching US$ 184,520 for a single year of home care. This increasing cost was attributed to rising complications of parenteral nutrition. The mean total cost of care per child over five years was US$ 1,619,851. Chyme recycling has been employed, and it has significantly reduced parenteral nutrition prescription, associated costs, and length of stay. However, the currently employed protocols vary widely, and some patients do not tolerate the approach, forcing intensivists to switch back to the parenteral nutrition option.

 **Study Objectives**

**Aim**

**To *develop* and *validate* a stoma refeeding protocol which utilises a novel device with the ultimate goals of enabling patients to: resume enteral nutrition, quit parenteral nutrition, gain weight, reduce distal enterostomy discrepancy in size, thus facilitating the reversal procedure.**

The stoma refeeding device is a simple directional flow appliance, which connects to three standard off-the-shelf components: i) an ordinary stoma bag on one side; ii) a standard syringe on the other side; iii) coupling to a traditional soft, flexible enteral feeding / nasogastric tube. The tube is inserted in the distal enterostomy to allow chyme reinfusion and enteral feeding when appropriate. The bottom of the device is equipped with a valve that enables the simple retrieval of accumulated chyme from the stoma bag when the syringe is drawn back. Pushing the plunger then reinfuses the content directly to the flexible catheter and distal limb, without reflux back to the bag. The use of a pump connected to the syringe may help to control the rate of infusion, thus reducing the likelihood of reflux. This presentation with a single access point gives the refeeding process a substantially improved clinical workflow, while also enabling the use of mechanical pumps to slowly reinfuse chyme into the distal bowel.

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Figure 1. Shows the directional flow appliance that will be used for chyme reinfusion in the study (left) and connected to a syringe (right). The device couples to a stoma bag and a reinfusion tube (not shown).

***Prior Research***

Feasibility studies by our group using a more complex concept in adults have been conducted with promising results [23]. Benchtop validation showed > 95% emptying completion with minimal disruption to the stoma point across a range of fluid viscosities. The adult device works well for patients on liquid, pureed and even low-residue diets. Neonates usually present liquid or semi-liquid enteric contents; therefore, issues with the system’s clogging due to high viscosity enteric contents are unlikely, even with the small calibre of the catheter, meaning that the same results can be achieved with a much simpler device.

**Hypothesis**

The current trial is a feasibility study conducted with the following hypothesis:

*The novel refeeding protocol which employs a novel device can safely and effectively return gut contents in a manner that is beneficial to patients and with an improved workflow for the clinical team.*

**Primary Objectives**

1. Validate the safety, effectiveness, and tolerability of a stoma refeeding device.
2. Evaluate the usability of the device in a NICU clinical workflow
3. Evaluate the adherence to the protocol by NICU staff

**Secondary Objective**

1. Obtain pilot clinical data on whether the chyme reinfusion device may reduce distal enterostomy incompatibility, facilitating later intestinal anastomosis.

**Study Design**

The study will involvea human feasibility study (up to 20 patients). Minor iterations may be required to optimise the design for ease and effectiveness of use during the trial.

**Study site(s):** NICU – Neonate intensive care unit -Auckland City Hospital (ADHB). Other NICUs will be invited to participate in the study in the near future including Christchurch Hospital.

**Inclusion Criteria:**

* Neonates with one or more small intestine stomas or entero-atmospheric fistula(s)
* Sufficient distal intestinal tract length able to handle chyme or enteral nutrition.
* Guardian able to understand the risks/benefits of the study.
* Guardian able to give informed consent.

**Exclusion Criteria:**

* Distal obstruction, anastomotic leak
* Inability to tolerate chyme reinfusion or enteral feeding.
* Clinical concern for ischaemic gut
* Inability to safely intubate the distal stoma.
* Septic or critically unwell patient

**Recruitment**

Patients with small bowel stoma(s) or an entero-atmospheric fistula(s) will be identified by the caring clinical team. Members of the clinical team who are not involved in the study (such as unit nurses) will approach parents, whānau and guardians to enquire if they may be interested in this study. In affirmative cases, their contacts will be sent to the investigators.

**Methods**

1. Patient’s parents, guardians, or whanau will be approached, with approval from the caring clinical team and invited to participate in this study. Upon gaining informed consent, guardians will authorise the inclusion in the stoma refeeding protocol, to be prescribed by intensivists or surgeons and performed by trained nurses.
2. Researchers will collect prospective data on the amount of chyme collected and discarded, the effectiveness of recycling, safety, rate of infusion, weight gain, adverse events, use of anti-secretory and anti-motility agents, and laboratory exams (A.L.P., G.G.T., bilirubin, electrolytes, haemoglobin, haematocrit, serum iron levels, albumin, urea, and creatinine) via clinical assessments.
3. Minor device improvements may be iteratively introduced during the trial until target performance is met; this is common practice in device feasibility studies.

**Outcomes:**

**Device performance criteria:** will be assessed with the support of our engineering team by structured reports by nurses, involving evaluations of stoma output quantity, reinfusion success rates, observation of any leakage, inspection for device wear/failures and successful interface with the bag, tube and enterostomy. Compatibility with existing products will be assessed. All data will be recorded onto study proforma.

**Nurse factors** will be assessed by a custom questionnaire employing Likert scales and free-text boxes for thematic analyses, encompassing ease of use, impact on workflow, need for maintenance, and days to proficiency. During the study, the device will only be operated by both the medical team.

**Clinical outcomes** will be recorded to help inform future controlled trials, recording stoma problems (e.g. leak/peri-stomal skin rash), hydration status, electrolytic imbalance, length of hospital stay, weight, use of parenteral nutrition, technical success and ease vs difficulty of anastomosis surgery (Likert scale), and bowel function (regain of bowel continuity).

**Safety** of participants will be monitored by the team daily with oversight by the high-risk register of the ADHB Research Review Committee, with monthly recruitment updates and adverse events all being reported. Urgent clinical assessment will be arranged if any concerns arise. Additionally, nursing staff and guardians will be given the contact details of one of the investigators to troubleshoot any problems, with study members being available at all times. Patients will be monitored for signs; the health of the bowel and peri-stomal skin will be inspected at least every three days. If the stoma refeeding device causes any adverse event or the patient’s guardian wants to exit the trial, the device will be removed, and the stoma managed with traditional clinical methods. Serious adverse events are not anticipated because it is a simple external low-risk directional flow appliance. Still, they will be immediately reported to the R.R.C., and the trial paused for evaluation if necessary.

**Patient population:**

The study population will consist of up to 20 subjects for the initial neonate feasibility study.

**Consent process**

Guardians will be approached and individually consented by a study researcher after their child’s intestinal operation. Both verbal and written information will be provided to ensure informed consent. The experimental nature of this device will be explained. The patient will be given the contact details (email and phone) of at least one of the investigators to troubleshoot any concerns, including withdrawal from the study.

**Withdrawal of consent**

Guardians/whānau are entitled to terminate the participation of their children in the study and withdraw their consent at any time, without providing any reason, and without there being any consequences to the quality of their care.

**Study Standard Operating Procedure (S.O.P.) and Investigator safety**

The study will be undertaken according to the ICH Good Clinical Practice (GCP) guidelines and Surgical Trials Unit (S.T.U.) S.O.P.s.

**Adverse Events (A.E.) & safety reporting**

A.E. will be reported according to the University of Auckland’s STU SOP 19 (“Reporting of research related adverse events in the S.T.U.”).

Clinical outcomes will be recorded, and any complications reported to and monitored by the high-risk register of the ADHB Research Review Committee.

In the unlikely event of any serious adverse events deemed secondary to the use of the directional flow refeeding appliance, we will pause the trial until further investigation and approval by the ethics committee.

A.E. will be recorded from consent to study completion or withdrawal. Investigators shall complete individual adverse event reports in the approved log detailing the event type, cause, seriousness, grading, device relatedness, treatment, and outcomes.

Should any unanticipated serious adverse event occur, it will be reported within 48 hours of the investigators’ awareness of the event. All adverse events, regardless of relationship to the device, will be followed to resolution – or stabilisation, if a solution is not expected.

If the serious A.E. leads to death, the Investigator must provide a narrative summary of circumstances and events related to the death, and cause of death, if known. All deaths throughout the study must be reported within 24 hours of the knowledge of the event.

The Investigator shall submit to the ethics committees a report of any serious unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible, but in no event later than five working days after the Investigator learns of the outcome.

**ADVERSE EVENT TERMINOLOGY:**

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| **TERM** | **DEFINITION** |
| Adverse Event (A.E.) | Any untoward medical occurrence in a subject, which does not necessarily have a causal relationship with the treatment or device intervention. An A.E. can be any unfavourable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study device, whether or not it is considered to be related to the study device. This includes any newly occurring event or previous condition that has increased in severity or frequency since enrolment in the study. |
| Serious Adverse Event (S.A.E.) | An adverse event will be considered serious if it meets at least one of the following criteria, regardless of causality or relationship to the study device.* results in fatality
* is life-threatening – the subject was at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
* results in persistent or significant disability/incapacity, or
* requires inpatient hospitalisation or prolongs a hospital stay during the period of the therapy or within 24 hours after completion of study exit.
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| Unanticipated adverse device or therapy effect | Any unanticipated, serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with the use of the device or therapy. |
| TERM | RELATEDNESS |
| Device-related | In the judgment of the Principal Investigator, there is a logical connection between the use of the device and the occurrence of the adverse event, above and beyond any underlying disease process itself. |
| Procedure-related | In the judgment of the Principal Investigator, there is a logical connection between the procedure and the occurrence of the adverse event, above and beyond any underlying disease process itself. |
| Pre-existing condition | In the judgment of the Principal Investigator, there is a logical connection to a pre-existing health condition and the occurrence of the adverse event. |
| Device malfunction | Failure of the device to meet its performance specifications, or otherwise perform as intended. |
| **OUTCOMES** |
| Outcomes | Outcomes will be coded as one of the following: resolved, resolved with sequelae, unresolved at the end of the study, death, and unknown |

**Study funding**

This study will be funded by The Insides Company Limited (sponsor).

**Disclosure**

Prof. Greg O’Grady and Prof. Ian Bissett are founders and shareholders of The Insides Company, which is sponsoring and manufactures the devices used in the study. None of them will participate in the statistical analysis of the results of the study.

**Ethical considerations**

**Risks and Benefits**

The main risk to patients will involve reflux or leak of stoma contents, although this risk is expected to be low because the device has been comprehensively tested in benchtop studies. Irritation of the skin could occur around the stoma bag, but these events should be minimised because the bag is firmly adherent to the directional flow appliance.

There is a risk of obstruction in the device; however, this risk is low because neonates’ enteral contents are usually liquid, and the catheter rarely becomes obstructed. If an obstruction occurs, reflux may present, and the catheter should be unclogged.

A further risk is bowel damage; however, this risk is unlikely because the catheter material is an off-the-shelf soft and pliable enteral feeding tube. The same catheter insertion and use processes are already in use in the NICU staff at Auckland, so the risks of this complication will not be increased in Auckland by including patients in this study. If bowel abrasion is suspected, the device will be removed. In the improbable event of bowel perforation, the patient will be treated by proper management, and the study will be stopped until a thorough evaluation is completed.

Any complications will be carefully monitored by the investigators, and a low threshold placed for simple removal of the device if any concerns arise at any stage. Problems with the effectiveness of the catheter placement to prevent leakage may also occur, and iterations in design will aim to minimise these to comparable or lower rates than with traditional stoma bags.

There are some potential benefits from being involved in this study. We aim to reduce the clinical morbidities associated with short bowel syndrome and high-output enterostomies and entero-atmospheric fistulas as described in detail above. Individual patients may benefit from weight gain, early enteral feeding, decreased parenteral nutrition morbidity, ability to be fed through the distal enterostomy when required, reduction in overall morbidity and mortality, and technical improvements to the rehabilitation surgery.

Overall, the investigators perceive the potential risks of the device as low. However, this protocol and the medical device have never been used in neonates. Therefore, while it is anticipated to be safe, there is not yet any evidence.

**Liability of injury**

The Insides Company has a clinical trial insurance policy that may compensate participants in the unlikely event of an injury occurring to them during the trial.

**Patient confidentiality**

Patient confidentiality will be maintained to study investigators only. No identifying information will be disseminated for publication. Information will be kept in a password protected computer/cloud service.

**Retention of information and disposal**

Data from this study will be kept for ten years after the youngest participant turns 16. It will be kept on a password-protected computer/cloud service based at the University of Auckland.

Upon reaching this time point, all electronic and paper copies of this information will be destroyed.

**Dissemination of results and publication of data**

The results of this study will be submitted for publication in a peer-reviewed journal and presented at appropriate national/international conferences. The device may also be commercialised in collaboration with Auckland UniServices should a successful trial be completed, benefitting patients worldwide.

If requested, patients will be presented with a summary of the study findings.

Study findings may be included in a research thesis towards a PhD degree.

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