Title:	Evaluation of Efficacy of Use of TubeClear® to Restore Patency to Occluded Enteral Access Devices in Pediatric Patients
Short Title	TubeClear® Evaluation in Pediatric Patients
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Drug or Device Name(s):	TubeClear®
FDA IND	Not applicable
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Study Sponsor:
Actuated Medical, Inc.
310 Rolling Ridge Drive
Bellefonte, PA 16823
United States

Site Co-Investigators:
Vijay Srinivasan, MD
The Children's Hospital of Philadelphia
Suite 8566, Critical Care Medicine
8th Floor NE Main
34th Street and Civic Center Blvd
Philadelphia, PA, 19104
Phone 215-590-5505
email: srinivasan@email.chop.edu

Sharon Y. Irving, PhD, CRNP
The Children's Hospital of Philadelphia
3401 Civic Center Blvd.
7th Floor Main, 7NE29
Philadelphia, PA 19104
Phone 215-430-3474
Email: irvings@email.chop.edu

Anne Marie Cahill
The Children's Hospital of Philadelphia
3401 Civic Center Blvd
3rd Floor Main
Philadelphia, PA 19104
Phone 267-425-7122
Email: cahill@email.chop.edu

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS OF TERMS

AE		Adverse Event
Pain Scales		Include but are not limited to: Face, Legs, Activity, Cry, Consolability (FLACC) - ≥ 7 years of age; may be used in the older child Revised Face, Legs, Activity, Cry, Consolability (rFLACC) - ≥ 7 years of age; may be used in the older child FACES Pain Scale Revised (FPS-R) - ≥ 3 years of age; may be used in the older neurologically impaired, non-verbal child Numeric Pain Scale - ≥ 8 years of age; cognitively intact patients, able to self-report
AMI		Actuated Medical, Inc.
BMI		Body Mass Index
BSA		Body Surface Area
CHOP		The Children's Hospital of Philadelphia
DOB		Date of Birth
EAD J ND NG NJ AMT GJ		Enteral Access Device Jejunostomy Tube Nasoduodenal Tube Nasogastric Tube Nasojejunal Tube Applied Medical Technology, Inc. Gastrojejunal 14 Fr Tube
EAD(A)		Adult Feeding and Decompression Access Device ND, NG, NJ, G, and J Tubes of size 10 – 18 Fr, 10 – 140 cm
EAD(P)		Pediatric Enteral Access Device ND, NG, and NJ 6 – 8 Fr, 38 – 140 cm; and NG tube (Corflo, Corpak MedSystems) used as a J tube inserted through a G tube 6 – 8 Fr, 38 – 140 cm; GJ tube (AMT) 14 Fr, 38 – 140 cm (15 – 55 in)
EAD(P) Adverse Event		EAD displacement, EAD damage, enteral tract tissue injury

EHR		Electronic Health Record
EPIC		Integrated Electronic Health Record system used at The Children's Hospital of Philadelphia
Fr		French gauge (conventional unit of measure used to describe tube diameter size (1 Fr = 0.33 mm))
IR		Interventional Radiology
MRN		Medical Record Number
MUSC		Medical University of South Carolina
NIH / NICHD		National Institutes of Health / National Institute of Child Health and Human Development
PCU		Progressive Care Unit
PICU		Pediatric Intensive Care Unit
SBIR		Small Business Innovation Research
Tube		Feeding tube
USA		United States of America

ABSTRACT

Context:
Occluded enteral access devices (EADs) are a significant problem for pediatric patients, with occlusion rates ranging from 12.5% to 35%. Occluded EADs can lead to extended times of decreased energy intake, resulting in patients quickly exhausting their energy reserves and developing dehydration with electrolyte abnormalities. Current methods used to restore patency to an occluded EAD at The Children's Hospital of Philadelphia (CHOP) involve application of enzymes and chemicals (e.g., Clog Zapper), which have variable rates of timely success. If these methods are unsuccessful and patency cannot be restored, the EAD must be replaced and may require radiological intervention with exposure to radiation and contrast material. TubeClear® addresses this clinical need to safely and efficaciously restore patency to occluded EADs at the patients' bedside while the EAD remains in the patient. Additionally, this reduces the need to transport the patient to the radiology suite with subsequent exposure to radiation and contrast material for EAD location conformation after replacement.

Objectives:
1) To evaluate feasibility and tolerability of TubeClear® to restore patency in occluded EAD(P)s, and 2) to compare efficacy of TubeClear® to the CHOP Standard Treatment to restore patency in occluded EAD(P)s.

Study Design: Phased Study (n=64).

Phase I: Feasibility and tolerability of TubeClear® intervention in consecutive eligible Subjects (n=15) with occluded EAD(P)s who have not attained their 18th birthday.

Following successful completion of Phase I as deemed by the IRB, the Study will proceed to Phase IIA and IIB to run concurrently.

Phase IIA: Ability of TubeClear® intervention to restore patency in consecutive eligible Subjects (n=15) with occluded EAD(P)s who have not attained their 11th birthday.

Phase IIB: Randomized efficacy comparison between TubeClear® intervention (experimental, n=17) and CHOP Standard Treatment (control, n=17) in eligible Subjects with occluded EAD(P)s who are between 11 years of age and have not attained their 18th birthday.

Setting:
This Study will take place in the CHOP Pediatric Intensive Care Unit (PICU),Progressive Care Unit (PCU), and Interventional Radiology Department (IR).

Inclusion criteria:
1. Males or females who have not attained their 18th birthday (Phase I), or
   Males or females who have not attained their 11th birthday (Phase IIA), or
   Males or females between 11 years of age and have not attained their 18th birthday (Phase IIB)
2. Indwelling occluded EAD(P) that is either:

a. ND, NG, NJ tube composed of Polyvinyl Chloride (PVC) and Polyurethane 6 – 8 Fr, 38 – 140 cm; or
b. NG tube (Corflo, Corpak MedSystems) used as a jejunal tube inserted through a gastrostomy tube, 6 – 8 Fr, 38 – 140 cm
c. GJ (AMT) tube 14 Fr, 38 – 140 cm (15 – 55 in)

Exclusion criteria:

1. Ward of the state
2. Positive pregnancy test/ Pregnant females
3. Any active gastrointestinal abnormalities or malformations, including but not limited to infections, inflammation, obstruction, and/or recent abdominal surgery or trauma
4. Constant dependency on the EAD(P) for a glucose source (e.g. hyperinsulinism states)
5. Unable to tolerate water volume needed for the EAD(P) flush
6. Allergies to the contrast agent(s) used in post-Intervention radiological imaging
7. Measured total length of EAD(P) less than 38 cm (15 inches) - from external port to EAD(P) distal end
8. Unknown length of EAD(P)
9. Attending physician declines enrollment based on clinical judgement
10. Subject attains 18 years of age during study duration

Study Interventions and Measures:

TubeClear® is the investigational device being studied and is deemed by the FDA to be non-significant risk for use in this study (**Appendix D**).

Potential eligible Subjects will be identified by screening the electronic health records. An occlusion is defined by direct identification of a clog or through a feeding pump alarm that sounds when patency of an EAD(P) is disrupted. Eligible subjects who meet inclusion/exclusion criteria will be approached for informed consent and, when applicable, assent to participate in the study. Eligible subjects may be enrolled more than once and up to a maximum of three times in the study for each instance of EAD(P) occlusion.

In Phase I, all enrolled subjects will receive the TubeClear® intervention. If the TubeClear® intervention is unable to restore EAD(P) patency, further steps to restore patency of the occluded EAD will be determined by the clinical team per usual practice.

In Phase IIA, all enrolled subjects will receive the TubeClear® intervention. If the TubeClear® intervention is unable to restore EAD(P) patency, further steps to restore patency of the occluded EAD will be determined by the clinical team per usual practice.

In Phase IIB, subjects will be randomized into either TubeClear® intervention or CHOP Standard Treatment. If either intervention is unable to restore EAD(P) patency, further steps to restore patency of the occluded EAD will be determined by the clinical team per usual practice.

Primary Endpoints:

The Phase I primary endpoints are feasibility and tolerability. Feasibility will be defined as ability of the user to operate TubeClear® from clearing stem insertion into the occluded EAD(P) through activation to patency restoration. Tolerability will be defined as ability of the Subject to withstand TubeClear® intervention.

The Phase IIA primary endpoint is ability of TubeClear® intervention to establish patency in Subjects with occluded EAD(P)s.

The Phase IIB primary endpoint is the efficacy of TubeClear® intervention to restore EAD(P) patency compared to CHOP Standard Treatment.

Secondary Endpoints:

In Phase I, Subjects will be monitored for 1) pain, using established age-appropriate pain scales, 2) physiologic changes in vital signs, 3) distress related EAD(P) events, and 4) adverse events related to TubeClear® use.

In Phase IIA, Subjects will be monitored for 1) pain, using established age-appropriate pain scales, 2) physiologic changes in vital signs, 3) distress related EAD(P) events, and 4) adverse events related to TubeClear® use.

In Phase IIB, Subjects will be monitored for 1) pain, using established age-appropriate pain scales, 2) physiologic changes in vital signs, 3) distress related EAD(P) events, and 4) adverse events related to either group.

Safety Monitoring:

This study will incorporate a data and safety monitoring plan with medical monitor to review study data for adverse events to ensure the safety of study subjects. Following the use of either standard treatment or TubeClear® intervention, all Subjects will receive an abdominal radiograph with contrast. Radiographs will be reviewed by a radiologist (blinded to the study) to assess for tube integrity and location, and enteral tract tissue injury that may be attributable to either intervention.

In all phases, surveillance will include assessment for adverse events related to the respective study intervention (i.e. EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) and will continue for three (3) days. Patients who are discharged from the hospital prior to 3 days will be followed up by phone until completion of 3 days following study interventions. All adverse events will be reported to the IRB and medical monitor.

Statistical Analysis:

Data from Phase I and Phase IIA will be observational in nature and will not test a hypothesis. In Phase IIB, intention-to-treat analysis will be used to compare the efficacy of the TubeClear® intervention to the CHOP Standard Treatment in accordance with the CONSORT guidelines. Exploratory-per-protocol analysis will also be reported.

Figure 1: Study Flow Chart

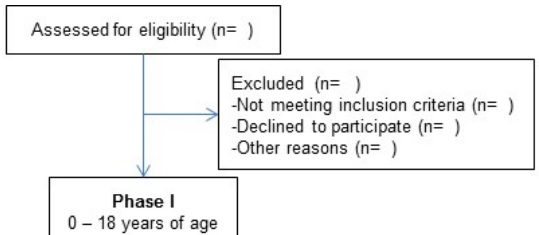


Table 1. Schedule of Study Procedures

Study Phase	PHASE I n=15	PHASE IIA n=15	PHASE IIB n=34
Screening - Review Health Record for Eligibility	X	X	X
Informed Consent/Assent	X	X	X
Medical History/Labs/Medication/Health Record Review	X	X	X
Pregnancy Test, **if not documented as completed in EMR**	X	X	X
Radiograph Review – **pre** TubeClear® Intervention or Standard Treatment	X	X	X
Physical Exam/Pain Assessment **Pre** – Day of TubeClear® or Standard Treatment	X	X	X
Study Intervention - TubeClear® Intervention	X	X	
Randomization to TubeClear® Intervention or Standard Treatment			X
Physical Exam/Pain Assessment **Post** – Day of TubeClear® or Standard Treatment	X	X	X
Radiograph Review – **Post** TubeClear® Intervention or Standard Treatment	X	X	X
Physical Exam/Pain Assessment/ Day 1 Follow up	X	X	X
Physical Exam/Pain Assessment/ Day 2 Follow up	X	X	X
Physical Exam/Pain Assessment/ Day 3 Follow up	X	X	X
Adverse Event Assessment	X	X	X

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Approximately, seven (7) million enteral access devices (EADs) are placed in the United States of America (USA), annually.[1] Recent literature reports as many as 24% of pediatric patients require an EAD(P) during their hospital stay.[2] With a reported 6.4 million hospitalized pediatric patients in 2009 across the US[3], it can be estimated that as many as 1.5 million children may have an EAD(P) during their hospital stay. An important limitation of EADs is that they can become occluded.[i] Reported EAD occlusion rates range from 12.5% to 35%.[3-8] Using 25% as an approximate occlusion percent, USA medical facilities treat over 1.7 million occlusions (adults and pediatrics) annually. Assuming twenty (20)[ii] minutes of nursing time at a mean of $55.24/hour[iii], occluded EADs cost the USA healthcare system over $30million, annually.

Current methods to restore patency to an occluded EAD(P) used at The Children's Hospital of Philadelphia (CHOP) involve application of enzymes and chemicals (e.g., Clog Zapper), which have variable rates of timely success. If these methods are unsuccessful and patency cannot be restored, the EAD must be replaced and may require radiological intervention with exposure to radiation and contrast material.

TubeClear® addresses this clinical need to safely and efficaciously restore patency to occluded EADs at the patients' bedside while the EAD remains in the patient. Additionally, this reduces the need to transport the patient to the radiology suite with subsequent exposure to radiation and contrast agent for EAD location conformation after replacement. The TubeClear® System is comprised of a reusable Control Box and a single use Clearing Stem (**Figure 1A**). The Control Box Model 101 and Clearing Stem Model TC-0608 [EAD(P) Clearing Stem Design], to be used in this Study, are FDA cleared[iv] for use with occluded EADs in adult patients.[v] Specifically, the Clearing Stem Model TC-0608 has been approved by the FDA for use with 6-8 Fr EADs measuring 38cm-140cm in adults.

[i] Occlusions are clogs, blockages, or obstructions of feeding formula, medications, supplements, ground food, or aspirated contents. Occlusions can be a complete blockage or a partial blockage resulting in a "sluggish" tube in accordance with the FDA-cleared indications for the TubeClear System. Occlusions are called clogs in the TubeClear® Operator's Manual and the Directions for Use (packaging insert) to agree with colloquial terminology used by end users.

[ii] Conclusions of Clinician Focus Groups, July 2009.

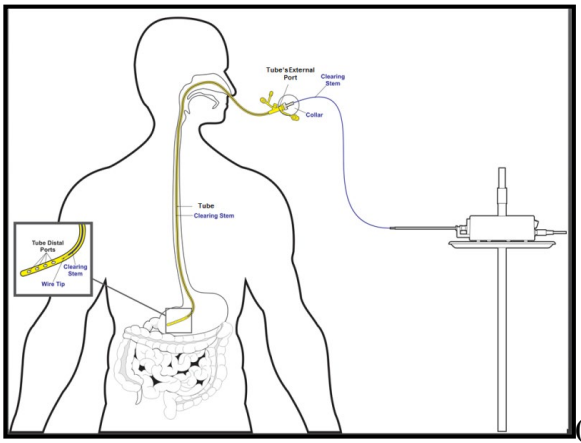
[iii] Nursing Time: Bureau of Labor Statistics (www.bls.gov), mean hourly wage for Registered Nurses is $33.23/hour + 25% fringe rate + 33% overhead rate = $55.24.

[iv] For medical devices that receive USA market sale permission via the FDA 510(k) regulatory path, the product is said to be "cleared" whereas for medical devices that receive USA market sale permission via the FDA Premarket Approval (PMA) path the product is said to be "approved". TubeClear® followed a FDA 510(k); therefore, TubeClear® was cleared by the FDA for USA market sale in EAD(A)s.

[v] TubeClear® Control Box Model 101 is also CE Marked for adults and pediatrics and available for sale in the EU.

Clearing Stem models for ND, NG, NJ, G, and J Tubes of size 10 – 18 Fr, 10 – 140 cm and ND, NG, NJ, and J Tubes of size 6 – 18 Fr, 15 – 36 cm for adults have been FDA cleared.[vi,vii] TubeClear® has been demonstrated to be safe and effective in bench and animal testing (**Section 1.3.1**), and has been successfully evaluated in more than 17 adult patients (**Section 1.3.2**).

(A)



(B)

Figure 2: (A) TubeClear® Control Box Model 101 with attached Clearing Stem Model NE-1043. (B) Illustration of Clearing Stem insertion into EAD. The Control Box remains external to the Patient. The Collar (see circled inset) limits the depth to which the Clearing Stem can be inserted; therefore, the Clearing Stem does not reach the EAD distal ports (see square inset).

In bench testing, TubeClear® restored patency to the occluded 14 Fr 48 inch long NE EAD in an average of 2.8 minutes, compared to 42.1 minutes for warm water and 57.5 minutes for enzyme treatment (**Table 2**, and **TP-5007-079 and TR-5007-079**). The shorter time to restore patency with TubeClear® reduces interruptions in nutrition and medication dosing from almost an hour to minutes. In the 17 adult documented cases, patency was restored and no pain was documented (**Appendix E**).

Method	Number of Runs	Number of Runs Unclogged	Average Procedure Time
TubeClear	30	30	2.8 minutes
Warm Water	30	26	42.1 minutes
Enzyme Treatment	30	29	57.5 minutes

Table 2: Bench Testing evaluated at AMI with Levin 14 Fr 48 inch long nasoenteral tubes.[x]

[vi] FDA 510(k) Clearance Numbers: K121571 (6/2012), K123659 (12/2012), K131052 (8/2013), K172556 (6/2016), K163092 (12/2016) see **Appendix A**.

[vii] TubeClear® for EAD(A)s is CE Marked for adults and pediatrics and available for sale in the EU.

The setting for the proposed Study is a large, tertiary, urban, pediatric hospital. It is appropriate as pediatric patients who develop an occluded EAD(P) are often current in-patients being managed for pre-existing medical and/or surgical conditions.

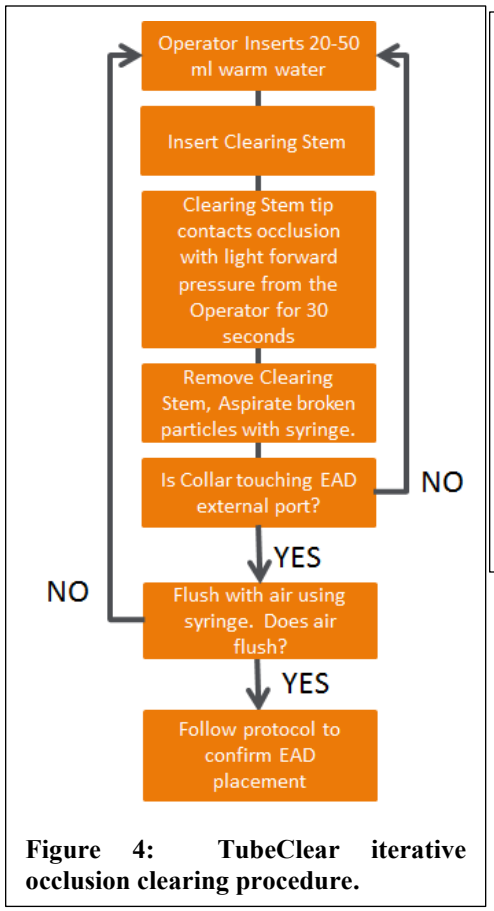


Figure 4: TubeClear iterative occlusion clearing procedure.

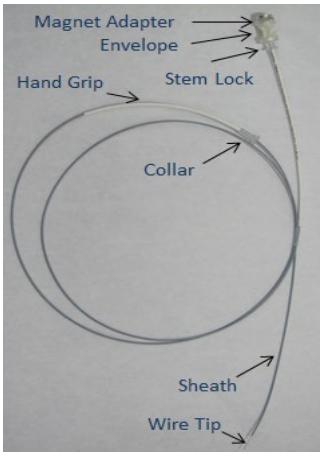


Figure 3: Clearing Stem with design features.

1.2 Name and Description of Investigational Product or Intervention

TubeClear® is comprised of a reusable Control Box and a single use Clearing Stem (**Figure 2A**). The Control Box is to be located and operated between five (25) inches and twenty-six (6) inches away from the patient (**Figure 2B**). The Control Box contains a motor that creates a linear reciprocating motion (i.e., forward and backward motion). The Clearing Stem contains a proximal end magnet. The magnet is connected to a specially designed flexible wire that is encased in a plastic sheath. The proximal end of the Clearing Stem connects to the Control Box via a magnetic connection.

The Operator manually inserts the distal end of the Clearing Stem (**Figures 2B and 3**), (set to the EAD length, measured in centimeters, cm) into the proximal end of the EAD. The Operator then turns the Control Box motor 'on' and manually directs the Clearing Stem's progression along the inside of the EAD. The distal Clearing Stem tip acts on the occlusion mechanically breaking up the occlusion restoring EAD patency.

The TubeClear® occlusion clearing procedure (**Figure 4**) is an iterative process of adding 20-50ml of warm water then inserting the Clearing Stem and allowing the distal wire tip to act on the occlusion for approximately 30 seconds, moving the Clearing Stem backward and forward approximately 10 cm (4 in) several times to disperse loosened occlusion particles, the Clearing Stem is removed and aspiration of the broken occlusion particles is performed by the Operator. This process is repeated until the Clearing Stem Collar (also interchangeably known

[viii] Half of the occlusions were made from 2:1 ratio coagulated protein and ground medical. Half from1:1 ratio of feeding formula and fiber. Enzyme Treatment was Clog Zapper (Corpak MedSystems (Buffalo Grove, IL)). .

as Depth Limiter hereinafter), preset to the measured EAD cm length, reaches the proximal port of the EAD (**Figure 2B, circled inset**).

Additional Information and Background on TubeClear® can be found in **Appendices A - E**.

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Non-Clinical Studies

Performance evaluations were conducted via Bench and Animal Testing (**Appendix C**). The TubeClear® Control Box model (i.e., Model 101) used in Bench and Animal Testing will be used in this Study. Therefore, the Control Box operation does not change for this Study. The EAD(A) and EAD(P) Clearing Stem designs are the same except that the EAD(P) Clearing Stem design is optimized for smaller lumens, and the Operator sets the collar (**Figure 5**). The Clearing Stem design changes for the smaller lumens do not change the Bench Testing outcomes; therefore, the EAD(A) Clearing Stem Bench Testing applies to the EAD(P) Clearing Stem design. Additionally, Benchtop verification and validation testing has been completed to confirm substantial equivalence of safety and effectiveness (as per 21 CFR 807.100) of the EAD(P) Clearing Stem to the FDA cleared EAD(A) Clearing Stem (K131052). The 510(k) submission for the EAD(P) Clearing Stem was cleared by the FDA for the adult indication (K131052/K163092/K172556). The test protocols and reports used in 510(k) submission K131052 are included in **Appendix C**. The test protocols and reports used in the EAD(P) Clearing Stem submission are included in Appendix C.2. The Control Box is the same between the EAD(A) and the EAD(P). Therefore, all test protocols and reports pertaining to the Control Box can be found in **Appendix C**.

For the EAD(P), an Operator Set collar (**Figure 5)** that is placed by the Operator is necessary to match varying EAD(P) lengths. Safety of this change with potential for Operator error was tested via an *in-vitro* and *in-vivo* animal models. Efficacy was also examined in the animal testing and found to be consistent with previous EAD(A) results.

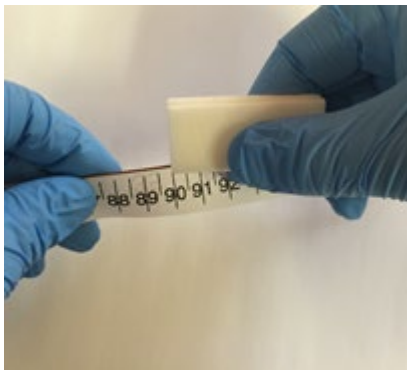


Figure 5: Placement of the Operator Set Collar

The Bench Testing focused on five (5) criteria: 1) Technical, 2) Efficacy, 3) Safety, 4) Usability and 5) Ambient Noise. Animal Testing focused on Safety and Efficacy. Clinical Testing was not required for the FDA cleared EAD(A) indication. Testing was compliant with CFR 21, Part 820 – Quality System Regulation and ISO 13485:2003 – Medical Devices – Quality Management Systems. (Non-Clinical Studies data, test protocols and test reports in **Appendix C**).

<u>Bench Testing</u>

1) Technical testing for the TubeClear® EAD(A) Clearing Stem included electrical safety, product specifications verification, product shelf life, transportation vibration, and packaging integrity (**TP-4010-005, TP-4010-006, TP-4010-018, TP-4010-019, TP-4010-**

028, TR-4010-005, TR-4010-005-1, TR-4010-006, TR-4010-006-8, TR-4010-018, TR-4010-018-1, TR-4010-019, and **TR-4010-028-1**). **Intertek Electrical: 100791030CLE-001 IEC 60601-1-6, 100791030CLE-003 IEC 60601-1, 100791030CLE-004 IEC**. Since the EAD(A) and EAD(P) Clearing Stem designs are the same except for optimization for smaller lumens and Operator-set collar, the technical test results for the EAD(A) Clearing Stem design are applicable to the EAD(P) Clearing Stem design.

Additional technical testing has been completed for the EAD(P) Clearing Stem design which included product specifications verification, product shelf life, transportation vibration, and packaging integrity (**TP-4021-022, TP-4017-013, TP-4017-014, TR-4021-022, TR-4017-013-1, TR-4017-013-2,** and **TR-4017-014**). Intertek Electrical safety testing did not change between the two models.

2) Efficacy was tested in a variety of EADs of different lengths, diameters, and material properties. TubeClear® EAD(A) Clearing Stem successfully restored patency (**TP-5007-079**, and **TR-5007-079**). Since the designs are similar for the EAD(A) and EAD(P) Clearing Stems and the same Control Box will be used, the Efficacy Test results for the EAD(A) Clearing Stem designs are applicable to the EAD(P) Clearing Stem design.

Efficacy testing has been completed for the EAD(P) Clearing Stem design (TC-0608). TubeClear® successfully restored patency (**TP-4021-018, TP-4017-001** and **TR-4021-018 TR-4017-007, see Figure 6**).

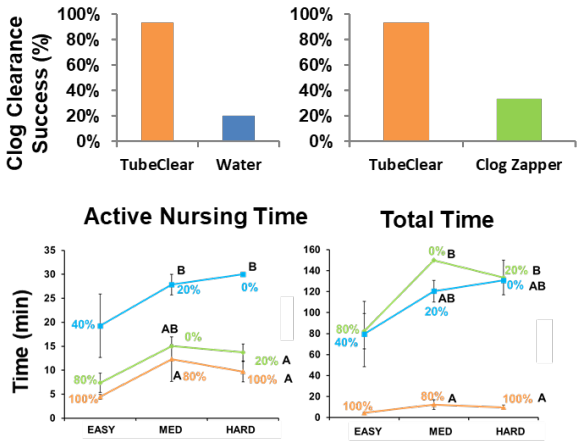


Figure 6: (TOP): The TC-0608 Clearing Stem (TubeClear-orange) was more successful (14/15=93%) at clearing clogs compared to warm water flushes (blue, 3/15=20%, p = 0.0002) and Clog Zapper enzymes (green, 5/15=33%, p = 0.002); (BOTTOM): Active nursing time and total procedure time for clearing various clog types (easy, medium and hard) using TubeClear with TC-0608 (orange), warm water flushes (blue) and Clog Zapper enzymes (green) with percentages representing success of different methods with different types of clogs (Kruskal Wallis, p<0.05), N=5 clog/treatment/clog formulation.

TC-0608 was used in preliminary testing to clear five (5) total occlusions in AMT GJ tubes, 14 Fr (**Figure 7**). Three (3) of these clogs were defined as "soft" clogs (i.e., Type 3) made out of feeding formula and fiber. The remaining two (2) clogs were defined as "hard" clogs (i.e., Type 1 and 2[ix]) made of crushed medication and coagulated protein. TC-0608 successfully restored patency to all five (5) GJ tubes, although it was noted that the Clearing Stem "moved smoothly, but slowly after encountering the second bend" of the GJ tube. Overall, it should be noted that while clearing 14 Fr AMT GJ tubes, the operator may feel an increase in resistance at the second bend of the GJ tube, but the TC-0608 Clearing Stem Model is capable of restoring full patency to this type of feeding tube.

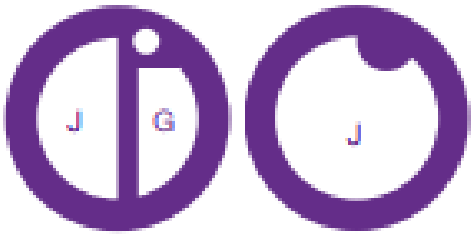


Figure 7: Cross-section of the gastric portion *(left)* and jejunal portion *(right)* of an AMT GJ feeding tube.

3) Safety testing verified that TubeClear® EAD(A) Clearing Stem did not cause physical damage to the EAD, excess EAD movement or migration, or EAD heating due to friction caused by actuation (**TP-4010-009, TP-4010-026, TR-4010-009-2,** and **TR-4010-026)**. Since the designs are similar for the EAD(A) and EAD(P) Clearing Stems and the same Control Box will be used, the Safety Test results for the EAD(A) Clearing Stem designs are applicable to the EAD(P) Clearing Stem design.

Safety testing has been completed for the EAD(P) Clearing Stem design. This testing verified that TubeClear® did not cause physical damage to the EAD, excess EAD movement or migration, or EAD heating due to friction caused by actuation (**TP-4021-017, TP-4021-019, TR-4021-017,** and **TR-4021-019**).

4) Usability Testing conducted in accordance with FDA Draft Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design. It was concluded that TubeClear® EAD(A) Clearing Stem is reasonably[x] safe and effective for the intended users, uses, and use environments (**TP-4010-015,** and **TR-4010-027**). Since the designs are similar for the EAD(A) and EAD(P) Clearing

[ix] See AMI Work Instruction WI-7.3.003

[x] Conclusion per recommendations of Guidance Documents (Medical Devices and Radiation-Emitting Products) - Draft Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design. Center for Devices and Radiological Health, 2011. (Accessed Dec 20, 2013, at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.)

Stems and the same Control Box will be used, the Usability Test results for the EAD(A) Clearing Stem designs are applicable to the EAD(P) Clearing Stem design. Additionally, for this Study, the Operator's will all be trained by Actuated Medical Staff (**Appendix F**).

Usability testing has been completed for the EAD(P) Clearing Stem design. It was concluded that TubeClear® is reasonably[ix] safe and effective for the intended users, uses, and use environments (**TP-4017-012** and **TR-4017-012**).

Table 3: Jejunum Thickness in Different Age Groups

Age (Year)	Jejunum Thickness (mm)
0 – 4	**0.6 – 0.8**
5 – 9	0.7 – 0.9
10 – 14	0.7 – 0.9
15 – 19	0.8 – 1.0
20 – 29	0.8 – 1.0
30 – 39	0.8 – 1.0

5) Ambient Environment Noise Level Testing was performed on the TubeClear® Control Box during simulated operating conditions. The Control Box motor generates sound during operation; therefore, the sound was measured to determine if it would significantly increase the noise levels in the clinical environment (**TP-5007-050, TR-5007-050 and TR-5007-050-2**). The Control Box 'on' noise level is very similar to the ambient noise level of an ICU; therefore, it is not anticipated to increase patient distress in the PICU, PCU, or IR.

In-vitro Animal Testing

Safety was evaluated in an over-insertion mode (contrary to the Instructions for use) in an *in-vitro* animal model. For normal operation, a depth control collar limits the insertion of the Clearing Stem into the EAD; thus prevents the Clearing Stem tip from exiting the EAD. To test safety, ex-*vivo* porcine stomach and small intestine tissue samples with thicknesses similar to humans of age 0 to 39 years of age were examined in the simulated over-insertion mode. A porcine model was selected due to similarity of gastric features to that of humans aged 0 to 39 years[4]. The range of intestinal thickness (jejunum) for human ages 0 to 39 years is 0.6 – 1.0 mm (**Table 3**). Tissue samples from the porcine intestine tissue used for testing were between 0.284 mm and 1.0 mm as measured via two independent methodologies.

As such, it was concluded that the tissue samples used for this safety testing were representative of both adult and pediatric patients and the results of the testing are applicable to both populations (**TR-4010-022**).

The EAD(A) Clearing Stem was advanced at a rate of 65-70 mm/min to simulate actual use. The maximum force of the Clearing Stem tip on the tissue sample was 3.597 N. The advancement of the Clearing Stem stopped when the wire was observed to be bent at approximately 45°. In the 60 trials run, the Clearing Stem caused small indentations, but no full puncture was observed (**TP-4010-008**, and **TR-4010-008**).

This testing was repeated for the EAD(P) Clearing Stem design. Tissue samples from the porcine intestine (jejunum) tissue were on average between 0.62 mm and 0.92 mm. It was concluded through statistical analysis that this was representative of both adult and pediatric patients and the results of the testing are applicable to both populations. No punctures of porcine intestine (jejunum) tissue samples were achieved in a realistic worst-case misuse test scenario (**TP-4021-020** and **TR-4021-020**).

In-vivo Animal Testing

The safety and efficacy of the Alpha (first design iteration) EAD(P) TubeClear® Clearing Stem design was tested in a live porcine model at the Medical University of South Carolina. Use of TubeClear® was performed in a porcine model to simulate pediatric insertion by M. Michael Swindle, VMD, a veterinarian, Mark H. Delegge, MD, FACG, CNSP, AGAF, FASGE, a gastroenterologist, conducted the standard Intervention and Kristi L. Helke, DVM, Ph.D., a board certified pathologist, conducted the pathology evaluations.

1) The efficacy of the EAD(P) Clearing Stem in clearing EAD(P)s with simulated occlusions was evaluated in a porcine model. Patency was restored in an average time of 2.37 minutes (**TP-5017-009**, **TR-5017-009** and **TR-5017-010**).

2) Safety was evaluated in an over-insertion mode (contrary to the Instructions for use). For normal operation, a depth control collar limits the insertion of the Clearing Stem into the EAD; thus prevents the Clearing Stem tip from exiting the EAD. To test safety, the collar was removed, and the Clearing Stem's distal tip was intentionally advanced approximately 2.5cm beyond the distal end of the EAD(P) so that the distal tip contacted and remained in contact with the porcine mucosal intestinal tissue for six (6) minutes while in 'on mode' (**TP-4010-008**, and **TR-4010-008**). No evidence suggested TubeClear® (consistent to instructions for use) produced intestinal trauma beyond that which can be caused by insertion of an EAD(P). In the over-insertion situation (inconsistent to instructions for use), the Clearing Stem caused lesions that were highly localized, but no full puncture was observed.

1.3.2 Clinical Studies

Human Pharmacokinetics

TubeClear® is a medical device. Therefore, human pharmacokinetics is not applicable.

Clinical Data from Field Use in Adults (including post-marketing surveillance data)

To date, one patient has been enrolled in an IRB approved TubeClear® clinical Study. The Study was at Walter Reed National Military Medical Center, but was terminated after the PI retired from the armed forces. TubeClear® restored patency, and there was no report of discomfort during use (**Appendix E**).

Once TubeClear® was FDA cleared for commercial use, several hospitals conducted post-marketing evaluations. Wexner Medical Center at the Ohio State University evaluated the device and completed evaluation questionnaires (**Appendix E**). Three other facilities have used TubeClear® and provided results (**Appendix E**). All seventeen (17) TubeClear®

applications in adults were successful in restoring patency. No adverse events or pain/discomfort in patients were reported.

TubeClear® undergoes an annual Post-Market Surveillance study. No adverse events or other significant issues have been reported by end users thus far. Moreover, FDA maintains an adverse event database known as MAUDE (Manufacturer and User Facility Device Experience), where end users report adverse events for medical devices for public disclosure. No adverse events have been reported to MAUDE for TubeClear® since original market clearance in 2012.

Clinical Studies in Children

To date, there have been no IRB-approved pediatric clinical studies.

A single male pediatric off-label use of TubeClear® has been reported for compassionate care in a 14 Fr NG EAD. This pediatric use was successful without any adverse event or patient discomfort.

1.4 Selection of Drugs and Dosages

TubeClear® is a medical device. Therefore, selection of drugs and doses is not applicable.

1.5 Relevant Literature and Data

The established age-appropriate pain scales used in this study have been validated and cited extensively.[5-7]

1.6 Compliance Statement

This Study will be conducted in full accordance with all applicable Children's Hospital of Philadelphia (CHOP) Research Policies and Procedures and all applicable Federal and State laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and Good Clinical Practice. All episodes of noncompliance will be documented.

The investigators will conduct the Study in accordance with this protocol, obtain informed consent and, where applicable, assent, and will report unanticipated problems involving risks to Subjects or others in accordance with the CHOP IRB Policies and Procedures and all Federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research Subjects during and following Study completion.

2 STUDY OBJECTIVES

The objectives of this study are to 1) evaluate feasibility and tolerability of TubeClear® to restore patency in occluded EAD(P)s, and 2) compare efficacy of TubeClear® to the CHOP Standard Treatment to restore patency in occluded EAD(P)s. This study will be carried out in phases – Phase I followed by Phase IIA and IIB to run concurrently. The objective of Phase I is to evaluate feasibility and tolerability of TubeClear® intervention to restore patency in occluded EAD(P)s in patients who have not attained their 18th birthday. The objective of Phase IIA is to measure the ability of TubeClear® intervention to restore patency in occluded EAD(P)s in a younger age group i.e. patients who have not attained their 11th birthday. The objective of Phase IIB is to compare efficacy of TubeClear® intervention with the CHOP Standard Treatment to restore patency in occluded EAD(P)s in patients who are between 11 years of age and have not attained their 18th birthday using a randomized controlled design.

For the purpose of this Study, EAD(P)s are ND, NG, and NJ 6 – 8 Fr, 38 – 140 cm; NG tube (Corflo, Corpak MedSystems) used as a J tube inserted through a G tube, 6 – 8 Fr, 38 – 140 cm; and AMT GJ tube, 14 Fr, 38 – 140 cm (15 – 55 in). In all phases, if the study intervention is unable to restore EAD(P) patency, further steps to restore patency will be carried out by the clinical team per usual practice.

2.1 Primary Objective (or Aim)

The primary objectives of this study are to 1) evaluate feasibility and tolerability of TubeClear® to restore patency in occluded EAD(P)s, and 2) compare efficacy of TubeClear® to the CHOP Standard Treatment to restore patency in occluded EAD(P)s.

The primary endpoints in Phase I are feasibility and tolerability of TubeClear® intervention. Feasibility will be defined as ability of the user to operate TubeClear® device (as per instructions and training in **Appendix F**) from insertion of the clearing stem into the occluded EAD(P) through device activation to patency restoration. Tolerability will be defined as ability of the Subject to undergo TubeClear® intervention.

The primary endpoint in Phase IIA is the ability of TubeClear® intervention to restore patency in Subjects with occluded EAD(P)s. This will be termed as EAD(P) patency restoration and will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes after completion of the intervention.

The primary endpoint of Phase IIB is the efficacy of TubeClear® intervention compared to CHOP Standard Treatment to restore patency in Subjects with occluded EAD(P)s. EAD(P) patency restoration will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes after completion of either intervention.

2.2 Secondary Objectives (or Aim)

The secondary objectives of this study are to assess subject pain, changes in physiological parameters, distress related EAD(P) events and adverse events related to the interventions.

In Phase I, Subject pain will be assessed before and after use of TubeClear® intervention using established age-appropriate pain scales. Acute changes in physiologic parameters will be measured, including changes in heart rate, blood pressure and respiratory rate. Distress related EAD(P) events which may be manifested by pulling or yanking of the EAD(P) will be monitored in relation to intervention. Following the TubeClear® intervention, each Subject will receive an abdominal radiograph with contrast. Radiographs will be reviewed by a radiologist (blinded to the study) for EAD(P) adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the TubeClear® intervention.

In Phase IIA, Subject pain will be assessed before and after use of TubeClear® intervention using established age-appropriate pain scales. Acute changes in physiologic parameters will be measured, including changes in heart rate, blood pressure and respiratory rate. Distress related EAD(P) events which may be manifested by pulling or yanking of the EAD(P) will be monitored in relation to intervention. Following the TubeClear® intervention, each Subject will receive an abdominal radiograph with contrast. Radiographs will be reviewed by a radiologist (blinded to the study) for EAD(P) adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the TubeClear® intervention.

In Phase IIB, Subject pain will be assessed before and after use of either intervention using established age-appropriate pain scales. Acute changes in physiologic parameters will be measured, including changes in heart rate, blood pressure and respiratory rate. Distress related EAD(P) events which may be manifested by pulling or yanking of the EAD(P) will be monitored in relation to either intervention. Following either intervention, each Subject will receive an abdominal radiograph with contrast. Radiographs will be reviewed by a radiologist (blinded to the study) for EAD(P) adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to either intervention. Incidence of adverse events attributable to the intervention (i.e. EAD displacement, EAD damage, enteral tract tissue injury) following the intervention will be monitored and reported in both groups.

In all phases, surveillance will include daily assessment for adverse events related to the respective study intervention (i.e. subject pain, feeding intolerance, EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) and will continue for three (3) days. Patients who are discharged from the hospital prior to 3 days will be followed up daily by phone until completion of 3 days following study interventions.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This Study will be carried out in phases in the CHOP Pediatric Intensive Care Unit (PICU), Progressive Care Unit (PCU), and/or Interventional Radiology Department (IR). Phase I will study the feasibility and tolerability of TubeClear® intervention to restore EAD(P) patency in consecutive eligible Subjects (n=15) with occluded EAD(P)s who have not attained their 18th birthday.

After completion of Phase I, a detailed summary of the 15 enrolled subjects will be submitted to the IRB for review of protocol compliance/feasibility, incidence of Adverse Events (if any), and subject pain/tolerability. Following successful completion of Phase I as deemed by the IRB, the Study will proceed to Phase IIA and IIB to run concurrently.

Phase IIA will measure the ability of TubeClear® intervention to restore patency in consecutive eligible Subjects (n=15) with occluded EAD(P)s who have not attained their 11th birthday.

Phase IIB will consist of a randomized efficacy comparison between TubeClear® intervention (experimental, n=17) and CHOP Standard Treatment (control, n=17) in eligible Subjects with occluded EAD(P)s who are between 11 years of age and have not attained their 18th birthday. The overall Study Design is summarized in the Study Flow Chart (**Figure 1**).

3.1.1 Screening Phase

In Phase I, potential Subjects are pediatric patients who have not attained their 18th birthday, and are admitted to the CHOP PICU, PCU, or IR with an existing or a newly inserted EAD(P) that becomes occluded.

In Phase IIA, potential Subjects are pediatric patients who have not attained their 11th birthday, and are admitted to the CHOP PICU, PCU, or IR with an existing or a newly inserted EAD(P) that becomes occluded.

In Phase IIB, potential Subjects are pediatric patients who are between 11 years of age and have not attained their 18th birthday, and are admitted to the CHOP PICU, PCU, or IR with an existing or a newly inserted EAD(P) that becomes occluded.

Patients will become eligible once an occlusion in the EAD(P) is reported and they meet all inclusion/exclusion criteria for the Study. An occlusion is defined by direct identification of a clog or through a feeding pump alarm that sounds when patency of an EAD(P) is disrupted. Potential eligible Subjects will be identified by screening the electronic health records (EHR). In addition, CHOP staff may notify the research personnel when there is a potential Subject. Eligible subjects will be approached for informed consent and, when applicable, assent to participate in the study. If ineligible, research personnel will document patient information to prevent further consideration. Eligible subjects may be enrolled more than once and up to a maximum of three times in the study for each instance of EAD(P) occlusion.

3.1.2 Study Treatment Phase

Following informed consent (assent when applicable) and prior to enrollment into any of the study phases (Phases I, IIA and IIB), female patients ≥ 10 years of age or those who have experienced the onset of menses must have a documented NEGATIVE pregnancy test (urine or blood).

In Phase I, all enrolled subjects will receive the TubeClear® intervention. Prior to the intervention, the location of the EAD(P) will be determined based on review of radiographs. The Investigator may obtain a new radiograph if the EAD(P) location is uncertain. The Investigator will determine the length and diameter of the EAD(P) from the EHR and/or the length marking (in cm) at the exit point of the EAD(P) from the body surface orifice. The Operator-set Collar on the clearing stem of TubeClear® will be placed corresponding to the EAD(P) measured length recorded by the Investigator. The TubeClear® Instructions for Use (i.e., Operator's Manual) will be followed by the user to restore patency to the EAD(P). EAD(P) patency restoration will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes after completion of the intervention. After successful air flushing, aspirate will be extracted through the EAD(P), and the pH of the contents checked to confirm location according to CHOP standard of care. Following confirmation of correct EAD(P) placement, 5-20 ml of water will be flushed through the EAD to assure continued patency. Following the TubeClear® intervention, the Subject will receive an abdominal radiograph with contrast. A radiologist (blinded to the study) will assess the radiographs for adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the intervention. If the TubeClear® intervention is unable to restore EAD(P) patency, further steps to restore patency of the occluded EAD will be determined by the clinical team per usual practice.

In Phase IIA, all enrolled subjects will receive the TubeClear® intervention. Prior to the intervention, the location of the EAD(P) will be determined based on review of radiographs. The Investigator may obtain a new radiograph if the EAD(P) location is uncertain. The Investigator will determine the length and diameter of the EAD(P) from the EHR and/or the length marking (in cm) at the exit point of the EAD(P) from the body surface orifice. The Operator-set Collar on the clearing stem of TubeClear® will be placed corresponding to the EAD(P) measured length recorded by the Investigator. The TubeClear® Instructions for Use (i.e., Operator's Manual) will be followed by the user to restore patency to the EAD(P). EAD(P) patency restoration will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes after completion of the intervention. After successful air flushing, aspirate will be extracted through the EAD(P), and the pH of the contents checked to confirm location according to CHOP standard of care. Following confirmation of correct EAD(P) placement, 5-20 ml of water will be flushed through the EAD to assure continued patency. Following the TubeClear® intervention, the Subject will receive an abdominal radiograph with contrast. A radiologist (blinded to the study) will assess the radiographs for adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the intervention. If the TubeClear® intervention is unable to restore EAD(P) patency, further steps to restore patency of the occluded EAD will be determined by the clinical team per usual practice.

In Phase IIB, subjects will be randomized into either TubeClear® intervention or CHOP Standard Treatment using a predetermined computer generated randomization sequence stored in opaque sealed envelopes. Prior to the intervention, the location of the EAD(P) will be determined based on review of radiographs. The Investigator may obtain a new radiograph if the EAD(P) location is uncertain. The Investigator will determine the length and diameter of the EAD(P) from the EHR and/or the length marking (in cm) at the exit point of the EAD(P) from the body surface orifice. If randomized to TubeClear®, the Operator-set Collar on the clearing stem of TubeClear® will be placed corresponding to the EAD(P) measured length recorded by the Investigator. The TubeClear® Instructions for Use (i.e., Operator's Manual) will be followed by the user to restore patency to the EAD(P). If randomized to CHOP Standard Treatment, the CHOP protocol to restore patency to occluded EAD(P) will be followed. EAD(P) patency restoration will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes after completion of the intervention. After successful air flushing, aspirate will be extracted through the EAD(P), and the pH of the contents checked to confirm location according to CHOP standard of care. Following confirmation of correct EAD(P) placement, 5-20 ml of water will be flushed through the EAD to assure continued patency. Following either intervention, the Subject will receive an abdominal radiograph with contrast. A radiologist (blinded to the study) will assess the radiographs for adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the intervention. If either intervention is unable to restore EAD(P) patency, further steps to restore patency of the occluded EAD will be determined by the clinical team per usual practice.

3.1.3 Follow-up Phase

Surveillance will include assessment for any adverse event(s) related to the intervention (i.e. EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) and will continue for up to three (3) days following interventions in all study phases regardless of study intervention allocation. Clinical Assessment Measurements (i.e., pain, feeding tolerance, and usual measures to determine EAD(P) location) will be performed prior to, immediately following, and for up to three days after the intervention. Patients who are discharged from the hospital prior to three days will be followed up daily by phone for Clinical Assessment Measurements i.e., pain, feeding tolerance and EAD(P) location as assessed by caregiver until post Intervention day three.

3.2 Allocation to Treatment Groups and Blinding

All Subjects in Phase I and Phase IIA of the Study will receive TubeClear® to restore patency of the occluded EAD(P).

All Subjects in Phase IIB will be randomized into the TubeClear® intervention (experimental) or CHOP Standard Treatment (control) group according to a predetermined computer generated randomization sequence. The randomization sequence will be kept in individual opaque sealed envelopes to be opened after the Subject is consented and enrolled in Phase IIB. To ensure an appropriate balance of participation in both the experimental and control groups, balanced, permuted block randomization will be used, as Phase IIB is not blinded.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The duration of study participation per Subject will be up to three (3) days in each phase following initiation of intervention. Clinical Assessment Measurements (i.e., pain, feeding tolerance, and usual measures to determine EAD(P) location) will be performed prior to, immediately following, and for up to three (3) days. Surveillance will include assessment for any adverse event(s) related to the intervention (i.e. EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) and will continue for up to three (3) days. Patients who are discharged from the hospital prior to three days will be followed up daily by phone for Clinical Assessment Measurements i.e., pain, feeding tolerance and EAD(P) location as assessed by caregiver until post Intervention day three. The Subject's actual time spent receiving the study intervention will vary based on whether the Subject is randomized to the TubeClear® intervention or CHOP Standard Treatment. It is estimated that the TubeClear® intervention will take thirty (30) minutes per Subject, including time to prepare and set up the device. It is estimated that CHOP Standard Treatment will take four (4) hours per Subject, including time to prepare for the application of CHOP Standard Treatment.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The Study will be conducted at one site, the Children's Hospital of Philadelphia (CHOP) in the Pediatric Intensive Care Unit (PICU), Progressive Care Unit (PCU), and Interventional Radiology Department (IR). A total of 64 Subjects will be enrolled in this Study – 15 in Phase I and 49 in Phase II.

3.4 Study Population

3.4.1 Inclusion Criteria

1. Males or females who have not attained their 18th birthday (Phase I)

   Or

   Males or females who have not attained their 11th birthday (Phase IIA)

   Or

   Males or females between 11 years of age and have not attained their 18th birthday (Phase IIB)

2. Indwelling occluded EAD(P) that is either:

   a. ND, NG, NJ tube composed of Polyvinyl Chloride (PVC) and Polyurethane 6 – 8 Fr, 38 – 140 cm; or

   b. NG tube (Corflo, Corpak MedSystems) used as a J tube inserted through a G tube, 6 – 8 Fr, 38 – 140 cm

   c. GJ tube (AMT) 14 Fr, 38 – 140 cm (15 – 55 in)

3.4.2 Exclusion Criteria

1. Ward of the state
2. Positive pregnancy test/ Pregnant females
3. Any active gastrointestinal abnormalities or malformations, including but not limited to infections, inflammation, obstruction and/or recent abdominal surgery or trauma
4. Constant dependency on the EAD(P) for a glucose source (e.g. hyperinsulinism states)
5. Unable to tolerate water volume needed for the EAD(P) flush
6. Allergies to the contrast agent(s) used in post-Intervention radiological imaging
7. Measured total length of EAD(P) less than 38 cm (15 in) - from external port to EAD(P) distal end
8. Unknown length of EAD(P)
9. Attending physician declines enrollment based on clinical judgement
10. Subject attains 18 years of age during study duration

Subjects that do not meet all of the enrollment criteria will not be enrolled. Any violations of these criteria will be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

Table 1 lists the study procedures in all study phases.

4.1 Screening Visit

- Potential eligible Subjects are patients in the PICU, PCU, or IR that are identified to have an occlusion of their EAD(P)s during the current admission.
- Potential eligible Subjects will be identified by screening the electronic health records (EHR). In addition, CHOP staff may notify the research personnel when there is a potential Subject.
- For a potential Subject who meets the inclusion/exclusion criteria, the Investigator will discuss the Study with the parent/guardian and obtain informed consent.
- Where appropriate, the Investigator will discuss the Study with the pediatric patient and obtain assent.

4.2 Study Treatment Phase

General overview of Study Treatment Phase - Phase I:

- Female patients $\geq$ 10 years of age or those who have experienced the onset of menses must have a documented NEGATIVE pregnancy test (urine or blood).
- Subject's most recent radiograph will be obtained and reviewed by the Investigator to identify EAD(P) characteristics and tube tip location, as well as pre-existing abnormalities, including damage to EAD(P) and/or tissue, if any.
- The Investigator has the option to order a new radiograph prior to the intervention if there is uncertainty about the status of the EAD(P) tube tip location and characteristics.
- The Subject's Nurse will obtain standard baseline measures of Subject pain.
- EAD(P) length will be determined by review of Subject EHR and/or markings on the EAD(P). The Investigator will place the Operator-set Collar to the same length determined by review of Subject's chart and/or markings on the EAD(P).
- Data will be gathered or abstracted from the EHR prior to, during the Subject receiving the intervention, and through the follow-up period. This data includes subject name, date of birth, contact information for parent/guardian, age, sex, race, ethnicity, weight, stature, BMI, location (PICU/PCU/IR), dates of hospitalization (length of stay), medical record number (MRN), contact serial number (CSN), diagnosis, procedures performed, medications administered, laboratory and radiology results, ventilator parameters (if ventilated), severity of illness, nutrition information, information on EAD and clog, and physical assessments with vital signs (patient temperature, heart rate, respiratory rate, blood pressure and pain level).

- The patient's Nurse will obtain standard measures of Subject pain following intervention.

- Intervention is deemed successful if EAD(P) is able to be flushed with 10 ml of air within five (5) minutes following the Intervention. The Intervention is deemed unsuccessful if EAD(P) is unable to be flushed with 10 ml of air within five (5) minutes following the Intervention.

- Subject will receive a portable abdominal radiograph with contrast agent following the intervention. The radiologist (blinded to the study) will assess and report the abdominal radiographs post-intervention for adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the intervention. Study procedures carried out in IR may utilize low-dose fluoroscopy as an alternative to the portable abdominal radiograph.

- If the intervention is unable to restore EAD(P) patency, further steps to restore patency will be determined by the clinical team per usual practice.

General overview of Study Treatment Phase – Phase IIA

- Female patients $\geq$ 10 years of age or those who have experienced the onset of menses must have a documented NEGATIVE pregnancy test (urine or blood).

- Subject's most recent radiograph will be obtained and reviewed by the Investigator to identify EAD(P) characteristics and tube tip location, as well as pre-existing abnormalities, including damage to EAD(P) and/or tissue, if any.

- The Investigator has the option to order a new radiograph prior to the intervention if there is uncertainty about the status of the EAD(P) tube tip location and characteristics.

- The Subject's Nurse will obtain standard baseline measures of Subject pain.

- EAD(P) length will be determined by review of Subject EHR and/or markings on the EAD(P). The Investigator will place the Operator-set Collar to the same length determined by review of Subject's chart and/or markings on the EAD(P).

- Data will be gathered or abstracted from the EHR prior to, during the Subject receiving the intervention, and through the follow-up period. This data includes subject name, date of birth, contact information for parent guardian, age, sex, race, ethnicity, weight, stature, BMI, location (PICU/PCU/IR), dates of hospitalization (length of stay), medical record number (MRN), contact serial number (CSN), diagnosis, procedures performed, medications administered, laboratory and radiology results, ventilator parameters (if ventilated), severity of illness, nutrition information, information on EAD and clog, and physical assessments with vital signs (patient temperature, heart rate, respiratory rate, blood pressure and pain level).

- The patient's Nurse will obtain standard measures of Subject pain following intervention.

- Intervention is deemed successful if EAD(P) is able to be flushed with 10 ml of air within five (5) minutes following the Intervention. The Intervention is deemed unsuccessful if EAD(P) is unable to be flushed with 10 ml of air within five (5) minutes following the Intervention.

- Subject will receive a portable abdominal radiograph with contrast agent following the intervention. The radiologist (blinded to the study) will assess and report the abdominal radiographs post-intervention for adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the intervention. Study procedures carried out in IR may utilize low-dose fluoroscopy as an alternative to the portable abdominal radiograph.

- If the intervention is unable to restore EAD(P) patency, further steps to restore patency will be determined by the clinical team per usual practice.

General overview of Study Treatment Phase – Phase IIB

- Female patients $\geq$ 10 years of age or those who have experienced the onset of menses must have a documented NEGATIVE pregnancy test (urine or blood).

- Subject will be randomized to either TubeClear® intervention (experimental) or CHOP Standard Treatment (control) group according to randomization sequence.

- Subject's most recent radiograph will be obtained and reviewed by the Investigator to identify EAD(P) characteristics and tube tip location, as well as pre-existing abnormalities, including damage to EAD(P) and/or tissue, if any.

- The Investigator has the option to order a new radiograph prior to the intervention if there is uncertainty about the status of the EAD(P) tube tip location and characteristics.

- The Subject's Nurse will obtain standard baseline measures of Subject pain.

- Subject will receive TubeClear® intervention or CHOP Standard Treatment based on the randomization assignment.

- If randomized to TubeClear®, EAD(P) length will be determined by review of Subject's EHR and/or markings on the EAD(P). The Investigator will place the Operator-set Collar to the same length determined by review of Subject's chart and/or markings on the EAD(P). The TubeClear® Instructions for Use (i.e., Operator's Manual) will be followed by the user to restore patency to the EAD(P).

- If randomized to CHOP Standard Treatment, the CHOP protocol to restore patency to occluded EAD(P) will be followed.

- Data will be gathered or abstracted from the EHR prior to, during the Subject receiving either intervention, and through the follow-up period. This data includes subject name, date of birth, contact information for parent/guardian, age, sex, ethnicity, weight, stature, BMI, location (PICU/PCU/IR), dates of hospitalization (length of stay),

medical record number (MRN), contact serial number (CSN), diagnosis, procedures performed, medications administered, laboratory and radiology results, ventilator parameters (if ventilated), severity of illness, nutrition information, information on EAD and clog, and physical assessments with vital signs (patient temperature, heart rate, respiratory rate, blood pressure and pain level).

- Nursing assessment using the appropriate scale of the Subject's pain prior to and following the respective intervention will be abstracted from the medical record.

- Intervention in either group is deemed successful if EAD(P) is able to be flushed with 10 ml of air within five (5) minutes following the respective intervention. The intervention is deemed unsuccessful if EAD(P) is unable to be flushed with 10 ml of air within five (5) minutes following the intervention.

- Subject will receive a portable abdominal radiograph with contrast agent following either intervention. The radiologist (blinded to the study) will assess and report the abdominal radiographs post-intervention for adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the intervention. Study procedures carried out in IR may utilize low-dose fluoroscopy as an alternative to the portable abdominal radiograph.

- In either group, if the intervention is unable to restore EAD(P) patency, further steps to restore patency will be determined by the clinical team per usual practice.

4.3 Follow-up Phase

Follow-up surveillance will include assessment for any adverse event(s) related to the intervention (i.e. EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) and will continue for up to three (3) days following interventions in all study phases regardless of study intervention allocation. Clinical Assessment Measurements (i.e., pain, feeding tolerance, and usual measures to determine EAD(P) location) will be performed prior to, immediately following, and for up to three days after the intervention. Patients who are discharged from the hospital prior to three days will be followed up daily by phone for Clinical Assessment Measurements i.e., pain, feeding tolerance and EAD(P) location as assessed by caregiver until post Intervention day three.

4.4 Unscheduled Visits

There are no anticipated unscheduled visits in this Study.

4.5 Concomitant Medication

All prior and concomitant medications used within 1 day prior to the Subject's Study Intervention procedure and through the end of the Study Intervention will be recorded. The total doses of medications administered throughout this time will be included.

4.6 Rescue Medication Administration

There are no Rescue Medications administered in this Study.

4.7 Subject Completion/Withdrawal

Subjects may withdraw from the Study at any time without any change in their clinical management for any reason that the Subject, parent(s) or guardian(s) provide. They may also be discontinued from the Study at the discretion of the Principal Investigator if any significant Adverse Events (AEs) occur, or if the attending physician requests discontinuing a Subject if there is a perceived interference with a planned procedure. The Principal Investigator or the Study Sponsor may also withdraw Subjects who are not compliant with the Study plan, or to protect the Subject for reasons of safety or for administrative reasons. It will be documented whether or not each Subject completes the clinical Study. If the Principal Investigator becomes aware of any serious, related adverse events after the Subject completes or withdraws from the Study, they will be recorded in the source documents as well as on the Case Report Forms (CRF) with appropriate notification to the IRB.

4.7.1 Early Termination Study Visit

Subjects who withdraw from the Study will receive care according to CHOP standard procedures without any change to their clinical care. Adverse events from Study Intervention will be assessed for up to three (3) days following Intervention or until patient discharge (whichever is earlier). Patients who are discharged from the hospital prior to three days will be followed up daily by phone for Clinical Assessment Measurements (i.e., pain, and feeding tolerance) until post Intervention day 3.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Information from the medical record will be recorded and used for this study. This information will include medical history, information about your condition, lab and radiology results, medications, treatments, vital signs, and the response to treatments. We will be reviewing the medical record throughout the study.

We plan to follow-up all subjects for 3 days post-intervention in all study phases. It is possible that some study subjects might be discharged from the hospital prior to this endpoint. In such instances, we will need to contact the parent/guardian of the subject (as third party and not part of research procedures) and administer the follow-up questionnaire on a daily basis (till post-intervention day 3). As we cannot predict which subject is likely to be discharged prior to 3 days, we will obtain contact information for parents/guardians of all subjects at the time of obtaining informed consent.

Variables that will be abstracted from the EHR will include the following.

- Basic demographic information including subject name, medical record number (MRN), account number (CSN), Date of birth (DOB), race, ethnicity, sex, age at time of Study Intervention, weight, stature, calculated BMI, location (PICU/PCU/IR) and dates of hospitalization (length of stay)
- Contact information of parent/guardian will be collected to follow-up subjects for study related events, (in case subject is discharged prior to post-intervention day 3)
- Type of EAD(P)
- Date and place of EAD(P) insertion
- Length of EAD(P)
- EAD clog information
- Medications
- Nutrition
- Diagnoses
- Procedures
- Severity of illness
- Ventilator parameters (if applicable)
- Medications administered through EAD(P) preceding clog

- Nutrition administered through EAD(P) preceding clog
- Past Medical History
- Past Surgical History
- Established age-appropriate pain scales
- Laboratory results and radiology results

5.1.2 Physical Examination

Confirmation of EAD(P) occlusion will be made by CHOP staff according to CHOP protocol.

Documentation of Subject's clinical status (i.e., abdominal exam for contour, symmetry, etc.) will be reviewed and/or assessed by Investigator.

5.1.3 Vital Signs

Vital signs will be collected both as part of routine clinical care (baseline and daily follow-up) and research procedures (before, during and after the study interventions). Baseline vital signs and daily follow-up vital signs will be extracted from the EHR (EPIC).

5.1.4 Laboratory Evaluations

None.

5.1.5 Pregnancy Testing

Prior to being enrolled in the study, a urine/blood pregnancy test will be performed for female Subjects ≥ 10 years of age OR females who have experienced the onset of menses.

5.1.6 Other Evaluations, Measures

Portable abdominal radiograph with contrast agent after intervention (and portable abdominal radiograph, prior to intervention, if needed).

Clinical Patient Assessment Measurements (i.e., pain, feeding tolerance, and usual measures to determine EAD(P) location) will be performed prior to, immediately following, and for up to three (3) days after all interventions. Patients who are discharged from the hospital prior to three days will be followed up daily by phone for Clinical Assessment Measurements i.e., pain, feeding tolerance and EAD(P) location as assessed by caregiver until post intervention day three.

Age Appropriate Pain Scale Assessments (these scales include, but are not limited to): Face, Legs, Activity, Cry, Consolability (FLACC) Scale; Revised Face, Legs, Activity, Cry, Consolability (rFLACC) Scale; FACES Pain Scale revised (FPS-R); Numeric Pain Scale; Nursing judgment

Behavioral Likert scale and Generic Behavioral Analysis developed in conjunction with The Food and Drug Administration (FDA) will be used to assess subject behaviors during the study intervention. The Behavioral Likert Scale will be used by the study investigators to objectively assess subject behavior, while the Generic behavioral Analysis consists of questions that will be administered by the study investigators to the subject and their parent/guardian to assess their subjective assessment of the study intervention.

EAD(P) air and water flush.

5.2 Efficacy Evaluations

Efficacy (i.e. patency restoration) will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes following the intervention by the investigator.

5.2.1 Diagnostic Tests, Scales, Measures, etc.

With the exception of abdominal radiographs as described, and the pain, stress and behavioral scales used, there are no other diagnostic tests, scales, or measures used for this Study.

5.3 Pharmacokinetic Evaluation

There is no pharmacokinetic evaluation for this Study.

5.4 Safety Evaluation

The FDA has deemed TubeClear® to be non-significant risk for use in this study (**Appendix D**). Following successful restoration of EAD(P), a portable abdominal radiograph with contrast agent will be obtained. A radiologist (blinded to the study) will assess the radiographs for adverse events related to the respective Intervention and report results.

Subjects will be monitored for the occurrence of adverse events defined as any untoward or unfavorable occurrence. A description of all events will be recorded in the Study database.

Anticipated adverse events (AE), or "TubeClear® Specified Events" include: EAD displacement, EAD perforation and enteral tract tissue injury.

The relationship of each event to the study protocol will be classified according to severity, expectedness and relatedness by the bedside clinicians and recorded.

Unanticipated Problems (UP) involving risk to Subjects or others will also be tracked. UP includes any incident, experience, or outcome that is unexpected, related or possibly related to Intervention, and suggests that research places Subjects or others at greater risk for harm.

An AE is a reportable Serious Adverse Event (SAE) if it is serious, unexpected and related or possibly related to the Intervention.

Expedited reporting timeline for all SAE and unanticipated problems related to the Intervention or from protocol violations:

a. Principal Investigator or designee will notify their local IRB, medical monitor and AMI **within 24 hours of the event**.

A full narrative report describing the event within 7 calendar days will be submitted to the local IRB, medical monitor and AMI. Such reports will include a detailed description of the SAE/UP, an explanation of the basis for determining that the event represents a SAE/UP, and a description of any corrective actions that are proposed in response to the SAE/UP.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Objective

The primary objectives of this study are to 1) evaluate feasibility and tolerability of TubeClear® to restore patency in occluded EAD(P)s, and 2) compare efficacy of TubeClear® to the CHOP Standard Treatment to restore patency in occluded EAD(P)s.

The primary endpoints in Phase I are feasibility and tolerability of TubeClear® intervention. Feasibility will be defined as ability of the user to operate TubeClear® device (as per instructions and training in **Appendix F**) from insertion of the clearing stem into the occluded EAD(P) through device activation to patency restoration. Tolerability will be defined as ability of the Subject to undergo TubeClear® intervention.

The primary endpoint in Phase IIA is the ability of TubeClear® intervention to restore patency in Subjects with occluded EAD(P)s. This will be termed as EAD(P) patency restoration and will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes after completion of the intervention.

The primary endpoint of Phase IIB is the efficacy of TubeClear® intervention compared to CHOP Standard Treatment to restore patency in Subjects with occluded EAD(P)s. EAD(P) patency restoration will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes after completion of either intervention.

6.2 Secondary Objectives (or Aim)

The secondary objectives of this study are to assess subject pain, changes in physiological parameters, distress related EAD(P) events and adverse events related to the interventions.

In Phase I, Subject pain will be assessed before and after use of TubeClear® intervention using established age-appropriate pain scales. Acute changes in physiologic parameters will be measured, including changes in heart rate, blood pressure and respiratory rate. Distress related EAD(P) events which may be manifested by pulling or yanking of the EAD(P) will be monitored in relation to intervention. Following the TubeClear® intervention, each Subject will receive an abdominal radiograph with contrast. Study procedures carried out in IR may utilize low-dose fluoroscopy as an alternative to the portable abdominal radiograph. Radiographs will be reviewed by a radiologist (blinded to the study) for EAD(P) adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the TubeClear® intervention.

In Phase IIA, Subject pain will be assessed before and after use of TubeClear® intervention using established age-appropriate pain scales. Acute changes in physiologic parameters will be measured, including changes in heart rate, blood pressure and respiratory rate. Distress related EAD(P) events which may be manifested by pulling or yanking of the EAD(P) will be monitored in relation to intervention. Following the TubeClear® intervention, each Subject will receive an abdominal radiograph with contrast. Study procedures carried out in IR may utilize low-dose fluoroscopy as an alternative to the portable abdominal radiograph. Radiographs will be reviewed by a radiologist (blinded to the study) for EAD(P) adverse

events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to the TubeClear® intervention.

In Phase IIB, Subject pain will be assessed before and after use of either intervention using established age-appropriate pain scales. Acute changes in physiologic parameters will be measured, including changes in heart rate, blood pressure and respiratory rate. Distress related EAD(P) events which may be manifested by pulling or yanking of the EAD(P) will be monitored in relation to either intervention. Following either intervention, each Subject will receive an abdominal radiograph with contrast. Study procedures carried out in IR may utilize low-dose fluoroscopy as an alternative to the portable abdominal radiograph. Radiographs will be reviewed by a radiologist (blinded to the study) for EAD(P) adverse events (i.e., EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) attributable to either intervention. Incidence of adverse events attributable to the intervention (i.e. EAD displacement, EAD damage, enteral tract tissue injury) following the intervention will be monitored and reported in both groups.

In all phases, surveillance will include daily assessment for adverse events related to the respective study intervention (i.e. subject pain, feeding intolerance, EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) and will continue for three (3) days. Patients who are discharged from the hospital prior to 3 days will be followed up daily by phone until completion of 3 days following study interventions.

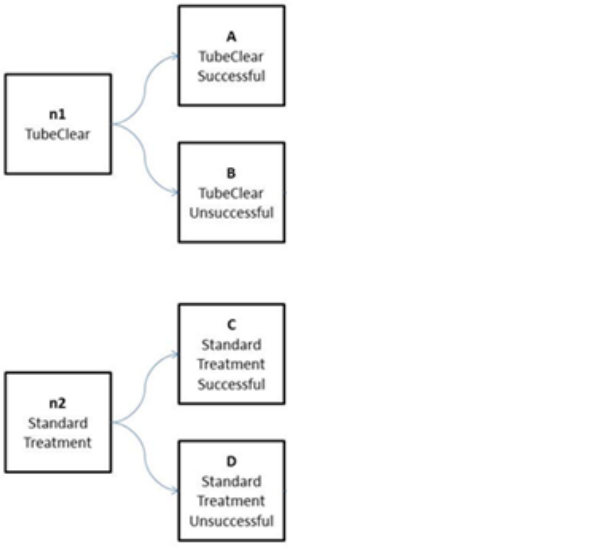
1. Intervention time (measured in minutes) is the time interval between commencement of intervention and achievement of EAD(P) patency (if successful).

2. Physiological parameters will be recorded from the Subject's EHR.

3. Distress related EAD(P) events which may be manifested by pulling or yanking of the EAD(P) will be monitored and recorded by Research Personnel or the Subject's nurse.

6.3 Statistical Methods

6.3.1 Group Allocation Flow Chart for Phase IIB



Intention To Treat	Successful	Unsuccessful
TubeClear	A	B
Standard Treatment	C	D

Figure 8: Group Allocation Flow Chart (Phase IIB)

6.3.2 Baseline Data

R Statistical Software[8] (Vienna, Austria) and G*Power[9,10] version 3.1.9.2 (Düsseldorf, Germany) will be used for data analysis. Prior to performing analyses, standard data cleaning Interventions will be applied. These Interventions include: screening the data for data-entry errors, checking for outliers, assessing the extent and pattern of missing data, and checking that appropriate assumptions of normality are met whenever necessary. Exploratory assessments will include the influence of covariates (i.e., the clinically relevant variables to be recorded) on outcome measures. Graphical displays, as appropriate, will be included as part of data analysis.

Baseline and demographic characteristics and other data will be summarized by standard descriptive summaries (e.g., means and standard deviations for continuous variables such as age, and percentages for categorical variables such as gender).

6.3.3 Primary Objective Analysis

Data from Phase I and Phase IIA will be observational and will not test a hypothesis. Data on feasibility and tolerability from Phase I and data on EAD(P) patency restoration will be reported as counts and percentages.

In Phase IIB, the primary objective is efficacy comparison between TubeClear® intervention and CHOP Standard Treatment. EAD(P) patency restoration will be measured by the ability to flush the EAD(P) with 10 ml of air within five (5) minutes following the Intervention. Efficacy is the proportion of EAD(P)s restored to patency in each group. A chi-square analysis (or Fisher's exact test) will be performed to compare the efficacy of TubeClear® intervention to the CHOP Standard Treatment. Intention-to-treat analysis will be used to compare the efficacy of the TubeClear® intervention to the CHOP Standard Treatment. Patients will be analyzed according to their randomized allocation. Full reporting of any deviations from random allocation and missing responses will be recorded and assessed in accordance with the CONSORT guidelines. Exploratory-per-protocol analysis will also be reported.

6.3.4 Secondary Objective Analysis

Data from Phase I and Phase IIA will be observational and will not test a hypothesis. Data on 1) pain, using established age-appropriate pain scales, 2) physiologic changes in vital signs, 3) distress related EAD(P) events, and 4) adverse events related to TubeClear® use will be described and reported as counts and percentages.

In Phase IIB, the secondary objectives between TubeClear® intervention and CHOP Standard Treatment include comparison of 1) time to intervention, 2) pain using established age-appropriate pain scales, 3) physiologic changes in vital signs, 4) distress related EAD(P) events, and 5) adverse events related to either group.

1. A log-rank test will be performed to compare intervention time of TubeClear® intervention to the CHOP Standard Treatment[15].

2. A Wilcoxon rank sum test will be performed to compare differences in subject pain and discomfort between TubeClear® intervention and CHOP Standard Treatment.

3. A t-test will be performed if the distributions are normal (or non-parametric equivalent, if the distributions are not normal) to compare differences in physiologic changes (i.e. vital sign changes) between TubeClear® intervention and CHOP Standard Treatment.

4. A Wilcoxon rank sum test will be performed to compare differences in distress related EAD(P) events (i.e. subject behavior such as pulling/yanking) between TubeClear® intervention and CHOP Standard Treatment.

5. A chi-square analysis (or Fisher's exact test) will be performed to compare the proportions of adverse events (i.e., EAD(P) displacement from the intervention; EAD(P) damage from the intervention; any enteral tract tissue perforation from the intervention) in TubeClear® intervention and CHOP Standard Treatment.

Intention-to-treat analysis will be used to compare the secondary endpoints between the TubeClear® intervention and the CHOP Standard Treatment. Patients will be analyzed according to their randomized allocation. Full reporting of any deviations from random allocation and missing responses will be recorded and assessed in accordance with the CONSORT guidelines. Exploratory-per-protocol analysis will also be reported.

6.3.5 Pharmacokinetic Analysis

No pharmacokinetic analysis is needed in this medical device Study.

6.3.6 Safety Analysis

All Subjects entering the Study will be included in the safety analysis. Clinical Patient Assessment Measurements (i.e., pain, feeding tolerance, and usual measures to determine EAD(P) location) will be performed prior to, immediately following, and for up to three (3) days after all Interventions. Clinically significant changes will be addressed and managed by the Subject's medical team, but recorded, reported, and followed by the Study team. Surveillance will include assessment for any adverse event(s) related to the intervention (i.e. EAD(P) displacement, EAD(P) damage, enteral tract tissue injury) and will continue for up to three (3) days following interventions in either group. Patients who are discharged from the hospital prior to three days will be followed up daily by phone for Clinical Assessment Measurements i.e., pain, feeding tolerance and EAD(P) location as assessed by caregiver until post intervention day three.

6.4 Sample Size and Power

Sample size has been selected such that the power (1- β) of primary endpoints is $1-\beta \geq 0.8$, with $\alpha = 0.05$.

- The efficacy of TubeClear® is expected to be at least 95% based on previous bench testing[xi]. The efficacy of CHOP Standard Treatment is expected to be about 50% based on focus group conclusions.[xii] Sample size results, displayed graphically, are as follows:

[xi] TP-5007-079 and TR-5007-079
[xii] Conclusions of Clinician Focus Groups, July 2009

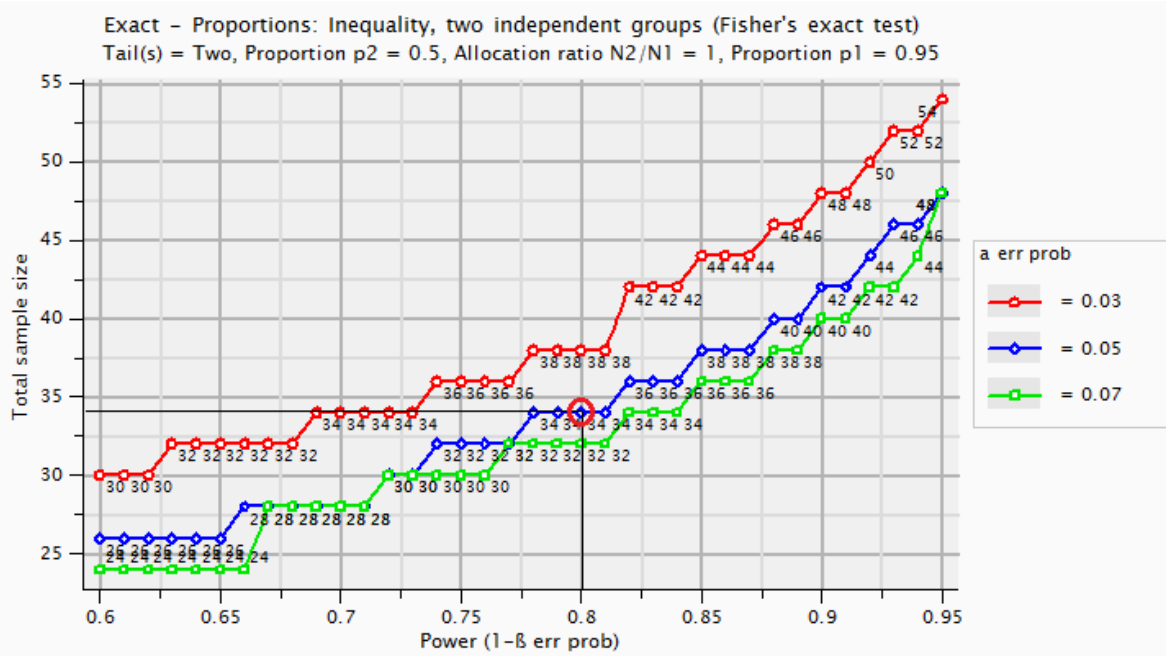


Figure 9: Sample size as a function of power at three different alpha levels

To ensure proper power is achieved a sample size of 17 Subjects in each group is needed (**Figure 9**).

- The efficiency of TubeClear® (Intervention time of TubeClear® to the CHOP Standard Treatment) is expected to be at least one standard deviation (40 minute difference of average time, 0.243 minute standard deviation[xiii]) greater than that of CHOP Standard Treatment based on bench testing.[xiv] Therefore, a sample size of 17 in each group is more than sufficient to show statistical significance of the desired effect.

6.5 Interim Analysis

No interim analysis will be performed. Phase I results will be complied into a report and submitted to the IRB for review. Continuation into Phases IIA and IIB will be determined by the IRB based on the reported results of Phase I.

[xiii] 40 minute difference = 42.8 minute average time for Standard Treatment – 2.8 minute average time for tube clear (data from section 1.1, **Table 2** of protocol). 0.243 standard deviation is calculated from data in TR-5007-079.
[xiv] TR-5007-079

7 STUDY DEVICE

7.1 Description

TubeClear® is the investigational device. TubeClear® is intended to clear the occlusions in EAD(P)s. TubeClear® is comprised of a reusable Control Box and a single use Clearing Stem. TubeClear® is currently FDA cleared for use ONLY and SOLELY in clearing occlusions/clogs from EAD(A)s. Clearing Stem models for ND, NG, NJ, G, and J Tubes of size 10 – 18 Fr, 10 – 140 cm and ND, NG, NJ, G, and J Tubes of size 6 – 18 Fr, 15 – 36 cm for adults have been FDA cleared (**Appendices A-E**). The FDA has deemed TubeClear® to be non-significant risk for use in this study (**Appendix D**).

This Study evaluates the use of TubeClear® in pediatric patients for the restoration of EAD(P) patency. The Clearing Stems being evaluated in this Study will be used with Pediatric Enteral Access Device ND, NG, and NJ 6 – 8 Fr, 38 – 140 cm; NG tube (Corflo, Corpak MedSystems) used as a jejunal tube inserted through a gastrostomy tube, 6 – 8 Fr, 38 – 140 cm; and AMT GJ tube, 14 Fr, 38 – 140 cm (15 – 55 in).

TubeClear® use will be compared to the CHOP Standard Treatment for restoring patency in occluded EAD(P) by efficacy and TubeClear® related adverse events will be monitored and reported. CHOP Standard Treatment administration during this Study will follow standard protocol at CHOP.

7.1.1 Packaging

TubeClear® is comprised of a reusable Control Box and a single use Clearing Stem. Both the Control Box and Clearing Stem are non-sterile. The Control Box can be stored in a custom carrying case or mounted to an IV pole. The exterior surfaces of the Control Box are to be wiped between uses with the disinfectant method used as part of CHOP's standard procedure for medical equipment that enters a patient's room. The Clearing Stems are disposable (for one-time use only) and individually packaged in a sealed bag. Each sealed bag contains a Clearing Stem and Directions for Use. The Directions for Use are a reference for using TubeClear® but do not replace the need to read, understand, and follow the TubeClear® Operator's Manual (i.e., Instructions for Use).

7.1.2 Labeling

TubeClear® Control Box is packaged with an Operator's Manual. Operators are responsible for reading, understanding, and following the Operator's Manual. Each Clearing Stem bag is labeled for the specific Clearing Stem Model, including EAD type, Fr size, Clearing Stem Model number, Clearing Stem Model color, intended use, cautions, and warnings.

7.1.3 Dosing

TubeClear® does not require dosing. In this Study, the Investigator will determine the EAD(P) length by Subjects chart or markings on the EAD(P). The Investigator will place the Operator-set Collar on the Clearing Stem to the centimeter marking that corresponds with the HER

and/or markings on the EAD(P). CHOP Standard Treatment will be administered according to CHOP standard protocol.

7.1.4 Treatment Compliance and Adherence

The Study intervention does not require ongoing treatments. Therefore, no compliance or adherence to ongoing treatment is needed.

7.1.5 Device Accountability

Records of the Study device (TubeClear®), and its disposition will be maintained by the Study Coordinator. These records will include device reception, device supply orders, device dispensing records, and disposition forms (in addition to model number and any other identifying information on the individual Clearing Stem). These records will be examined during the course of the Study by the Investigators and the Study Sponsor. The purpose of these records is to ensure to regulatory authorities and the Sponsor that the investigational device will not be distributed to any person who is not a Study Subject under the terms and conditions set forth in this protocol. At Study completion, all device supplies, including partially used and empty containers, must be returned to the Study Sponsor with the exception of the used Clearing Stems.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Clinical adverse events (AEs) (any unfavorable and unintended sign including an abnormal finding, symptom or disease associated with the use of a medical intervention, regardless of whether it is considered related to the medical intervention, that occurs during the course of the Study) will be monitored throughout the Study. While no clinical adverse events are anticipated, potential adverse events include:

- Clearing Stem exits the distal end of the EAD(P) and punctures the intestinal mucosal membrane.
- Clearing Stem causes damage to the EAD(P) that requires replacement of the EAD(P).
- A possible clinical adverse event for either intervention would be that the occluded medication is bolus flushed into the Subject's digestive system when patency is restored. The medication will have a varying rate of absorption in the digestive system that may cause unanticipated side effects to the Subject depending on the medication's safe therapeutic range. However, when using the TubeClear® occlusion clearing procedure (**Figure 4**) (i.e., an iterative process of partially clearing the occlusion then aspirating the broken occlusion particles, repeating until the collar reaches the EAD external ports (**Figure 2B**) would minimize potential for this clinical adverse event. Since the medication is periodically aspirated from the EAD(P), the final EAD(P) patency flush should contain minimal medication.
- The contrast used in the post-intervention radiograph could result in an allergic reaction to contrast agent. The post-intervention radiograph will also incur a dose of radiation. However, this dose replaces the dose that would be received for EAD(P) replacement if the occlusion was not cleared.

8.2 Adverse Event Reporting

The Investigator is responsible for recording and reporting unanticipated problems related to research that occurs during and after the Study Intervention. The plan for AE reporting is consistent with CHOP IRB Guidelines.

Since TubeClear® is a non-significant risk device (**Appendix D**) in adults, serious adverse events (SAEs) are not expected. If any unanticipated problems related to the research involving risks to Subjects or others occur during the course of this Study (including SAEs), they will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but are notable and could involve risks to Subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

A randomization sequence will be generated by computer program by the Study Sponsor for the randomized efficacy comparison in Phase IIB. The Study Team will be responsible for maintenance and execution of randomization sequence. The randomization sequence will be kept in individual sealed envelopes to be opened after the Subject is consented and enrolled in the Study. To ensure an appropriate balance of participation in both the TubeClear® intervention and CHOP Standard Treatment Groups, balanced, permuted block randomization will be used, as the Study is not entirely blinded.

9.1.2 Blinding

This Study will be blinded to the radiologist reading the abdominal radiographs post-intervention. The Study will not be blinded to the Investigators, Study Nurse, or other research staff due to the nature of the interventions in this Study.

9.1.3 Unblinding

This is not applicable to this Study, as the Investigators, Study Nurse, and research staff are not blind to the Intervention.

9.2 Data Collection and Management

The Study plan for collection and management of records is consistent with CHOP Policy A-3-6: Acceptable Use of Technology Resources that defines the requirements for encryption and security of computer systems.

1. Confidentiality will be protected by utilizing a code number as the only identifier for each Subject and the master list will be kept under lock and key by the Study Coordinator with access limited to the Investigators or Study Sponsor. All Study computer files will be password protected.

2. Data security will be maintained by having a backup copy of the password-protected file on the Study Coordinator's office computer, with the original in one of the CHOP's secure research servers in a separate protected drive.

3. All Subjects will be given a unique identification number. This identification number will be used on all Study forms and materials, except the Enrollment Log where the number is assigned. Only the primary Study team will have access to the Enrollment Log and will keep the Enrollment Log under secured lock and key. Study data including links (key) to PHI will be retained for at least 2 years after last marketing approval per FDA regulations.

9.3 Confidentiality

All data and records generated during this Study will be kept confidential in accordance with Institutional policies and HIPAA on Subject privacy and the Investigator(s) will not use such data and records for any purpose other than conducting the Study. Confidentiality will be protected by utilizing a code number as the only identifier for each Subject and the master list (i.e., Enrollment Form) will be kept secured with access limited to the immediate Study team only.

No identifiable data will be used for any future research Study without first obtaining IRB approval. The Investigator will obtain a data use agreement between the provider of the data (the Investigators) and any recipient researchers (both internal and external to CHOP) before sharing a limited dataset (PHI limited to birth date, date of admission, date of visit, date of service, and ZIP code).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

This study will incorporate a data and safety monitoring plan with a medical monitor to ensure adequate human subject protection. The medical monitor (TBD) will review study data monthly for adverse events to ensure the safety of study subjects. The medical monitor will be a physician knowledgeable in pediatric critical illness and unrelated to the study. The study PI will be notified of all serious adverse events within 24 hours of knowledge of event. Notification will be by any member of the study staff who is made aware of a serious adverse event. Study data are collected daily by the research personnel, and therefore review for SAE/AE's occurs daily while patients are actively on the study protocol. Identification of an SAE will prompt chart review by the site PI to determine possible relatedness to the study protocol. Should study subjects have serious adverse events related to study interventions, the PI will report these to the IRB, the Medical Monitor, and AMI to determine continuation of the study protocol within 24 hours of being notified of an SAE.

Oversight for the conduct of the Study will be provided by the Investigators. Adverse events are not anticipated, but any occurring will be documented and reported according to IRB policies and procedures. Study personnel will be solely responsible for data collection and verification. Confidentiality will be protected by utilizing a code number as the only identifier for each Subject and the master list (i.e., Enrollment Form) will be kept secured with access limited to the immediate Study team only.

- Investigators are responsible for oversight in conducting the Study.
- Study Sponsor will conduct monthly monitoring of the Study to verify that the protocol is being followed, data collected accurately, and reports filed as required.

9.5 Data Collection and Management

1. Confidentiality of the data will be ensured through the following

- A master list will be used and kept separate from other data forms. The master list will contain enrolled and screened patients and will link Personal Health Information (PHI) to the Subject ID number. This list will be kept in two forms: 1) an electronic file that will be kept on a secure clinical research drive maintained by the Department of Anesthesiology and Critical Care Medicine and 2) a paper file that will be kept in a locked file cabinet in the office of the PI, Co-PI, or Research Coordinator.

- The Subject ID# will be used to organize the demographic information (containing PHI), and data collection forms for enrolled Subjects. This information will be electronically stored on the password-protectedREDCap website provided through CHOP. (https://tiu.research.chop.edu/redcap/redcap/index.php?action=create). Paper copies of the coded data only will be kept in binders or file folders in a locked office cabinet.

2. Security.

- Demographic information (containing PHI), and data collection forms for enrolled Subjects will be stored on the password-protected REDCap website as well as a backup on a secure clinical research drive maintained by the Department of Anesthesiology and Critical Care Medicine. Paper copies of the coded data only will be kept in binders or file folders in a locked office cabinet.

3. Anonymization, de-identification or destruction.

- Study data including links (key) to PHI will be retained for at least 2 years after last marketing approval per FDA regulations. Completed consent forms and their associated assent will be maintained for 6 years following Study closure or publication. De-identified data will be maintained for 6 years as well.

4. REDCap

- Data used for publishing will be managed and stored using the research-focused electronic data capture system REDCap, under an agreement with the software's development consortium, led by Vanderbilt University. REDCap supports two secure, web-based applications designed exclusively to support data capture for research studies. REDCap is a PHP web application served by Apache Tomcat over a 128 bit SSL connection using a signed certificate. The application relies on a Study-specific data dictionary defined in an iterative self-documenting process that will be conducted by all members of the research team. The data dictionary is the foundation for custom case report form design and validated coding of variables. Authentication of research staff will be performed via LDAP using CHOP's enterprise Active Directory service. The application generates a complete audit trail of user activity, provides reporting, and has an automated export mechanism to common statistical packages (SAS, SPSS, Stata, R/S-Plus).

- The REDCap project used in this study will be validated to 21 CFR Part 11 requirements for controlled system access and electronic signatures, as data gathered from this study may be used in an FDA premarket notification (i.e., 510(k)). REDCap, as an overall software system, has the required components for compliance to Part 11. However, each individual project must be made compliant by adding in applicable features. Access will be limited to study personnel only, the electronic signatures will be enabled, study personnel will be delegated the appropriate role within the REDCap project to ensure that only a PI or co-PI can electronically sign a Subject record. AMI will compose a Software Requirements Document (identifying requirements that the REDCap project will need for compliance), a Validation Protocol (procedure to verify compliance to Part 11), and a Validation Report (execution of the Validation Protocol). The Validation Report will serve as documentation of the REDCap project compliance to Part 11 and will be maintained in the Regulatory Master File (RMF) by AMI. Lastly, AMI will compose an Instructions for Use document for filling out subject records within REDCap, which the study personnel will be trained on.The REDCap MySQL database is replicated in real time to a completely redundant instance of MySQL. The redundant instance is available for restoration of the primary database or for manual failover in the case of primary database failure. Time-stamped backup files are made from the replicated database daily by CHOP Research Information Systems using automated backup routines. Backup files are encrypted and transferred to a secure file server accessible only to designated personnel. A rolling seven-day window of backup files is maintained in an immediately available online state, with a larger window maintained in a compressed file archive available at a reduced speed of access. Daily destructive database backup files are stored on the database server and are deleted only after successful backup of the entire database to file. In the event of data error, loss or corruption, Research Personnel will work with CHOP Research Information Systems to determine the most appropriate recovery strategy.

- Data and backups are stored in the CHOP Research Information Systems Storage Area Network (SAN). Access to the SAN directories where data are stored will be limited to Research Information Systems personnel, with authentication performed using CHOP's enterprise Active Directory service.

9.5.1 Risk Assessment

The FDA has deemed TubeClear® to be non-significant risk for use in this study (**Appendix D**). TubeClear® is currently FDA cleared for use ONLY and SOLELY in clearing occlusions/clogs from EAD(A)s (**Appendix A**).

9.5.2 Potential Benefits of Trial Participation

The potential benefit to the Study Subjects is restored EAD(P) patency so that treatment via EAD(P) can continue and so EAD(P) removal and replacement procedure(s) are avoided. Results from this Study will benefit future individuals with an occluded EAD(P) by developing a method to restore patency to the EAD(P). TubeClear® addresses this clinical

need to safely and efficaciously restore patency to occluded EADs at the patients' bedside while the EAD remains in the patient.

9.5.3 Risk-Benefit Assessment

The potential Study benefits outweigh the potential risks. When an EAD(P) becomes occluded and patency cannot be restored, the EAD(P) must be replaced. Risks associated with EAD(P) replacement vary depending on the type of EAD(P) to be replaced. Risks associated with NG, ND, NJ replacement include nasopharyngeal irritation and pain, incorrect EAD(P) placement, EAD(P) coiling, perforation of lung, esophagus, stomach or small intestines, aspiration and abscess.[11,12] Risks associated with G and J EAD(P) replacement include loss of access, bleeding, infection, fistulas, aspiration, and perforation of abdominal organs.[12] Risks associated with GJ EAD(P) replacement include loss of access, bleeding, infection, and leakage.[13,14] These risks are reduced by reducing or eliminating EAD(P) replacement for Subjects selected for Study participation. Risks of the Study related to the post treatment radiograph with contrast include allergic reaction to the contrast agent and radiation dose. The risk for allergic reaction to contrast agent is low as most Subjects will have received contrast agent during initial EAD(P) placement. The risk of exposure to radiation is not substantially changed as an abdominal radiograph and/or fluoroscopy would be utilized to replace an EAD(P) and EAD(P) replacement will be reduced or eliminated with the Study. Subjects selected for Study participation will be monitored closely for adverse events, although no adverse events are anticipated. It is possible that younger Subjects may be enrolled before and/or in disproportionate numbers than older Subjects as younger Subjects may be more likely to experience EAD(P) occlusions.

9.6 Recruitment Strategy

Subjects will be recruited from patients in the CHOP PICU, PCU, and/or IR that are identified to have an occlusion of their EAD(P)s during the current admission. Potential eligible Subjects will be identified by screening the electronic health records (EHR). In addition, CHOP staff may notify the research personnel when there is a potential Subject. The Research Personnel will screen potential Subjects using the protocol inclusion and exclusion criteria. Information about this study will be disseminated electronically via email and described on the PICU website on the intranet.

9.7 Informed Consent/Assent and HIPAA Authorization

The Investigator will be responsible for obtaining informed consent from the parent/guardian and patient assent, if appropriate. The Investigator will provide a detailed description of the Study and allow adequate time for questions and discussion. The Investigator will ascertain Study comprehension by asking the parent/guardian and, if appropriate, the eligible Subject to describe the Study. Parent/guardian and, if appropriate, the eligible Subject will be provided with as much time as needed to make a determination on Study participation. Parent/guardian and, if appropriate, the eligible Subject will sign the informed consent/assent form. Interpreter services or language line will be utilized to obtain consent for non-English speaking potential Subjects using short forms and Study Summary documents. Coercion will be avoided by allowing the parent/guardian and, if appropriate, the eligible Subject ample time to elect Study

participation and by inviting the parent/guardian and, if appropriate, the eligible Subject to seek counsel from other family members, friends, and medical professionals about the Study. HIPPA authorization will be included in the informed consent/patient assent form. Once signed, the forms will be maintained in a secured place with access limited to the immediate Study team only.

9.8 Payment to Subjects/Families

There is no payment to Subjects/families for participation in this Study.

10 PUBLICATION

Publication of Study results will not contain Subject identifying information.

11 REFERENCES

1. ARMY Medical Field Feeding Operations. In: ARMY, ed. Washington, DC2003.
2. Lyman B, Kemper C, Northington L, et al. Use of Temporary Enteral Access Devices in Hospitalized Neonatal and Pediatric Patients in the United States. Journal of Parental and Enteral Nutrition: American Society for Parenteral and Enteral Nutrition; 2015.
3. Yu H, Wier L, Elixhauser A. Hospital Stays for Children, 2009. Healthcare Cost and Utilization Project: Agency for Healthcare Research and Quality; 2011.
4. Haber H, Stern M. Intestinal Ultrasonography in Children and Young Adults: Bowel Wall Thickness is Age Dependent. J. Ultrasound Med2000:315-321.
5. Merkel S, Shayevitz J, Voepel-Lewis T, Malviya S. The FLACC: A Behavioral Scale for Scoring Postoperative pain in Young Children. Vol 23. Pediatric Nursing: Practice Applications of Research; 1997.
6. Malviya S, Voepel-Lewis T, Burke C, Merkel S, Tait AR. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. *Pediatric Anesthesia.* 2006;16(3):258-265.
7. Hicks C, von Baeyer C, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale – Revised: toward a common metric in pediatric pain measurement. Vol 93. Pain: Elsevier; 2001:173-183.
8. R, Core, Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.
9. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods.* 2007;39(2):175-191.
10. Faul F, Erdfelder E, Lang A-G, Buchner A. Statistical power analyses using G*Power 3.1:Tests for correlation and regression analyses. *Behavior Research Methods.* 2009;41(4):1149-1160.
11. Durai R, Venkatraman R, Ng PC. Nasogastric tubes. 2: Risks and guidance on avoiding and dealing with complications. *Nurs Times.* 2009;105(17):14-16.
12. Beyer P. Complications of Enteral Feedings. In: Matarese LE, Gottschlich MM, eds. *Contemporary nutrition support practice : a clinical guide*. 2nd ed. Philadelphia: Saunders; 2003:215-226.
13. Rosenberg J, Amaral J, Sklar C, et al. Gastrostomy and gastrojejunostomy tube placements: outcomes in children with gastroschisis, omphalocele, and congenital diaphragmatic hernia. *Radiology.* 2008;248(1):247-253.
14. Friedman J, Ahmed S, Connolly B, Chait P, Mahant S. Complications associated with image-guided gastrostomy and gastrojejunostomy tubes in children. *Pediatrics.* 2004;114(2):458-461.
15. Sedgwick P. Statistical tests for independent groups: time to event data. BMJ 2012;345:e5257-e5257.

Appendices

Appendix A: FDA 510k clearance documentation for K121571, K123659, K131052, K163092, and K172556..

Appendix B: Research Plan and Device Description: National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development Phase II Small Business Innovation Research Grant: In-Patient Pediatric Gastrojejunal Tube Cleaner Eliminating Surgical Intervention (2R44HD065365-02).

Appendix C: Test Reports and Test Protocols for the EAD(A) Clearing Stems listed in this Protocol in numerical order.

Appendix C.2: Test Reports and Test Protocols for the EAD(P) Clearing Stem design listed in this Protocol in numerical order.

Appendix D: FDA & Walter Reed Heath Care System NSR Determination.

Appendix E: TubeClear® Clinical and Trial Evaluation Forms

Appendix F: TubeClear® Training Procedure