The Follow-up Automatically vs. As-Needed Comparison (FAAN-C) Trial
Protocol Number 1.00

The Patient-Centered Outcomes Research Institute

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PROTOCOL TITLE:

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Short Title: FAAN-C
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I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

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1 Study Summary

Title	The Follow-up Automatically vs. As-Needed Comparison (FAAN-C) trial
Short Title	FAAN-C (pronounced “fancy”)
Design	FAAN-C is a multicenter randomized controlled trial that will enroll 2,674 patients across participating hospitals
Study Duration	5 years
Data Coordinating Center	University of Utah
Primary objectives	Compare the effectiveness of as-needed vs. automatic post-hospitalization follow-up
Number of Subjects	2,674 patients
Eligibility Criteria	Children, hospitalized for pneumonia, skin and soft tissue infection, acute gastroenteritis, or urinary tract infection will be eligible for enrollment. Excluded: Children with a history of comorbid disease that is both chronic and complex
Statistical Methodology	Analyses will be conducted in an intention-to-treat (ITT) manner, in which all randomized subjects are included and analyzed according to their randomization assignment.

2 Background and Rationale

2.1 Background

Follow-up visits are common A “follow-up visit” occurs when a medical provider instructs a patient to schedule an additional medical visit for the purpose of re-evaluating the patient’s condition in the future. Follow-up visits are utilized in nearly every clinical setting, including follow-up after acute visits to primary care, urgent care, specialty care, the emergency department, or the hospital. Nationally representative survey data from the 2018 Medical Expenditure Panel Survey demonstrate that US children attend nearly 20 million follow-up visits annually, at a cost of $4.3 billion.[1]

Automatic post-hospitalization follow-up has intuitive appeal The present proposal focuses on one type of pediatric follow-up visit: the post-hospitalization follow-up visit. Most hospitalized patients (>80%) are prescribed automatic post-hospitalization follow-up, meaning they are routinely instructed to visit their primary care provider (PCP) shortly after hospital discharge, regardless of

symptom improvement.[2, 3] The majority of patients comply with these instructions and attend the follow-up visit.[3–5] The intuitive appeal of automatic follow-up is to provide an opportunity for PCPs to connect with patients and their families to: verify that a patient is following an expected course, adjust the treatment regimen if needed, provide additional reassurance about the patient's illness, and address any gaps in continuity of care (e.g., immunizations). Automatic follow-up is especially intuitive for children with chronic and/or complex medical needs, who are at increased risk for adverse events[6, 7] and readmission.[8–11] For this reason, discharge improvement interventions that include automatic follow-up have focused on populations of children with chronic and/or complex medical needs, such as children hospitalized for asthma,[12] premature birth,[13, 14] or major surgery.[15]

Automatic follow-up for previously healthy children recovering from common infections may not be necessary While the rationale for automatic follow-up is compelling for children who have chronic and complex medical needs, most hospitalized children are previously healthy and hospitalized for acute conditions from which complete recovery is expected.[16, 17] Five of the top 10 reasons for pediatric hospitalization are acute infections, including: pneumonia, bronchiolitis, skin and soft tissue infections, gastrointestinal infections, and urinary tract infections.[18] Together, these infections are responsible for over 500,000 pediatric hospitalizations each year in the US.[18] After hospital discharge, the vast majority of previously healthy children recover from these infections within a matter of days and rarely experience an interim worsening of their illness (readmission rates are <5%[10]). Given such a reassuring prognosis, the benefit of automatic follow-up for previously healthy children recovering from common infections is unclear.

PRN follow-up is a patient and family-centered alternative to automatic follow-up Patient and family-centered care means that patient and family values guide all clinical decisions.[19] Patients and families whose preferences are incorporated into their plan of care make more value-congruent choices[20] and are more likely to follow the plan of care.[21] A PRN (*pro re nata*, "as-needed") follow-up strategy is aligned with the principles of patient and family-centered care, encouraging families to monitor their child's symptoms after hospital discharge and schedule a visit if the child does not improve or if new concerns arise. As such, PRN follow-up empowers families with greater autonomy and allows them to consider their preferences and values when deciding whether or not to pursue post-hospitalization follow-up. Taking this decision-making away from families runs the risk of undermining their sense of self-efficacy—a patient's or parent's confidence to solve self-identified problems.[22] Despite being patient and family-centered, PRN follow-up is prescribed to a minority of patients (10–15%) largely because of limited evidence.[2, 3]

Preliminary data Families and medical providers struggle, not knowing which follow-up option is best. To better understand the perspectives of end users of post-hospitalization follow-up, we conducted three separate focus groups (Table 1), among: 1) parents of children who had been hospitalized, 2) hospitalists (physicians who care for hospitalized children), and 3) PCPs. Focus groups consisted of 6–8 participants each. Participants in each focus group came from at least 3 different FAAN-C institutions. Overall, families felt that their circumstances and the options available to them were not adequately considered in post-hospitalization follow-up decision-making.

Hospitalists expressed uncertainty about the available evidence to help guide their recommendations. PCPs saw advantages to some follow-up visits, but worried that others were unnecessary. The unifying theme for end-users was the need for better evidence to guide conversations and decision-making around follow-up.

Table 1: Representative comments from family, hospitalist, and PCP focus groups

Focus group question	Representative participant comments
For families: What has been your experience with follow-up care instructions after your child's hospitalization?	"They tell you to go visit the doctor but they have no idea if you have transportation, money for gas, money for parking, help with child care" "Whatever option they give you, you think that's all there is"
For hospitalists: Please describe your decision-making for post-hospitalization follow-up recommendations to families.	"It's a historical norm [automatic follow-up], that gives us some reassurance, but it's never been evidence tested" "We normally do this [automatic follow-up], we always have done it, but it isn't backed in any confidence or any evidence"
For PCPs: Please describe your experience with post-hospitalization follow-up visits.	"For anxious families or families with unanswered questions it's been helpful" "I feel bad when they're in clinic and they look great, and I say ok you're better, sorry you have to pay a copay" "Our schedules are really packed full and you hate to have a family come in if they don't really need to be there"

BeneFIT RCT demonstrates promise of PRN follow-up for one common pediatric infection. Our team completed an RCT comparing PRN vs. automatic follow-up, called the Bronchiolitis Follow-up Intervention Trial (BeneFIT).[23] BeneFIT was a multicenter trial conducted across 4 hospitals. BeneFIT participants were 304 children hospitalized for a common infection called bronchiolitis. Results from BeneFIT are presented in Table 2. Four-fold fewer families attended post-hospitalization follow-up visits in the PRN group (19%) compared to the automatic group (81%). Both groups otherwise had similar outcomes, including no significant differences in parent anxiety, symptom duration, or readmission.

Table 2: Results of the BeneFIT RCT

Outcome	PRN N = 138	Automatic N = 131	Absolute Difference (95% CI)
Attendance of a follow-up visit, *n* (%)	26 (19)	106 (81)	−63 (−53 to −72)
Parent anxiety score,[a] mean	3.9	4.2	−0.3 (−1.0 to 0.7)
Days to symptom resolution, mean	10	11	−1 (−3 to 1)
Readmission, *n* (%)	3 (2)	5 (4)	−2 (−6 to 2)

[a]Primary outcome, scored by validated instrument;[24] higher scores= greater anxiety

2.2 Rationale

The importance of examining post-hospitalization follow-up Observational studies have reached conflicting conclusions about post-hospitalization follow-up, with some studies finding an association between automatic follow-up and decreased rates of hospital revisit[25–31] and other studies finding no association or increased rates of hospital revisit.[32–37] BeneFIT remains one of the only pediatric RCT to examine patient and family-centered outcomes for post-hospitalization follow-up.[23] Generalizations about post-hospitalization follow-up after BeneFIT are limited because BeneFIT was not powered to detect differences in hospital readmission, and BeneFIT only enrolled children with one specific type of infection, bronchiolitis. A systematic review of hospital discharge interventions highlighted post-hospitalization follow-up as its first "Persistent Literature Gap."[38] A national collaboration sponsored by the American Academy of Pediatrics' Quality Improvement Innovation Networks and the Section on Hospital Medicine concluded that certain quality measures, including post-hospitalization follow-up, "require further study for feasibility, measurement reliability and validity, and effectiveness in preventing harm."[39] Despite substantial gaps in the literature, multiple quality metrics have been developed recently to promote automatic post-hospitalization follow-up, including Pedi-BOOST, the Center of Excellence on Quality of Care Measures for Children with Complex Needs, and the Pediatric Transition Experience Measure.[40–43] Hospitals are adopting these measures and promoting automatic post-hospitalization follow-up.[4, 5]

PRN follow-up has potential to improve delivery of care High-value care makes efficient use of resources and ensures that patients receive meaningful benefit.[44] The "Triple Aim" in high-value care is to simultaneously improve the patient experience of care, reduce the cost of care, and improve the health of populations.[45] PRN follow-up has the potential to achieve this status by decreasing the amount of time that patients spend seeking medical care, decreasing patient costs, and decreasing exposure to unnecessary medical tests and treatments.

1) Time and cost-savings. Clinic visits require an average of two hours of a family's time and result in out-of-pocket expenses and lost income.[46] Out-of-pocket expenses include money for travel, parking, co-pays, and child care. These burdens disproportionately affect racial/ethnic minority and lower income families. For example, attendance of a clinic visit requires 30% more time

for Hispanic and Non-Hispanic Black families compared to Non-Hispanic white families due to increased travel and in-clinic time.[47] Out-of-pocket healthcare expenditures relative to income are >300% higher for families whose income is less than the Federal Poverty Level, compared to high-income families.[48] Lost income occurs when parents take time away from work to attend the visit, which is particularly challenging for parents who may have already taken time away from work during their child's hospitalization. Lost income at the time of hospitalization is highest for racial minority and single-parent households.[49] PRN follow-up could mitigate these burdens without compromising quality of care.

2) Decreased exposure to unnecessary medical tests and treatments. Seemingly benign medical interventions have the potential to precipitate additional tests and interventions that are unnecessary, costly, and potentially harmful.[50–52] Four recent pediatric RCTs have compared PRN follow-up or usual care to an intervention that augments follow-up (Table 3). In each RCT, augmented follow-up resulted in more medical care, without otherwise improving patient outcomes. A pattern of increased medical care that does not improve patient outcomes is concerning for overtreatment.[53] For children recovering as expected, avoidance of a post-hospitalization follow-up visit might reduce exposure to overtreatment.

Table 3: RCTs that suggest efforts to augment follow-up can potentially result in overtreatment

RCT	Population	More intensive follow-up group	Less intensive follow-up group	Primary Outcome	Potential Overtreatment
Auger et al[54]	Hospitalized children (variety of diagnoses)	Post-discharge nurse-led home visit	No home visit	30-day reutilization rate for urgent health care services	The 30-day reutilization rate was higher in the augmented follow-up group.
Auger et al[55]	Hospitalized children (variety of diagnoses)	A post-discharge telephone call	No phone call	30-day reutilization rate for urgent health care services	No significant difference, but point estimate for the 30-day reutilization rate higher in augmented follow-up group.
Colaco et al[56]	Children with distal radius buckle fractures	Automatic PCP follow-up	PRN follow-up	Parent report of child's physical function 3 weeks after injury	No difference in primary outcome; more physician visits, higher costs, and more radiographs for augmented follow-up.
Coon et al[23] (BeneFIT)	Hospitalized children with bronchiolitis	Automatic PCP follow-up	PRN follow-up	Parental anxiety 7 days after discharge	No difference in primary outcome; new prescriptions at follow-up visits for therapies discouraged by national guidelines.[57]

3 Objectives and Outcomes

3.1 Primary Objective

The primary objective of this study is to compare the effect of a recommendation for PRN vs. automatic post-hospitalization follow-up on hospital readmission within 14 days of hospital discharge. We hypothesize that a recommendation for PRN follow-up will be non-inferior to a recommendation for automatic follow-up in terms of hospital readmission rates.

3.2 Secondary Objectives

Our secondary objectives are to determine the effect of a recommendation for PRN follow-up, compared to a recommendation for automatic follow-up, on:

- medical interventions that a child receives after hospital discharge
- child health-related quality of life

3.3 Study Process Measure

The proportion of participants who attend a follow-up visit (in-person or via telehealth) within 7 days of hospital discharge will be reported but will not be categorized as a formal outcome. Rather, the proportion of participants who attend a post-hospitalization follow-up visit will be a study process measure. A prior trial demonstrated that randomization to a recommendation of PRN vs automatic follow-up does result in a large difference in follow-up visit attendance.[23] We hypothesize that recommendations for PRN vs automatic follow-up in FAAN-C will similarly result in large differences in follow-up visit attendance.

4 Study Outcomes

4.1 Selection of Outcomes

Selection of study outcomes was informed by the previously described focus groups involving parents of hospitalized children, hospitalists, and PCPs. Illustrative quotes that influenced selection of specific outcomes are presented in Table 4. Parents, PCPs, and hospitalists were clear that hospital readmission should be the primary outcome.

Table 4: Selection of outcomes informed by focus groups

Participant	Representative participant responses to a question asking which outcomes would be important to study	Outcome added to FAAN-C
Parent	"The impact on parents, their time away from work"	Parent time
Parent	"We're all very invested in making sure things work out the best for our kids, often at the expense of our own health. Anxiety would be interesting to see because that plays into the situation and comes back to impact our kids as well."	Parent anxiety
Parent	"The one that really stands out to me is the number of times we have to go back to the hospital after being sent home."	Hospital readmission as the primary outcome
PCPs	"I feel like I develop my relationship with my patients and families through their well-child check-ups, not the sick or hospital follow-up appointments."	Well-child visits
PCPs	"I like to at least call my patients and parents after they are discharged from the hospital to maintain that relationship."	Telephone and electronic communications with medical providers
PCPs	"We worry that if kids don't follow-up, are they going to get so bad they need to be readmitted, so we hope that the follow-up prevents readmission."	Hospital readmission as the primary outcome
Hospitalist	"I think it helps to strengthen the relationship between the PCP and the family, so that they can see their PCP as not just the well doctor, but the well and sick doctor."	Usual place of medical care
Hospitalist	"I would look at health outcomes, readmission number one and emergency department utilization."	Hospital readmission as the primary outcome; total additional ambulatory visits

4.2 Primary Outcome

The primary outcome is the proportion of participants who experience a hospital readmission within 14 days of their index hospital discharge. All causes of hospital readmission, even if seemingly unrelated to the index infection, will be scored as a hospital readmission for the purpose of the primary outcome. Hospital readmission will be measured primarily by parent report. On days 7, 14, and 30 after hospital discharge, parents will be surveyed and asked about hospital readmissions since discharge. Parent report allows capture of readmissions that occur outside of a given hospital's electronic health record (EHR) system. However, parent report may be inaccurate for a proportion of participants and will be missing for others. Parent report will be assumed inaccurate in two cases: (1) a parent reports a readmission at a hospital whose records are available in the EHR, but there is no readmission documented in the EHR. These cases will not be counted as readmissions. (2) Cases in which a parent reports no readmission but there is a readmission documented in the EHR. These cases will be counted as readmissions. When parent report is missing, imputation will be utilized, as described in the missing data section.

4.3 Secondary Outcomes

Medical interventions and child health-related quality of life are pre-specified as the main secondary outcomes under consideration. Medical interventions are a main secondary outcome because decreasing exposure to unnecessary medical tests and treatments is a core component of improving healthcare value and a potential advantage of PRN follow-up. Medical interventions will be measured by parent report. Child health-related quality of life is a main secondary outcome because it is a patient-centered measure of how much a child's health is impacting their usual activities or routines. Child health-related quality of life will be measured by child report, unless the child is too young to self-report or prefers parent report.

4.4 Exploratory Outcomes

Exploratory outcomes are listed in Table 5. If participants in the PRN follow-up group are able to attend fewer post-hospitalization follow-up visits, the cost burden to parents, the child's time away from school or daycare, and parent time away from work and other responsibilities might be lower. We hypothesize that a recommendation for PRN follow-up might result in greater telephone and electronic communications between families and the child's medical providers. It is possible that a recommendation for PRN follow-up could serve as a missed opportunity to reconnect a child and their primary care provider, resulting in small decreases in well-child visits, immunizations, participants who report having a usual place of medical care, and medical interventions related to the index infection. We hypothesize that the remainder of the exploratory outcomes (symptom duration, parent self-efficacy, parent anxiety, and satisfaction with care) will be similar between participants randomized to a recommendation for PRN follow-up compared to participants randomized to a recommendation for automatic follow-up. All exploratory outcomes are measured by parent report, from the time of hospital discharge until the specified time after discharge.

4.5 Safety Outcomes

Safety outcomes are also listed in Table 5. Safety outcomes were selected with the goal of capturing adverse consequences (beyond hospital readmission, the primary outcome) that families might experience as a result of a recommendation for PRN follow-up, compared to a recommendation for automatic follow-up. A recommendation for PRN follow-up may result in those participants having to attend a greater number of other types of ambulatory visits (e.g., emergency department visits). The subset of non-primary care ambulatory visits will be measured because these visits have the potential to be more burdensome for participants (i.e., larger co-pays and urgent, less convenient visits), relative to a primary care visit. It is also possible that a recommendation for PRN follow-up could result in greater exposure to medical errors after hospital discharge (e.g., medication problems, complications of care), since another medical provider may not connect with the child and family shortly after hospital discharge. In addition to the primary outcome of all-cause hospital readmission, an additional safety outcome will be hospital readmissions related to the index infection. All safety outcomes are measured by parent report, from the time of hospital discharge

until the specified time after discharge.

Table 5: Secondary, exploratory, and safety outcomes

Outcome	Definition	Expected outcomes type for analysis[a]
Secondary outcomes		
Medical interventions	Proportion of participants who receive either a laboratory test, imaging test[b], or a new medication within 14 days of hospital discharge	Binary
Child health-related quality of life	Mean health-related quality of life score 7 days after hospital discharge, measured by the Impact on Activities and Routines instrument	Normal
Exploratory outcomes		
Cost burden	Mean total costs to parents (missed income and expenses) related to the participant's illness within 14 days of hospital discharge, measured by the cost burden survey in Chang et al[49]	Binomial-Gamma hurdle
Child time	Mean number of hours of school or daycare missed by the participant within 14 days of hospital discharge as a result of their medical needs	Over-dispersed Binomial
Parent time	Mean number of hours spent away from responsibilities (work or non-work related) by parents within 14 days of hospital discharge as a result of their child's medical needs	Normal or Gamma
Symptom duration	Proportion of participants who have completely recovered from their infection at 7 days after hospital discharge	Binary
Total additional ambulatory visits	Mean number of ambulatory visits (in-person or via telehealth) that a participant attends, apart from the post-hospitalization follow-up visit, within 30 days of hospital discharge; Ambulatory visits include clinic, urgent care, and emergency department (not resulting in hospital admission) visits.	Negative Binomial
Non-primary care ambulatory visits	Mean number of ambulatory visits (in-person or via telehealth) to non-primary care providers, within 30 days of hospital discharge; Non-primary care providers will include all providers outside of the clinic that families identify as their primary care clinic.	Negative Binomial
Parent self-efficacy	Mean self-efficacy score 7 days after hospital discharge, measured by the PROMIS self-efficacy short form[58]	Normal
Parent anxiety	Mean anxiety score 7 days after hospital discharge, measured by the PROMIS anxiety short form[58]	Normal or Gamma
Satisfaction with care	Proportion of participants who report agreeing or strongly agreeing with the statement, "I am satisfied with the medical care my child has received since hospital discharge," 7 days after hospital discharge	Binary
Telephone and electronic communications with medical providers	Mean number of telephone and electronic (excluding telehealth visits) communications with a medical provider within 14 days of hospital discharge	Negative Binomial
Well-child visits	Proportion of participants who attend a well-child visit within 6 months of hospital discharge	Binary
Immunizations	Proportion of participants who receive an immunization within 6 months of hospital discharge	Binary

Usual place of medical care	Proportion of participants who report having a usual place of medical care 6 months after hospital discharge	Binary
Medical interventions related to the index infection	Proportion of participants who receive either a laboratory test, imaging[b] test, or a new medication related to the index infection within 14 days of hospital discharge	Binary
Safety outcomes		
Medical errors	Proportion of parents who report that their child experienced a medical error within 14 days of hospital discharge, measured by the Family Safety Interview[59]	Binary
Hospital readmissions related to the index infection	Proportion of participants who experience a hospital readmission related to the index infection within 14 days of hospital discharge	Binary

[a]Outcome type designations, particular as normal or gamma, are preliminary and may be updated based on the observed skewness in the outcome variables.
[b]Urogenital imaging for urinary tract infections will be excluded from this measure because urogenital imaging is often recommended by guidelines and the potential benefits of such imaging have a longer time horizon than the present study.

4.6 Child health-related quality of life instrument

All instruments will be scored as described in the referenced publications. The Impact on Activities and Routines Instrument, used to measure child health-related quality of life, has not been published yet. For this reason, we describe this instrument and its scoring here. The Impact on Activities and Routines Instrument has the option of using a child-reported question or a parent-reported question. The child-reported question will be utilized, unless the participant is too young to self-report or prefers parent report. The child reported question is: In the past 7 days, how much did the medical concern that led to your hospitalization impact your usual activities or routines (e.g., go to school, play, eat, sleep)? The parent-reported questions that will be used, if necessary, is: In the past 7 days, how much did the medical concern that led to your child's hospitalization impact their usual activities or routines (e.g., go to school, play, eat, sleep)? Answer choices to both questions are: 1, Not at all | 2, Slightly | 3, Moderately | 4, Quite a lot | 5, Extremely. Mean score responses will be used in analyses.

5 Overall Study Design

FAAN-C is a multicenter RCT that will enroll 2,674 patients across approximately 10 hospitals, including children's and community hospitals. Inclusion of community hospitals is a priority because community hospitals care for the majority of hospitalized children in the US[17] but are historically underrepresented in research.[60, 61] FAAN-C is powered for non-inferiority of a recommendation for PRN follow-up compared to a recommendation for automatic follow-up, with 14-day all-cause

hospital readmission as the primary outcome. Non-inferiority trials test the hypothesis that one intervention is not worse than a comparator with respect to the primary outcome. This design is useful when evaluating an intervention that is more efficient, less prone to adverse events, and/or less costly than the accepted comparator.[62] If non-inferiority is demonstrated, patients can benefit from a simpler, safer alternative intervention. In the case of FAAN-C, there are clear advantages to PRN follow-up over automatic follow-up. Namely, a recommendation for PRN follow-up affords families the convenience of not necessarily having to attend another medical appointment, which means decreased costs and decreased time away from work and school. As such, FAAN-C fits a non-inferiority trial design. If PRN follow-up is shown to be non-inferior to automatic follow-up for the primary outcome (and safety outcomes are similar), the convenience and cost advantages of PRN follow-up are manifest enough that PRN follow-up would generally be preferred to automatic follow-up.

6 Study Population

Table 6 details the inclusion and exclusion criteria for participants in FAAN-C. Eligible participants must meet all inclusion criteria and none of the exclusion criteria.

Table 6: Study Population

	Inclusion Criteria		Exclusion Criteria	
Pneumonia	– Age <18 years – Hospitalized (including observation visits) – Parent speaks English or Spanish	– Attending diagnosis of pneumonia as the principal disease that led to hospital admission	– Presence of a comorbid disease that is both chronic and complex* – principal disease required surgical intervention (beyond superficial incision and drainage) – Immunodeficiency (innate or receiving a long-term immunosuppressive medication) – A well-child check-up or post-hospitalization follow-up visit is already scheduled within 7 days of hospital discharge – Parent or participant strongly prefers PRN or automatic follow-up – A medical provider feels strongly that a post-hospitalization follow-up visit is needed within 7 days of hospital discharge – Sibling concurrently hospitalized – Unable to identify a clinic where the participant would receive any needed post-hospitalization follow-up	– Received a chest tube
Urinary Tract Infection		– Attending diagnosis of urinary tract infection as the principal disease that led to hospital admission		– History of neurogenic bladder or urologic surgery (beyond circumcision) – Renal imaging anticipated within 7 days of hospital discharge – Complicated by a renal abscess
Skin and soft tissue infection		– Attending diagnosis of skin and soft tissue infection as the principal disease that led to hospital admission		– Chronic wound – Postoperative infection – Predisposition to poor wound healing – Discharging with a drain in place – Complicated by necrotizing fasciitis or toxic shock syndrome
Acute Gastroenteritis		– Attending diagnosis of acute gastroenteritis as the principal disease that led to hospital admission		– Complicated by hemolytic uremic syndrome

*Definition of comorbid disease that is both chronic and complex: Any disease that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several different organ systems or 1 organ system severely enough to require specialty pediatric care and probably some period of hospitalization in a tertiary care center[63]

6.1 Treatment of Subjects

At the time of hospital discharge, families will be randomly assigned to either PRN or automatic follow-up recommendations as described below:

PRN follow-up: "You do not need to schedule a follow-up visit with your child's regular doctor today. If your child's illness continues to improve, you do not need to have a visit with your child's regular doctor within the next 7 days. If your child's illness does not seem to be getting better or you develop any new concerns, we recommend that you contact your child's regular doctor to discuss whether a follow-up visit might be necessary."

Automatic follow-up: "Please schedule a follow-up visit with your child's regular doctor before leaving the hospital. Please schedule the visit to occur within the next 7 days and plan to attend the visit even if your child's illness is getting better."

The automatic follow-up instructions are aligned with proposed quality metrics[40] and previous studies of automatic follow-up.[25, 26, 28, 32, 34] Both the PRN and automatic follow-up instructions were utilized successfully for our prior trial, BeneFIT.[23]

Pragmatic features of comparators. Pragmatic features that will make findings from FAAN-C more generalizable and quickly scalable include the following: 1) Follow-up visits, whether automatic or deemed necessary in the PRN group, can be conducted either in-person or via telehealth. The decision about whether a visit should occur in person or via telehealth will be at the discretion of families and their medical providers. 2) Beyond randomization to either PRN or automatic post-hospitalization follow-up recommendations, FAAN-C is not otherwise prescriptive for a participant's medical care. Hospitalists have complete autonomy about the patient's care while hospitalized, and PCPs have complete autonomy for the patient's care after hospitalization. 3) Beyond embedding follow-up instructions in the electronic health record, the discharge process is otherwise preserved according to each hospital's usual procedures.

7 Treatment Assignment Procedures

7.1 Randomization

Randomization will be performed using randomly permuted blocks of random sizes, stratified by the four types of infection and hospital site. Children will be assigned in a 1:1 ratio to receive a recommendation for either PRN or automatic post-hospitalization follow-up. Randomization sequence generation will be performed by study investigators who are not involved in the intervention assignment of enrolled participants. Allocation concealment will be maintained by a central, automated computer platform (REDCap).

7.2 Blinding

Owing to the nature of the comparators, blinding of participants and their medical providers is not possible. However, outcomes that require adjudication will be adjudicated by persons blinded to the subject's randomized group. Outcomes requiring adjudication in FAAN-C are the safety outcomes (hospital readmissions related to the index infection and medical errors). Specifically, a clinician will determine if the readmission was related to the index infection and a separate clinician will score parent-reported medical errors in terms of severity (as described in the Safety Reporting section of this protocol). The clinicians performing adjudication of these outcomes will be blinded to the subject's randomized group.

8 Study Procedures

8.1 Study Schedule

A schedule of study events for each participant is outlined in Table 7. "While hospitalized" events will occur between the time of hospital admission and the time of hospital discharge.

Table 7: Study Schedule

	While hospitalized	After hospital discharge			
		Day 7	Day 14	Day 30	Day 180
Screening	/				
Informed consent	/				
Parent interview	/				
Randomization	/				
Notify family, PCP, and inpatient team of assignment	/				
Chart review				/	
Process measure					
Completion of a post-hospitalization follow-up		×			
Outcomes					
All-cause hospital readmissions		○	×	○	
Medical interventions		○	×	○	
Child health-related quality of life	○	×	○	○	
Cost burden		○	×	○	
Child time		○	×	○	
Parent time		○	×	○	
Symptom duration	○	×	○	○	
Total additional ambulatory visits		○	○	×	
Non-primary care ambulatory visits		○	○	×	
Parent self-efficacy	○	×		○	○
Parent anxiety	○	×		○	
Satisfaction with care	○	×			
Telephone or electronic communications with medical providers		○	×	○	
Well-child visits	○				×
Immunizations	○				×
Usual place of medical care	○				×
Medical interventions related to the index infection		○	×	○	
Medical errors		○	×	○	
Hospital readmissions related to the index infection		○	×	○	

/ = task performed at the specified timepoint
○ = measured at the specified timepoint
× = measured at the specified timepoint and this is the timepoint used for primary analyses

8.2 Screening and Informed Consent

Study staff will regularly review the list of hospitalized patients at their site. Study staff will verify eligibility by a combination of reviewing the subject's medical record and discussion with the inpatient team caring for the patient, as necessary. After study eligibility has been verified, study staff will approach the parents of the eligible child for consent (and assent from the child, as appropriate). Parents who consent to study participation will then be asked to participate in the parent interview. Within REDCap, a record will be kept of all screened but not enrolled participants. Reasons for not enrolling will be recorded.

8.3 The Parent Interview

The parent interview will obtain sociodemographic data (e.g., race, ethnicity, financial hardship) about the child and the child's parents. Baseline measurements of the outcomes that are measured during hospitalization will also be measured during the parent interview. Screening, consent, and the parent interview will occur before randomization.

8.4 Randomization Process

Randomization will occur when study staff learn that hospital discharge for the study participant is likely to be that day and/or discharge orders have been placed. Prior to randomization, study staff will complete an enrollment checklist in REDCap. The enrollment checklist will verify that all necessary pre-randomization items have been completed. When the enrollment checklist is complete, REDCap will supply the study staff with the patient's randomization assignment. Study staff will notify the patient and their parents of their randomization assignment and their recommended follow-up strategy (PRN or automatic follow-up). Study staff will also communicate the participant's randomization assignment to the participant's inpatient medical team and PCP.

8.5 Chart Review

Study staff will perform chart review. We will collect data elements related to each child's past medical history (e.g., comorbidities), as well as the complexity and severity of their acute infection while hospitalized (e.g., presence of bacteremia, need for intensive care). Chart reviewers will also record readmissions. For each readmission, data elements for the severity and complexity of the illness(es) for which the participant was readmitted will be collected. Chart review can begin anytime after a participant is discharged from the hospital but cannot be completed until the participant is at least 30 days out from discharge.

8.6 Outcome Measurement

Outcomes will be measured according to the timing in Table 7. "While hospitalized" outcomes will be measured prior to randomization. "After hospital discharge" outcomes will be measured by surveying parents on days 7, 14, 30, and 180, as specified. An additional 4 days will be permitted for the collection of data on the 7, 14, and 30 day timepoints and ± 7 days for the day 180 timepoint. For example, day 7 outcomes can be collected between day 7 and day 11. These intervals allow for holidays, weekends, and other reasons for parent unavailability that may preclude contact on the exact day.

8.7 Strategies to Promote Retention

We will utilize the following strategies to promote study retention: 1) Participating families will receive a $20 gift card at enrollment and an additional $20 gift card for answering each subsequent study-related survey ($100 in total); 2) We will use multiple methods of contact for parents, including home and cell phone numbers and email addresses. 3) Parents will provide days and times when a phone call is most convenient.

9 Data Analysis

9.1 Intent-to-Treat (ITT) population

Analyses will be conducted in an intention-to-treat (ITT) manner, in which all randomized subjects are included and analyzed according to their randomization assignment.[64] Subjects who withdraw or get removed from the study will be included in the ITT population. The ITT population will be used for the primary analysis as well as for safety analyses.

9.2 Multiple Comparisons

The studywise Type-1 error will be controlled by designating a single primary outcome, defined as all-cause hospital readmission within 14 days of discharge. The primary analysis will test the noninferiority of a recommendation for PRN follow-up compared to a recommendation for automatic follow-up on hospital readmission within 14 days of hospital discharge using a 1-sided α-level of 0.05.

The trial design also includes two secondary outcomes, the occurrence of a medical intervention, and health-related child quality of life as measured by the Impact on Activities and Routines instrument. We will evaluate both of these secondary outcomes for treatment efficacy using 2-sided hypothesis tests. We will use the Bonferroni-Holm procedure to assure a studywise α-level of 0.05 for the two

secondary outcomes considered jointly. In the Bonferroni-Holm procedure, we will first compute 2-sided p-values for both secondary outcomes. If the smaller of the two p-values is < 0.025, the treatment comparison for that outcome will be declared statistically significant, and the larger p-value will be compared to 0.05 to determine if the other comparison is also statistically significant. If the smallest of the two p-values is ≥ 0.025, then the treatment comparisons for both secondary outcomes will be regarded as not statistically significant.

To avoid reducing statistical power, comparisons of safety outcomes will be performed using 2-sided α-levels of 0.05 for each safety outcome on a comparisonwise basis, without adjustment for multiple comparisons.

All other outcomes are exploratory.

9.3 Analysis of the primary outcome

The risk of all-cause hospital readmission within 14 days of hospital discharge will be compared between the groups who receive a recommendation for PRN vs. automatic follow-up by applying maximum likelihood estimation under a log binomial generalized linear model with indicator variables for randomized treatment, the four infection types, and hospital site included in the models as predictor variables. The primary results will be expressed as a risk difference with a 95% upper confidence bound. In the event that log binomial model fails to converge, the risk ratio with the 95% upper confidence bound will be estimated by applying logistic regression (with a logistic link function) and using the marginal means approach to estimate the risk of the outcome first setting the treatment variable to "automatic" for all patients and then setting the treatment variable to "PRN" for all patients, and performing statistical inference using bootstrap resampling.

The test of noninferiority will be performed by constructing a 95% upper confidence bound for the difference in risk of a hospital readmission within 14 days under the as-needed treatment group vs. automatic follow-up group. Noninferiority will be inferred if this confidence bound excludes the noninferiority margin of 2.5%.

9.4 Analysis of secondary outcomes

Similarly to the primary outcome, the probability of a medical intervention within 14 days of hospital discharge will be compared between the groups who receive a recommendation for PRN vs automatic follow-up by applying maximum likelihood estimation under a log binomial generalized linear model with indicator variables for randomized treatment, the four infection types, and hospital site included in the models as predictor variables. The estimated treatment effect will be expressed as a risk difference with a 2-sided 95% confidence interval. In the event that log binomial model fails to converge, the risk ratio with 95% confidence intervals will be estimated by applying logistic regression (with a logistic link function) and using the marginal means approach to estimate the risk of the outcome first setting the treatment variable to "automatic" for all patients and then setting the treatment variable to "PRN" for all patients, and performing statistical inference using bootstrap

resampling.

The mean health-related quality of life score 7 days after hospital discharge, measured by the Impact on Activities and Routines instrument, will be compared between the groups who receive a recommendation for PRN vs automatic follow-up by applying an analysis of covariance, with the baseline quality of life score, the four infection types, and hospital site included in the model as covariates. The estimated treatment effect will be expressed as a mean difference in the health-related quality of life score between the randomized groups with a 2-sided 95% confidence interval.

9.5 Analysis of exploratory outcomes

Generalized linear models with normal, gamma or lognormal, binary, binomial, and negative binomial outcome models will be used in ITT analyses to compare symmetric numeric, positively skewed numeric, dichotomous, count outcome assessed a designated number of times, and count outcomes without a fixed number of assessments, respectively, between the PRN and automatic follow-up recommendation groups.[65, 66] Hospital site and type of infection will again be included as covariates. Effects will be expressed as a difference in means between the PRN and automatic follow-up recommendation groups for normal outcomes, as a ratio of means for gamma and log-normal continuous outcomes, as risk ratios for binary outcomes, and as rate ratios for binomial and negative binomial outcomes. As for the primary outcome, if the log binomial model fails to converge, relative risks for binary outcomes will be analyzed by applying logistic regression with the marginal means approach and bootstrap resampling. Analyses using the binomial outcome model will account for overdispersion. Several numeric outcomes will be evaluated longitudinally. For these outcomes, we will adjust for the baseline level of the outcome (measured on day 0), which improves statistical power by framing the analysis as an analysis of covariates (ANCOVA), as is recommended in randomized trials. Log-rank tests with stratification of the baseline hazard by hospital site and type of infection will compare time-to-event outcomes between groups. The log-rank test will be used to compare child symptom duration between randomized groups, with a hazard ratio estimating using Cox regression.

9.6 Heterogeneity of treatment effect (HTE)

HTE analyses will be hypothesis-generating, with the goal of identifying populations of patients for whom a recommendation for PRN follow-up is particularly effective. HTE analyses will evaluate the consistency of treatment effects on the primary outcome across the four types of infection, as well as patient race, ethnicity, finacial and social hardship, and use of telehealth for follow-up. The log-binomial generalized linear model for the primary outcome will be repeated for each subgroup. In addition, for each subgroup factor the log-binomial model for the full cohort will be extended by including interaction terms between the randomized treatment and the subgroup factor. The results of these subgroup analyses will be displayed by a forest plot containing risk ratios with 95% confidence intervals for each subgroup, with interaction p-values displayed on the plot.

9.7 Instrumental variable analysis

We will supplement the ITT analysis with an instrumental variable analysis, which is a type of per-protocol analysis and is a recommended component of non-inferiority trials.[67, 68] We will use randomization as the instrument to approximate the average causal effect on patient outcomes of actually attending a post-hospitalization follow-up visit. While the ITT analysis evaluates the average effect of assigning subjects to a recommendation for PRN vs automatic follow-up in the full cohort, an instrumental variable analysis estimates the average effect of actually receiving a follow-up visit among patients who would attend the visit if assigned to an automatic follow-up recommendation, but not if assigned to a PRN follow-up recommendation. The instrumental variable analysis depends on two key assumptions: 1) the randomized treatment influences outcomes only through the effect of treatment assignment on the occurrence or nonoccurrence of a follow-up visit, and 2) randomization to a PRN follow-up recommendation does not cause any subjects to attend a follow-up visit when they would not have done so if randomized to an automatic follow-up recommendation.[69]

9.8 Missing Data

We will use multiple imputation based on fully sequential imputation with predictive mean matching to impute missing data.[70] Multiple imputation will be particularly useful because we expect to have strong auxiliary variables—that is, variables that are highly correlated with study outcomes and risk of missingness. Auxiliary variables we will utilize include patient demographic factors (e.g., race, ethnicity) measures of illness severity (e.g., length of stay, disease-specific characteristics), and hospital readmission documented in the electronic medical record.

9.9 Sample Size and Power

The RCT will be powered for non-inferiority of a recommendation for PRN follow-up compared to automatic follow-up for the primary outcome, 14-day all-cause hospital readmission. In 2019, the mean 14-day all-cause readmission rate across FAAN-C sites among patients who would meet inclusion criteria for FAAN-C was 3.5% (extracted from the Pediatric Health Information Systems database on April 29, 2020). Given that automatic post-hospitalization follow-up is recommended to the majority of hospitalized children, we used 3.5% as the estimated readmission rate for the automatic post-hospitalization follow-up group. We set the non-inferiority margin at 2.5% because hospitalists and PCPs reported in focus groups that they would consider a recommendation for PRN follow-up to be inferior to a recommendation for automatic follow-up if the PRN follow-up recommendation resulted in a more than 2–3% absolute increase in hospital readmissions. At a margin of 2.5%, the parents of 40 children would need to be instructed to have automatic follow-up visits before 1 hospital readmission would be prevented (that is, the number needed to treat[71] =40). If $\geq$ 40 parents would need to be instructed to have automatic follow-up to prevent a hospital readmission, we will conclude that a recommendation for PRN follow-up is non-inferior to a recommendation for automatic follow-up. We assume that the primary outcome will be available

for at least 85% of subjects (15% attrition). Under these assumptions, a total sample size of 2,674 patients (1,337 patients in each group) will provide 90% power with 1-sided α=0.025 to demonstrate non-inferiority of a recommendation for PRN follow-up. We defined the non-inferiority margin without adjusting for non-compliance for two main reasons. First, patients randomized to a recommendation for PRN follow-up are compliant whether or not they choose to attend a follow-up visit. Secondly, the assumed readmission rate for the automatic follow-up group (3.5%) is derived from a sample from which non-compliance occurred. Non-compliance is expected to be greater outside of a trial setting, which preserves our conservative power estimate.

10 Data Management

10.1 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Study monitoring is critical to this process. Monitoring has been a very effective tool for maintaining data quality in previous studies, and we will utilize this process to ensure excellent quality data in the proposed study. The Data Coordinating Center utilizes risk-based methodology to identify and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and preventing or mitigating key risks to data quality, as well as to processes critical to human subject protection and integrity of the trial or study.

Study monitors must be provided with appropriate access to study materials and the medical records for study subjects. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the study monitor's review of data in the electronic medical record.

10.1.1 Site Monitoring Plan

A supplemental study-specific risk-based monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan may include the number of planned site visits, criteria for focused visits, additional visits or remote monitoring, a plan for chart review and a follow-up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g., sample of all subjects within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found.

10.1.2 Clinical Site Monitoring

Site monitoring visits may be performed during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. The site monitor will provide each site with

a written report, and sites will be required to follow-up on any deficiencies. The site initiation may take place as group training made up of site investigators and research assistants.

10.1.3 Remote Monitoring

The Data Coordinating Center may supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by each site and consultations with each site investigator and/or research coordinator to review safety and data quality. This may require uploading copies of medical records, patient study files, regulatory documentation, or other source documents for the monitor to review. Alternatively, other methods, such as remotely viewing source documentation, may be utilized. This helps assure protocol compliance and accurate data collection. The Data Coordinating Center may conduct more remote monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Remote monitoring documents will be retained in accordance with federal requirements. Safety of subjects will be monitored and ensured in accordance with the Data and Safety Monitoring Board (DSMB) plan.

10.2 Record Access

The medical record and study files (including informed consent, permission, and assent documents) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives (when applicable) of the, NIH, other Federal funders or study sponsors, and the Institutional Review Board (IRB) for each study site.

11 Protection of Human Subjects

11.1 Institutional Review Board (IRB) Approval

The Institutional Review Board (IRB) at the University of Utah will serve as the single IRB. The Utah IRB has extensive experience with single IRB implementation due to our participation in the NCATS funded Trial Innovation Center, which has implemented over 35 SIRB studies, several with EFIC.

In addition to SIRB activities, each institution has Human Research Protection activities that will be completed prior to site activation. These include conflict of interest, assuring competence of investigators, impact on hospital services, etc., and are individualized to each site.

The Data Coordinating Center will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial IRB approval and local review

sign-off. The Data Coordinating Center will also track the maintenance of that approval throughout subsequent years of the project.

11.2 Informed Consent Process

SIRB procedures should be well understood by all research staff and clearly documented in the Essential Documents Binder or eBinder.

GCP Reminder (Informed consent advice from OHRP): Informed Consent is a process, not a form. Information must be presented to enable the person to voluntarily decide whether or not to participate as a research subject. It is a fundamental mechanism that ensures respect for persons through provision of thoughtful consent for a voluntary act. The procedures used in obtaining informed consent should be designed to educate the subject population in terms that they can understand. Think of the document primarily as a teaching tool not as a legal instrument. http://www.hhs.gov/ohrp/regulations-and-policy/guidance/informed-consent/index.html

The informed consent process can be a collaborative effort between research staff, the site PI and Co-PIs, and clinicians. However, if the site PI/Co-PI are unavailable research staff may introduce the study and proceed through the informed consent process. A PI or CO-PI should always be available by phone to the research staff to answer any additional questions the family may have as needed in the rare case that the research staff is unable to answer specific questions.

11.3 Informed Consent

The informed consent/parental permission document must be approved by the SIRB and local HRPP prior to conducting any research activities. The informed consent/parental permission must be signed before any study procedures begin. ALL subjects participating must have a signed and dated consent form/parental permission form as part of the patient study file. An electronic or paper copy of the signed and dated consent form/parental permission form will be provided to the patient. At some institutions the form must also be signed and dated by the person obtaining the consent/parental permission.

Parental Permission

Subjects who are eligible for this study are under 18 years of age, and written permission from parents or legal guardians will be required for participation. After determining that a subject is eligible, the site investigator or designee will approach the parent or legal guardian to offer participation for their child in the study. The parent or legal guardian will be informed about the objectives of the study and the potential risks and benefits of participation. Subject will only be enrolled if their parent or guardian provides permission for their child to participate.

Child Assent

Children who are capable of giving assent and who are alert and competent, will be asked, following an age-appropriate discussion of risks and benefits, to give assent to the study or further study procedures. Assent will be waived if the child is too young, has a severely reduced mental age, decreased level of consciousness, psychological problems, or other legitimate reasons as judged by the Institutional Review Board.

Subject Consent

If a subject attains the age of 18 years during the study period, informed consent is required. Subjects who are capable of giving consent and who are alert and competent, will be asked, following an appropriate discussion of risks and benefits, to give consent to the study. For those with diminished mental capacity, a Legal Authorized Representative will be used.

11.4 Waivers Requested

Waiver of Authorization

A waiver of authorization is requested in order to be able to pre-screen/establish eligibility for subject prior to approaching, consenting, and enrolling a subject.

Waiver of Documentation of Informed Consent

The waiver is requested for subjects who reach the age of majority (18 years), after randomization.

11.5 Potential Risks

Loss of confidentiality of the subject is a potential risk of the study; however, safeguards are in place to protect against this.

11.6 Protections Against Potential Risks

To protect against a loss of confidentiality, the information gathered for this study will be coded with a special study number. A child's or parent's name and information that could identify them will be stored securely at the site where they were enrolled or in the study database.

11.7 Potential Benefits

There are no likely benefits anticipated from participation in this study; however, there is potential benefit to others because of the knowledge that may be gained from this research.

12 Data and Safety Monitoring Plan

12.1 Data Safety Monitoring Board (DSMB)

The study will have a Data Safety Monitoring Board (DSMB). The DSMB will have a charter, will approve the protocol prior to implementation, and will review interim analyses as applicable. The purpose of the DSMB is to advise the sponsors and Principal Investigator(s) regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, performance of individual site, review of serious adverse events and other subject safety issues. There will be no formal stopping rules for efficacy or futility.

12.2 Safety Reporting

Hospital readmissions and medical errors are outcomes being collected for this study. These data constitute safety events and will provide an adequate method of assuring subject safety in the study. Safety events will be reported to the DSMB at regular meetings in a standard fashion and will be reviewed regularly at the DCC.

12.2.1 Definition of Medical Errors

Medical Errors Medical errors will be collected as described in the outcomes section above. Examples of medical errors captured within this outcome include parent-reported medication problems, miscommunications, diagnostic mistakes, delays in care, complications of care, and equipment problems. Medical errors will be categorized into levels of harm using the National Coordinating Council for Medication Error Reporting and Prevention Index for Categorizing Medication Errors Algorithm.[72] This algorithm categorizes harms on a continuum from A–I, with the extremes being the absence of a true error (harm level A) and an error that resulted in patient death (harm level I). Harm levels F (initial or prolonged hospitalization required), G (life-sustaining intervention required but harm was not permanent), H (life-sustaining intervention required and harm was permanent), and I (death resulted) meet the definition of serious adverse events outlined below and will be reported as described below.

12.2.2 Definition of a Serious Adverse Event (SAE)

Serious Adverse Event (SAE): A serious adverse event (SAE) for this population is an error or event that:

- results in death; or
- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Hospital readmission will already be captured as the primary outcome so these will not be reported as SAEs unless the PI determines this is necessary. SAEs will be captured between randomization and 14 days after hospital discharge.

12.2.3 Classification of an SAE (Relatedness, Severity, and Expectedness)

Relatedness: The suspected relationship between study interventions and any SAE will be determined by the site investigator using the criteria below. *Relatedness must be assessed by an investigator and may **not** be assessed by a research coordinator.*

Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and *cannot be reasonably explained* by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Severity: The severity, which is a measure of intensity, of clinical SAEs and laboratory abnormalities will be recorded by the site investigator and categorized. The following guidelines will be used to describe severity.

Mild: The event requires minimal or no treatment and does not interfere with the participant's daily activities.

Moderate: The event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: The event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Expectedness of the Event: SAEs will be evaluated as to whether their occurrence was expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described for the study intervention.

Expected: An event is considered expected if it is known to be associated with the underlying condition or is related to the study intervention and is mentioned in the protocol, informed consent, or other study documents. An event may be expected despite the study subject's clinical state immediately prior to the event. Any symptom related to the primary diagnosis for which the participant was initially hospitalized is expected. For example, symptoms that would be expected for all of the FAAN-C conditions are fevers, vomiting, and diarrhea. Expected symptoms for pneumonia are complaints like cough, shortness of breath, and trouble breathing. Expected symptoms for urinary tract infection are complaints like abdominal pain and dysuria. Expected symptoms for skin and soft tissue infections are complaints like pain, swelling, and redness at the site of infection. Expected symptoms for gastroenteritis are complaints like diarrhea.

Unexpected: An event is considered unexpected if there are no prior data linking this event with either the condition or intervention under study or an event that occurred unexpectedly in the course of treatment.

Treatment or Action Taken: For each SAE, the site investigator will record whether an intervention was required:

- Medical or surgical procedure
- Concomitant medication: started, changed, or discontinued
- Other, specify
- No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each SAE as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms persist

12.2.4 Data Collection Procedures for SAE

After patient randomization all SAEs will be recorded according to relatedness, severity, and expectedness, as well as their duration and any treatment prescribed. Any medical condition present at the time of randomization, recorded in the patient's baseline history at study entry, which remains unchanged or improves (unless the clinician feels it is clinically relevant), will not be recorded as an SAE at subsequent evaluations. However, worsening of a medical condition that was present at the time of randomization will be considered a new SAE, if it otherwise meets the SAE definition, and reported.

SAEs will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center as this requires specific training.

12.2.5 Unanticipated Problems (UP)

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related or possibly to participation in the study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The site investigator will report unanticipated problems to the Data Coordinating Center within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event. After receipt of the complete report, the Data Coordinating Center will notify PCORI promptly, but no later than 10 days after:

- reporting any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem) relating the to the research study to the sponsor, DSMB, IRB, the FDA, or other regulatory or oversight body; and
- Any decision, finding, recommendation, action, or direction of a DSMB, IRB, the FDA, or any other regulatory or oversight body relating to any serious unanticipated problems (e.g., serious adverse event, serious safety issue, or other serious problem).

In accordance with local IRB requirements, the site investigator may be required to report such unanticipated problems to the IRB in addition to notifying the Data Coordinating Center. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, the Data Coordinating Center will notify the study investigator (Dr. Coon) and all site investigators to cease enrollment in the trial.

12.2.6 Monitoring Serious Adverse Events

A qualified physician will be designated to fulfill the function of the medical monitor for this study. Site investigators and/or research coordinators will report serious adverse events to the Data Coordinating Center within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of the event, and the medical monitor will assess all serious adverse events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign off on each SAE report after review. All SAE reports will be retained at the Data Coordinating Center, and all SAE reports will be available for review by DSMB members and PCORI staff. The SAE reporting process may be incorporated into the Electronic Data Capture System in use for the study.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, the DSMB chairperson will be immediately consulted. If the DSMB chairperson concurs with the judgment of the medical monitor, or if the DSMB chairperson cannot be reached expeditiously, the Data Coordinating Center will notify the study investigator (Dr. Coon) and all site investigators to cease enrollment in the trial.

In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the Data Coordinating Center.

After notification of the PCORI Program Official or Project Officer, and the DSMB chairperson, of *serious, unexpected, and study-related* adverse events or unanticipated problems (UP), decisions will be made whether to continue the study without change, and whether to convene the entire DSMB for an emergent meeting. If a decision is made to suspend enrollment in the trial, this will be reported to the study investigator (Dr. Coon) and all clinical investigators, who will be instructed to report this to their local IRB.

The DSMB will review medical errors and serious adverse events during scheduled DSMB meetings. The Data Coordinating Center will prepare a Summary Report of medical errors and serious adverse events.

12.2.7 Follow-up of Serious Adverse Events

All SAEs will be followed by the study team until the events are resolved, subject is lost to follow-up, the SAE is otherwise explained or has stabilized, or 14 days have passed from the time of hospital discharge.

13 Study Training

13.1 Study Training

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics and Good Clinical Practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of operations will be provided to each investigator prior to the start of enrollment.

The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically. The Data Coordinating Center, in collaboration with the study investigator (Dr. Coon), will be the main contact for study questions.

14 Regulatory Considerations

14.1 Health Insurance Portability and Accountability Act

Data elements collected include the date of birth, date of admission, date of discharge, date of medical visits, phone numbers, and email addresses. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de-identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

For purposes of the Data Coordinating Center handling potential protected health information and producing the de-identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the Data Coordinating Center.

14.2 Inclusion of Women and Minorities

There will be no exclusion of patients based on gender, race, or ethnicity.

14.3 ClinicalTrials.gov Requirements

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

14.4 Retention of Records

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least 3 years after completion of the research. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR §46.115(b)].

14.5 Public Use Data Set

After subject enrollment and follow-up have been completed, the Data Coordinating Center will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identity of any patient. The database will not contain any institutional identifiers.

The Data Coordinating Center will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies determined by the investigators and funding sponsors, the releasable database will be provided to users in electronic form.

15 Bibliography

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