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"Let's talk about antibiotics": A randomized trial of a higher vs. lower intensity patient-provider communication interventions to reduce antibiotic misuse in pediatric ambulatory clinics.

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Abstract

Introduction: Children with acute respiratory tract infections (ARTIs) are prescribed up to 11.4 million unnecessary antibiotic prescriptions annually. Inadequate parent-provider communication is a chief contributor, yet efforts to reduce overprescribing have only indirectly targeted communication or been impractical. This paper describes our multi-site, parallel group, randomized trial comparing two feasible interventions for enhancing parent-provider communication on the rate of inappropriate antibiotic prescribing (primary outcome) and re-visits, adverse drug reactions, and parent rated quality of shared decision-making, parent-provider communication and visit satisfaction (secondary outcomes).

Methods/analysis: We will attempt to recruit all eligible pediatricians and nurse practitioners (currently 47) at an academic children's hospital and a private practice. Using a 1:1 randomization, providers will be assigned to a Higher Intensity education and communication skills or Lower Intensity education only intervention and trained accordingly. We will recruit 1,600 eligible parent-child dyads. Parents of children ages 1-5 who present with ARTI symptoms will be managed by providers trained in either the Higher or Lower Intensity intervention. Before their consultation, all parents will complete a baseline survey and view a 90-second gain-framed antibiotic educational video. Parent-child dyads consulting with providers trained in the Higher Intensity intervention will, in addition, receive a gain-framed antibiotic educational brochure promoting cautious use of antibiotics and rate their interest in receiving an antibiotic which will be shared with their provider before the visit. All parents will complete a post-consultation survey and a two-week follow-up phone survey. Due to the 2-stage nested design (parents nested within providers and clinics), we will employ generalized linear mixed-effect regression models.

Conclusion: This trial will generate evidence about the advantage of training providers in communication skills to enhance antibiotic prescribing compared to an education only approach.

Ethics/dissemination: Ethical approval has been obtained. Results will be submitted for publication in peer-reviewed journals.

Trial registration: NCT03037112

Strengths and limitations

- Implements a parent-provider communication intervention based on a previously effective intervention and adapted for feasibility in the US pediatric ambulatory setting.
- Works closely with parent, provider and other stakeholders to ensure the feasibility and appropriateness of the interventions' components and study procedures.
- All educational materials and assessments will be available in Spanish and are being developed in consultation with Spanish-speaking stakeholders.
- Adequately powered to detect differences between the Higher and Lower Intensity interventions, with a 1:1 randomization of providers to intervention arms and a target sample of 1600 parents/child dyads.
- Data on primary outcomes (i.e., rates of inappropriate antibiotic prescribing), secondary outcomes (i.e., re-visits and adverse drug reactions, shared decision-making, quality of parent-provider communication and satisfaction), and potential covariates will yield novel insights into the effectiveness of each intervention.

Antibiotic overuse and misuse contribute to the development of antibiotic resistant infections that if left unchecked are estimated to cause 10 million deaths worldwide by 2050.[1] In the United States (US), antibiotic resistant infections are responsible for at least 23,000 deaths and an additional 2 million infections annually.[2] Inappropriate antibiotic use also increases incidence of antibiotic-associated adverse drug reactions (e.g., rash, diarrhea, nausea, and vomiting), which result in over 140,000 Emergency Department visits every year.[3]

The majority of all antibiotic prescribing in the US occurs in the outpatient setting where children receive 49 million prescriptions annually.[4] Children with acute respiratory tract infections (ARTIs) receive over 70% of these prescriptions of which 29% are unnecessary (i.e., either to treat a viral illness or an unnecessary broad-spectrum antibiotic).[4] Despite some improvements, the most recent estimates suggest that antibiotics are prescribed for approximately 50% of ARTIs while it is estimated that only 27% of ARTIs are caused by bacterial infection.[5] As a result, children are receiving up to 11.4 million unnecessary antibiotic prescriptions annually.[5] Strikingly, an almost identical number was noted in a similar study conducted 16 years earlier (11.1 million unnecessary antibiotic prescriptions) suggesting there are considerable gains still to be made in reducing inappropriate use.[6]

Inappropriate antibiotic prescribing in the ambulatory setting has many causes, but the interaction between parents/legal guardians (hereafter referred to as parents) and providers is central. For their part, some parents still harbor misconceptions that make them think antibiotics are necessary when they aren't.[7] Nevertheless, parents generally desire antibiotics for their children only when absolutely necessary[8] and do not expect antibiotics for common colds.[9] Instead, parents become dissatisfied when providers minimize children's symptoms, fail to acknowledge parents' appropriate concerns and/or do not offer a contingency plan if symptoms fail to resolve.[10,11]

Despite evidence to the contrary, providers perceive significant parental pressure for antibiotics and fear damaging the parent-provider relationship if they withhold prescriptions.[12,13]

Combined with the ever-increasing time constraints and focus on parent satisfaction ratings inherent in modern clinical practice, these beliefs greatly contribute to ineffective parent-provider communication about antibiotics. When providers perceive that a parent expects or hopes for an antibiotic, they are more likely to prescribe one.[14,15] In a study of children with viral ARTIs where no prescription should have been given, providers gave a prescription to 52% of parents they believed were expecting an antibiotic as compared to only 9% of parents who they believed were not expecting an antibiotic.[16] Adding to this problem is providers' mistaken belief that they can accurately predict parents' desires. In fact, providers' ability to accurately predict parents' expectation for an antibiotic is significantly worse than chance at 24% to 41% concordance.[12,16] Even though parents rarely state a desire for antibiotics (1% of the time in clinical recordings) providers report frequent parent demands for antibiotics.[17] Providers also mistakenly believe that meeting perceived parental expectations for antibiotics is necessary for parent satisfaction.[13] Parental satisfaction, however, is not related so much to whether or not they receive an antibiotic but more to the quality of communication with their provider.[10,13] In fact, a recent observational study demonstrated that the use of what they termed "positive treatment recommendations" (i.e., comfort care) plus "negative treatment recommendations" (i.e., antibiotics won't help) was associated with the highest parent satisfaction.[18]

Current efforts to improve appropriate antibiotic use have only indirectly targeted parent-provider communication [19,20] or have been found to be impractical.[21] As described in several meta-analytic and systematic reviews, interventions have typically focused on education about antibiotics for providers or patients.[19,20] While many have been successful in increasing knowledge about antibiotics and nationally antibiotic prescribing has evidenced modest reductions,[8,22] more effective strategies that go beyond educational targets are needed to reduce overprescribing rates to levels that will have a significant impact. A limited number of studies have been conducted that target parent-provider communication or shared decision-

making, and they have already produced superior results.[20] Of the communication interventions tested, only one has directly targeted provider perceptions of parental expectations alongside antibiotic education and shared decision-making.[23] This study, which employed intensive provider training and a multi-page patient-provider interactive educational booklet, resulted in a significant decrease in antibiotic use. The intervention, however, was viewed as burdensome by providers and impractical for most real world settings.[21] Effective, practical interventions are needed that address provider misconceptions about parent expectations, facilitate shared-decision making, and improve aspects of communication that are most likely to increase parental satisfaction.

The goal of this study is to compare two feasible interventions for enhancing parent-provider communication to reduce the rate of inappropriate antibiotic prescribing. This study will compare the efficacy of a Higher Intensity provider education and communication skills intervention to a Lower Intensity provider education only intervention. We hypothesize that the parent-child dyads managed by providers trained in the Higher Intensity intervention will demonstrate superiority to dyads managed by providers trained in the Lower Intensity intervention on the primary outcome of rate of inappropriate antibiotic prescribing, as well as, the secondary outcomes of re-visits, adverse drug reactions, and parent rated quality of shared decision making, parent-provider communication and satisfaction.

Methods

Trial design, setting and participants

Trial design: A multi-site parallel group, randomized trial with balanced randomization (1:1) will be performed in three ambulatory pediatric clinics in the Unites States. Providers (physicians and nurse practitioners) will be randomly assigned to training in either Higher Intensity or Lower Intensity intervention described below. Once providers have been randomized and trained, eligible parent-child dyads will be enrolled and exposed to management by a provider who was

trained in one of the interventions. Parents in both arms will receive education on the pros and cons of antibiotics for common infections and tips for communicating with their provider. Blinding of providers will not be feasible in this study, however, parents will be blinded as they will not be told what study arm their provider is in, nor informed about differences between the study interventions. Study team members who conduct chart review to code appropriateness of antibiotic prescriptions and code session audiotapes for intervention fidelity will be blinded. The study protocol is in compliance with the Helsinki Declaration and was reviewed and approved by the Institutional Review Board of Children's Mercy Hospital (#16060466). PI (KG) will monitor recruitment, retention (bimonthly) and adverse events (quarterly; blinded to study arm) in this low risk study. Adverse events, collected from parents at 2-week follow-up, through chart review and spontaneously from clinic staff. Any protocol modifications will be submitted for IRB review and communicated to all relevant parties before implementation.

Randomization: To protect against practice effects (tendency for providers to have more consistent beliefs and behaviors within their practice as compared to providers in other practices), we will randomize providers rather than clinic sites. We did this because the intervention components are not easily transferred between providers making the risk of contamination a much smaller threat to validity than practice effects. As detailed below in the Higher Intensity Provider Training section, we will employ several strategies to reduce the chance of contamination across study arms. We will use clinic data on visits among our target population from the past six months to assign each provider to a large or small patient volume group. The study statistician will then stratify the randomization of providers to ensure each study arm is balanced across large and small volume providers and across clinics. The study statistician will place the intervention group assignment in sealed envelopes labeled with providers' names. Providers will be given their envelopes at the conclusion of a brief study orientation and informed consent meeting and before completing the baseline assessment.

Setting: Study sites will be an academic medical center (Children's Mercy Hospital Primary Care Clinic - CMH PCC) and both locations of a private practice (Heartland Primary Care - HPC). CMH PCC sees a racially and ethnically diverse group of patients (41% African American/Black, 29% Hispanic, 18% White) from the Kansas City metropolitan area, of which 73% are covered by Medicaid. CMH PCC has 38 providers (28 pediatricians and 10 nurse practitioners) and treats approximately 2100 children with an ARTI that meet study inclusion criteria yearly. HPC is a community-based private practice with two locations in sub-urban Kansas City serving a diverse patient population (14% African American/Black, 16% Hispanic, 75% White; 42% covered by Medicaid). HPC has 9 pediatric providers (6 pediatricians and 3 nurse practitioners) who care for 2000 children that meet study inclusion criteria annually. Approximately 20% of parents at study sites are Spanish speaking.

Participants: This study involves providers and parent-child dyads. We will attempt to recruit all eligible providers at all study sites (pediatricians, pediatric nurse practitioners; n = 47), defined as those who regularly treat patients that meet our inclusion criteria. Providers primarily assigned to administration, urgent care or specialty clinics that serve complex care patients will not be eligible. We will conduct brief study orientation and informed consent meetings to enroll providers during regularly scheduled clinic meetings or individual contacts.

We will recruit up to 1600 parent-child dyads. Dyads will be eligible if the patient is between ages 1-5 years (i.e., before sixth birthday), presents with ARTI symptoms (e.g., cough, congestion, difficulty breathing, sore throat, ear ache) and his/her parent is fluent in English or Spanish. Children will not be eligible if they have received an antibiotic in the last 30 days, have a concurrent probable bacterial infection (e.g., UTI, soft tissue infections), known immunocompromising conditions (e.g., HIV, malignancy, solid-organ transplant, chronic

corticosteroid use), or factors that make shared decision-making around prescribing an antibiotic extremely complex, like children with complex chronic care conditions (e.g., cystic fibrosis),[24] or who require hospitalization during the visit. We will include patients with penicillin allergy as shared decision-making with this group is especially important given more limited treatment options. Parents or children who have previously participated in the study will not be eligible to participate again. Potentially eligible dyads will be identified through prescreening all appointments and parents will be given a study flyer upon check-in. Potential eligible dyads will be greeted in the exam room before the provider arrives, given a short synopsis of the study, and offered eligibility screening. If more than one caregiver is with the child, they will be asked to designate one person who will complete the informed consent and all assessments.

Trial Interventions

Higher Intensity Intervention. With attention to the feasibility in the US healthcare system, this intervention will be informed by a series of evidence-based interventions conducted in the UK and Europe: Enhancing the Quality of Information-sharing in Primary care (EQUIP),[23,25] Improving the Management of Patients with Acute Cough Trial (IMPACT),[26,27] Stemming the Tide of Antibiotic Resistance (STAR)[28,29] and Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE).[30]

Higher Intensity Arm Provider Training: Providers in this arm will receive two trainings. First, a 20-minute, in-person general education training provided by a study physician (ALM, JGN) will cover the pros and cons of antibiotics, the impact of inappropriate use, CDC antibiotic prescribing guidelines, common reasons for antibiotic misuse, and viewing/discussion of the parent educational cartoon (described below). Didactic and interactive learning strategies will be employed to review the appropriate diagnostic criteria to help distinguish a viral ARTI from a

bacterial ARTI, as well as, the recommended narrow spectrum antibiotic for bacterial ARTI. Second, providers will receive a 50-minute, in-person training on parent-centered communication skills provided by a behavioral psychologists (KG). The training will use a variety of educational strategies including viewing/discussion of motivational and role model videos, lecture, and group discussion. The goal is to enhance providers' confidence in use of parent-centered communication strategies (e.g., open ended questions, affirming and elicit-provide-elicit) and the study tri-fold brochure to conduct key aspects of the EQUIP/IMPACT/STAR/GRACE interventions during consultations. Specifically, they will learn to: 1) elicit parents' expectations, 2) affirm parents' concerns, 3) provide an evidence-based estimate of likely illness duration, 4) provide gain-framed antibiotic information, 5) recommend options for symptom relief, 6) identify triggers for re-consult and contingency plans, and 7) elicit parents thoughts on the plan. Providers will also learn to use the study tri-fold brochure to ensure that they complete all necessary aspects of the intervention and provide written notes for parents to refer to after the visit. The inside of the study tri-fold brochure provides gain-framed information about when antibiotics are and are not necessary and what risks are involved in taking antibiotics. Research has shown that people react to the same tradeoff in different ways depending on whether the possible outcomes are presented as losses or gains.[31] In this study, we will train providers and tailor our parent materials to highlight the gains of not using antibiotics (e.g., staying safe from side effects, making sure that effective cures are available in the future, knowing that their child's body will fight off most ARTI on its own) that may increase parents' comfort with not getting an antibiotic prescription for their child. Drawing from the EQUIP study,[25] the outside of the brochure includes a place to write the child's first name; check boxes to indicate the diagnosis, recommended home care treatments, and reasons for re-consultation; expected recovery time, if antibiotics are needed, and tips for communicating with providers.

To reduce their reliance on guessing what parents want, providers will also be trained to

rely on parents' antibiotic desire ratings taken from their baseline survey and provided at the start of each visit via a sticky note on the exam room door where parent-child dyads will be waiting. To assess fidelity to the communication skills, we will audio record a subsample of visits (10%) in both Higher and Lower Intensity arms and objectively code use of key communication strategies using established methods that we have successfully employed in other studies.[32,33] We will deliver in-person provider training as studies have shown the value of an active approach over more passive web-based versions,[34] but we will also develop web-based refresher trainings.

Higher Intensity Arm Parent Training: In exam rooms prior to the consultation, parents will complete the baseline survey, view a 90 second educational cartoon video with accompanying educational tri-fold brochure and rate their desire for antibiotics via a tablet computer. The educational video uses gain-framed messages[31,35] to explain when antibiotics are and are not indicated while emphasizing the risk of side effects and the creation of resistant organisms. It also highlights what information should be provided during the consultation (e.g., an estimate of illness duration, recommendations for system relief, and triggers for re-consult and contingency plans). Parents in this arm will receive a hard copy of the study tri-old brochure.

Lower Intensity Intervention: This intervention will be modeled on proven parent and provider focused educational interventions used in previous studies.[19,34,36–44] Providers will complete the same 20 minute, in-person general education training described above. Parents will receive the same parent training described above except that parents will not receive a hard copy of the study tri-fold brochure and their antibiotic desire ratings will not be shared with providers.

Several measures will be taken to reduce the likelihood of contamination between arms. Specifically, we will: 1) ensure that any communications (written or in person) with providers in the Lower Intensity arm do not reveal any of the strategies from the Higher Intensity training, 2)

review the importance of keeping intervention arms distinct in RCT designs during training, 3) directly ask providers to pledge not to share any details of the additional communication skills training with their colleagues randomized to the Lower Intensity arm, 4) control the dissemination of the tri-fold brochure to ensure that only parents who are consulted by providers in the Higher Intensity arm receive them, and 5) offer communication strategies for dealing with colleagues who ask for more information.

Data Collection

Providers/Administrators: At baseline, providers will complete a brief survey collecting demographic data, and providers' views on parent interest in antibiotics for viral illness, their comfort with telling parents that antibiotics are not necessary, and their concern about parents' responses. Once parent-child dyad recruitment is complete, a brief survey mirroring the baseline provider assessment and a brief (<10 min) semi-structured individual interview will be conducted with providers and administrators to learn about their experience of being in the study, suggestions for improvement and ideas about disseminating to other settings. Providers/Administrators will not receive incentives for study participation.

Parents: At baseline, immediately before their scheduled visit with a provider, parents will complete a brief tablet computer administered Research Electronic Data Capture (REDCap) survey about their antibiotic knowledge and interest in antibiotics for their child's current condition. They will then view the educational video and indicate their interest in antibiotics for their child's current condition again and rate the likelihood of actually receiving antibiotics during their visit. After meeting with their provider, parents will complete a brief survey about their experience of the visit including their rating of shared decision making, satisfaction with parent-provider communication and overall satisfaction with the visit. Two weeks later, parents will be

contacted via phone to complete a follow-up survey to assess: resolution of child's illness, any additional healthcare visits and/or treatment, if contingency or "back-up" prescriptions were filled, presence and severity of side effects from any antibiotics administered, use of home care treatment suggested by provider, assessment of the educational video and brochure, and satisfaction with study participation. EMR data will be abstracted using a standardized data collection form and evaluated by study physicians to determine the appropriateness of antibiotic prescribing. Parents will be provided with $10 per completed survey in recognition of their time and effort.

Measures

Interest in assessing patient/parent-provider communication has garnered significant attention, but measurement challenges remain. Despite a large number of published instruments, availability of valid, reliable, and scalable measures is a recognized barrier to progress in research and implementation of patient-centered care.[45] Lack of patient involvement in scale development has been cited as a contributing factor, so we have engaged parent and provider stakeholders in the selection of measures for this study. All measures have been adapted based on their feedback, pilot testing including cognitive debriefing was performed to ensure the briefest possible assessment of study outcomes. All measures were translated into Spanish using standard methods and appropriate pilot testing.

Primary Outcome

Antibiotic Prescribing: Our primary research question is which of the two interventions leads to a lower rate of inappropriate antibiotic prescribing. We hypothesize that the rate among providers in the Higher Intensity arm will be lower than the rate produced by providers in the Lower Intensity arm. If the rates do not significantly differ, we will conclude that the Lower Intensity intervention is superior and should be considered for dissemination. Inappropriate prescribing will be assessed on a weekly basis by study physicians, blinded to study arm, who

will review the medical record documentation for each enrolled patient's visit to determine if inappropriate antibiotic prescribing occurred. Prescriptions will be considered inappropriate if they meet any of the following criteria: 1) antibiotic prescribed for a viral ARTI, 2) antibiotic prescribed for a presumed bacterial ARTI that does not meet Table 1 criteria, 3) broad-spectrum antibiotic prescribed for a bacterial ARTI in a child without a penicillin allergy, or 4) non-recommended alternative antibiotic prescribed for a bacterial ARTI (see Table 2) in a child with a penicillin allergy. Instead of relying on diagnostic codes as has been done in previous studies,[46,48] the study physicians will assess the appropriateness of the patient's diagnosis by reviewing detailed symptoms, physical examination findings, and diagnostic tests in the EMR. This will guard against the potential bias of relying on diagnostic codes alone, as clinicians sometimes match diagnostic codes to support their antibiotic prescribing.[12] Children determined to have a bacterial infection will need documentation of the specific diagnoses and the clinical criteria confirming that diagnosis (listed in Table 1). Ten percent of all chart reviews will be verified by the other study physician blinded to the initial coding and study group.

Table 1. Diagnostic criteria for ARTIs [19,36,34,46,47]

Bacterial ARTI	Diagnostic criteria
Acute Otitis Media (either criteria)	1. Fever ≥38.3°C (101°F) with either a or b: a. Moderate to severe bulging of tympanic membrane on exam, or b. Mild bulging of TM and recent (<48hrs) onset of ear pain 2. New onset of otorrhea not due to acute otitis externa
Sinusitis (any of the 3 criteria)	1. Daytime cough or nasal discharge for greater than 10 days 2. High fever (>39°C) with purulent nasal discharge or facial pain lasting 3 consecutive days at the beginning of the illness 3. Worsening signs or symptoms characterized by the new onset of fever, headache, or increase in nasal discharge following a typical viral URI
Community acquired Pneumonia (either criteria)	1. Fever, tachypnea, and focal findings on pulmonary exam 2. a) Fever, b) Tachypnea, cough, or retractions AND c) Chest radiograph consistent with a focal consolidation
Streptococcal pharyngitis (both criteria)	1. Fever, pharyngitis, & positive rapid streptococcal antigen test or culture 2. Lack of viral signs and symptoms

Table 2. Appropriate Antibiotic Selection [19,36,46,47]

Bacterial ARTI	Primary Antibiotic	Secondary Antibiotics for Penicillin Allergy
Acute Otitis Media	amoxicillin	cefdinir, cefpodoxime, ceftriaxone, cefuroxime, clindamycin
Community-acquired Pneumonia	amoxicillin	cefpodoxime, cefprozil, cefuroxime, clindamycin
Sinusitis	amoxicillin	cefdinir, cefpodoxime, cefuroxime, clindamycin
Streptococcal pharyngitis	amoxicillin	cephalexin (preferred unless previous type I hypersensitivity reaction to penicillin) clindamycin, azithromycin

Secondary Outcomes

Re-visits and Adverse Drug Reactions: We will determine if children seen by providers in the two study arms differ in terms of re-visits and/or adverse drug reactions. Data on these clinical outcomes will be collected via follow-up phone calls with parents conducted two weeks after the visit. Parents will be asked if any additional healthcare visits and/or treatment occurred and, if antibiotics were given to the child, if any side effects or adverse drug reactions occurred. Parents will also be asked to report on when their child's symptoms improved, if contingency prescriptions were filled, use of home care treatment suggested by the provider, assessment of the educational video and brochure, and satisfaction with study participation.

Shared Decision-Making: We will assess parent ratings of shared decision-making using an adapted version of the 3-item CollaboRATE questionnaire.[49] This very brief (< 30 seconds) scale was developed with input of end-users and assesses the "effort" that providers put forward to initiate shared decision-making. Members of our CAB and participants in several studies have strongly preferred the CollaboRATE scale to other measures of shared decision-making, especially for more routine health care issues.[50] Items are: "How much effort was made to… (1) help you understand your child's health issue?; (2) listen to the things that matter most to you about your child's health issues?; and (3) include what matters most to you in choosing what to do next?" Items are scored on a 10-point response scale ranging from 0 "No effort was made" to 9 "Every effort was made." In a simulation study the CollaboRATE scale demonstrated discriminative validity between 6 standardized patient-provider encounters that included varied amounts of shared decision making, concurrent validity with other measures of SDM, excellent test-retest reliability, and sensitivity to change.[51]

Quality of Parent-Provider Communication: We will use a single item: "How satisfied were you with the communication between you and your child's health care provider?" with a five

point Likert type response format ranging from “Very dissatisfied” to “Very satisfied.”

Overall Satisfaction with the Visit: We will use a single item: “Overall, how satisfied were you with the visit?” with a five point Likert type response format ranging from “Very dissatisfied” to “Very satisfied.”

Data Analyses

Power and sample size

Prior research examining our primary outcome has shown that 30% of the antibiotics prescribed in the outpatient ARTI visits are inappropriate.[5] Prior behavioral intervention studies have produced 20% to 81% reductions in inappropriate prescribing,[46,47] with statistically significant differences between intervention and control arms (effect sizes: 8.3%[46] and 13.1%[47]). Based on the ICC observed in the Meeker et al. study which is most similar to our study, we assume an ICC of .04. Assuming 30% inappropriate prescribing at baseline and a 20% decrease in the Lower Intensity arm and a conservative 50% decrease in the Higher Intensity arm following intervention, with 40 providers (clusters), α of .05, and 80% power, we will need a sample size of 760 per arm to detect a 9% difference between arms (inappropriate antibiotic 24% in Lower Intensity arm vs. 15% in Higher Intensity arm after intervention). Consistent with our historical retention rates in similar studies in the same setting, we will protect against an attrition rate of 5% and aim to recruit 1,600 participants to ensure adequate power to assess our primary outcome and secondary outcomes.

Planned statistical analyses

Missing Data: All analyses will be conducted using an intent-to-treat strategy with available data. We do not anticipate important amounts of missing data, as all data for primary outcomes are

collected in a single visit before incentives are offered and we will require responses in the REDCap form.

Analytic strategy*:* Initial analyses will examine the underlying distributions of the primary and secondary outcomes. “Ceiling effects” on these measures of parent satisfaction are not uncommon and depending on the level of skewness, we may elect to dichotomize specific scales. We will construct an analytic model to assess the impact of intervention type on our primary outcome of inappropriate antibiotic prescribing. This is a 2-stage nested design, with parents nested within providers (Level-1 units) and study site (Level-2 units). Consequently, ordinary least squares (OLS) and logistic regression models are not appropriate since the data violate the independently and identically distributed (IID) assumption. We will use generalized linear mixed-effect regression models (GLMM) using Stata[52] which allow for easy specification of both fixed and random effects, including accommodating ≥1 cluster variables. Alternative covariance structures will be investigated; though we hypothesize the exchangeable (or compound symmetry) structure will suffice. We will employ robust standard errors to help minimize misspecification and examine time as a potential random effect. The data will be analyzed using a post-test only approach. Next, we will examine the effects of the potential covariates (e.g., parent/patient’s gender, insurance type, parent’s self-reported race and ethnicity, parent’s educational attainment and provider’s years of clinical experience) on the primary and secondary outcomes. Our goal is to identify parsimonious final models with the fewest covariates that best describe the outcomes.

Additionally, we will explore the heterogeneity of treatment effect, or the possibility that one or both of the interventions work better for specific groups. Variables for consideration include: language spoken at home, language the visit was conducted in, and age of child. We will create a binary indicator for each variable and include each as an interaction term in the regression

models. We will examine these interaction terms across intervention arms and explore within-arm differential trends in our primary and secondary outcomes over time.

Discussion

Effective parent-provider communication facilitates rapport-building, exchange of critical information, and shared decision-making which ultimately has the potential to reduce inappropriate antibiotic prescribing and use. Nevertheless, efficacious and feasible training interventions that enhance effective parent-provider communication, shared decision making and antibiotic prescribing are lacking. This study will be the first to compare the efficacy of two interventions directly targeting parent-provider communication about antibiotics in the US outpatient pediatric setting. It will also provide novel insights about parental expectations for antibiotics following the receipt of gain-framed information and providers' experience of the interventions. If successful, the superior intervention could be widely disseminated and potentially lead to reduced health care costs through more appropriate antibiotic use, decreased additional visits by parents who may not have felt satisfied with their initial visit and ultimately less antibiotic resistance.

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Author Contributions

All authors made substantial contributions to the design of the study. KG, ABE, ALM, BRL, EAH and JGN contributed to drafting the protocol and revising it critically for important intellectual content. KBD SS AR KP DY KW SL CCB contributed critical revisions to the draft for important intellectual content. All authors reviewed and approved of the final version submitted for publication and agree to be accountable for all aspects of the work in ensuing that questions related to accuracy and integrity are appropriately investigated and resolved.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___3_____
	2b	All items from the World Health Organization Trial Registration Data Set	throughout document and NCT trial registry
Protocol version	3	Date and version identifier	__1_____
Funding	4	Sources and types of financial, material, and other support	__20_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1_____
	5b	Name and contact information for the trial sponsor	__20_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None (see acknowledgements, p. 20)

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__N/A_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__5-7_____
	6b	Explanation for choice of comparators	__6-7_____
Objectives	7	Specific objectives or hypotheses	___7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__8-9_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__9-10_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__10-13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_11-12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_9-10_____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__14-17_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__13-14_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___17_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___9-10, 14____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___8,14,15____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___N/A_____
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_13-17_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_13-16_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13, 17_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_17-18_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__18_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__17_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__8_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__8_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__8_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__8_____
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___8_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___8_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__8-10_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___9-10_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___20_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__N/A_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___2_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	Authorship contributions detailed in BMJ submission system
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_N/A_____

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_N/A_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Protocol for a randomized trial of higher versus lower intensity patient-provider communication interventions to reduce antibiotic misuse in two pediatric ambulatory clinics in the United States

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Protocol for a randomized trial of higher versus lower intensity patient-provider communication interventions to reduce antibiotic misuse in two pediatric ambulatory clinics in the United States

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Abstract

Introduction: Children with acute respiratory tract infections (ARTIs) are prescribed up to 11.4 million unnecessary antibiotic prescriptions annually. Inadequate parent-provider communication is a chief contributor, yet efforts to reduce overprescribing have only indirectly targeted communication or been impractical. This paper describes our multi-site, parallel group, cluster randomized trial comparing two feasible interventions for enhancing parent-provider communication on the rate of inappropriate antibiotic prescribing (primary outcome) and re-visits, adverse drug reactions, and parent rated quality of shared decision-making, parent-provider communication and visit satisfaction (secondary outcomes).

Methods/analysis: We will attempt to recruit all eligible pediatricians and nurse practitioners (currently 47) at an academic children's hospital and a private practice. Using a 1:1 randomization, providers will be assigned to a Higher Intensity education and communication skills or Lower Intensity education only intervention and trained accordingly. We will recruit 1,600 eligible parent-child dyads. Parents of children ages 1-5 who present with ARTI symptoms will be managed by providers trained in either the Higher or Lower Intensity intervention. Before their consultation, all parents will complete a baseline survey and view a 90-second gain-framed antibiotic educational video. Parent-child dyads consulting with providers trained in the Higher Intensity intervention will, in addition, receive a gain-framed antibiotic educational brochure promoting cautious use of antibiotics and rate their interest in receiving an antibiotic which will be shared with their provider before the visit. All parents will complete a post-consultation survey and a two-week follow-up phone survey. Due to the 2-stage nested design (parents nested within providers and clinics), we will employ generalized linear mixed-effect regression models.

Ethics/dissemination: Ethical approval was obtained from the Children's Mercy Hospital Pediatric Institutional Review Board (#16060466). Results will be submitted for publication in peer-reviewed journals.

Trial registration: NCT03037112

Strengths and limitations

- Implements a parent-provider communication intervention based on a previously effective intervention and adapted for feasibility in the US pediatric ambulatory setting.
- Works closely with a multicultural group of parents, providers and other stakeholders to ensure feasibility and appropriateness of intervention components, study procedures, and study materials in Spanish and English.
- Adequately powered to detect differences between the Higher and Lower Intensity interventions, with a 1:1 randomization of providers to intervention arms and a target sample of 1600 parents/child dyads.
- Data on primary outcomes (i.e., rates of inappropriate antibiotic prescribing), secondary outcomes (i.e., re-visits and adverse drug reactions, shared decision-making, quality of parent-provider communication and satisfaction), and potential covariates will yield novel insights into the effectiveness of each intervention.
- Provider training was limited to one 20-minute session for all providers and one additional 50-minute session for providers in the Higher Intensity arm.

Antibiotic overuse and misuse contribute to the development of antibiotic resistant infections that if left unchecked are estimated to cause 10 million deaths worldwide by 2050.[1] In the United States (US), antibiotic resistant infections are responsible for at least 23,000 deaths and an additional 2 million infections annually.[2] Inappropriate antibiotic use also increases incidence of antibiotic-associated adverse drug reactions (e.g., rash, diarrhea, nausea, and vomiting), which result in over 140,000 Emergency Department visits every year.[3]

The majority of all antibiotic prescribing in the US occurs in the outpatient setting where children receive 49 million prescriptions annually.[4] Children with acute respiratory tract infections (ARTIs) receive over 70% of these prescriptions of which 29% are unnecessary (i.e., either to treat a viral illness or an unnecessary broad-spectrum antibiotic).[4] Despite some improvements, the most recent estimates suggest that antibiotics are prescribed for approximately 50% of ARTIs while it is estimated that only 27% of ARTIs are caused by bacterial infection.[5] As a result, children are receiving up to 11.4 million unnecessary antibiotic prescriptions annually.[5] Strikingly, an almost identical number was noted in a similar study conducted 16 years earlier (11.1 million unnecessary antibiotic prescriptions) suggesting there are considerable gains still to be made in reducing inappropriate use.[6]

Inappropriate antibiotic prescribing in the ambulatory setting has many causes, but the interaction between parents/legal guardians (hereafter referred to as parents) and providers is central. For their part, some parents still harbor misconceptions that make them think antibiotics are necessary when they aren't.[7] Nevertheless, parents generally desire antibiotics for their children only when absolutely necessary[8] and do not expect antibiotics for common colds.[9] Instead, parents become dissatisfied when providers minimize children's symptoms, fail to acknowledge parents' appropriate concerns and/or do not offer a contingency plan if symptoms fail to resolve.[10,11]

Despite evidence to the contrary, providers perceive significant parental pressure for antibiotics and fear damaging the parent-provider relationship if they withhold prescriptions.[12,13]

Combined with the ever-increasing time constraints and focus on parent satisfaction ratings inherent in modern clinical practice, these beliefs greatly contribute to ineffective parent-provider communication about antibiotics. When providers perceive that a parent expects or hopes for an antibiotic, they are more likely to prescribe one.[14,15] In a study of children with viral ARTIs where no prescription should have been given, providers gave a prescription to 52% of parents they believed were expecting an antibiotic as compared to only 9% of parents who they believed were not expecting an antibiotic.[16] Adding to this problem is providers' mistaken belief that they can accurately predict parents' desires. In fact, providers' ability to accurately predict parents' expectation for an antibiotic is significantly worse than chance at 24% to 41% concordance.[12,16] Even though parents rarely state a desire for antibiotics (1% of the time in clinical recordings) providers report frequent parent demands for antibiotics.[17] Providers also mistakenly believe that meeting perceived parental expectations for antibiotics is necessary for parent satisfaction.[13] Parental satisfaction, however, is not related so much to whether or not they receive an antibiotic but more to the quality of communication with their provider.[10,13] In fact, a recent observational study demonstrated that the use of what they termed "positive treatment recommendations" (i.e., comfort care) plus "negative treatment recommendations" (i.e., antibiotics won't help) was associated with the highest parent satisfaction.[18]

Current efforts to improve appropriate antibiotic use have only indirectly targeted parent-provider communication [19,20] or have been found to be impractical.[21] As described in several meta-analytic and systematic reviews, interventions have typically focused on education about antibiotics for providers or patients.[19,20] While many have been successful in increasing knowledge about antibiotics and nationally antibiotic prescribing has evidenced modest reductions,[8,22] more effective strategies that go beyond educational targets are needed to reduce overprescribing rates to levels that will have a significant impact. A limited number of studies have been conducted that target parent-provider communication or shared decision-

making, and they have already produced superior results.[20] Of the communication interventions tested, only one has directly targeted provider perceptions of parental expectations alongside antibiotic education and shared decision-making.[23] This study, which employed intensive provider training and a multi-page patient-provider interactive educational booklet, resulted in a significant decrease in antibiotic use. The intervention, however, was viewed as burdensome by providers and impractical for most real world settings.[21] Effective, practical interventions are needed that address provider misconceptions about parent expectations, facilitate shared-decision making, and improve aspects of communication that are most likely to increase parental satisfaction.

The goal of this study is to compare two feasible interventions for enhancing parent-provider communication to reduce the rate of inappropriate antibiotic prescribing. This study will compare the efficacy of a Higher Intensity provider education and communication skills intervention to a Lower Intensity provider education only intervention. We hypothesize that the parent-child dyads managed by providers trained in the Higher Intensity intervention will demonstrate superiority to dyads managed by providers trained in the Lower Intensity intervention on the primary outcome of rate of inappropriate antibiotic prescribing, as well as, the secondary outcomes of re-visits, adverse drug reactions, and parent rated quality of shared decision making, parent-provider communication and satisfaction.

Methods and Analysis

Patient and Public Involvement: In the early planning stages for this study, we conducted focus groups and individual interviews with clinical, parent, payer and community stakeholders to assess the viability and inform the design of the study. We then recruited a Parent Research Associate who is a core member of our research team, attends all meetings, contributes to all decisions about the study and co-leads our Community Advisory Board (CAB). Our CAB is comprised of 15 parent, provider and community stakeholders and is diverse (i.e., 3 males, 7

Latinx [3 exclusively Spanish speaking] and 3 African Americans). CAB meetings will occur every other month during year 1 and twice yearly in years 2 and 3. All aspect of the study design, settings, participant burden, materials, procedures, interpretation of data, and dissemination of study findings have and will be informed by the CAB and Community Research Associate. Study results will be disseminated to all clinic providers. A parent summary of findings will be developed and provided to study sites who will be encouraged to post in their facilities and/or mail to parents.

Trial design, setting and participants

Trial design: A multi-site parallel group, cluster randomized trial with balanced randomization (1:1) will be performed in three ambulatory pediatric clinics in the Unites States. Recruitment of providers will start in January of 2017 and continue throughout the study as new providers are hired. Providers (physicians and nurse practitioners) will be randomly assigned to training in either Higher Intensity or Lower Intensity intervention described below. Once providers have been randomized and trained, eligible parent-child dyads will be enrolled and exposed to management by a provider who was trained in one of the interventions. Recruitment of parent-child dyads will start in March of 2017 and continue through December of 2018. Parents in both arms will receive education on the pros and cons of antibiotics for common infections and tips for communicating with their provider. Blinding of providers will not be feasible in this study, however, parents will be blinded as they will not be told what study arm their provider is in, nor informed about differences between the study interventions. Study team members who conduct chart review to code appropriateness of antibiotic prescriptions and code session audiotapes for intervention fidelity will be blinded. The study protocol is in compliance with the Helsinki Declaration and was reviewed and approved by the Institutional Review Board of Children's Mercy Hospital (#16060466). PI (KG) will monitor recruitment, retention (bimonthly) and adverse

events (quarterly; blinded to study arm) in this low risk study. Adverse events, collected from parents at 2-week follow-up, through chart review and spontaneously from clinic staff. Any protocol modifications will be submitted for IRB review and communicated to all relevant parties before implementation.

Randomization: To protect against practice effects (tendency for providers to have more consistent beliefs and behaviors within their practice as compared to providers in other practices), we will randomize providers rather than clinic sites. We did this because the intervention components are not easily transferred between providers making the risk of contamination a much smaller threat to validity than practice effects. As detailed below in the Higher Intensity Provider Training section, we will employ several strategies to reduce the chance of contamination across study arms. We will use clinic data on visits among our target population from the past six months to assign each provider to a large or small patient volume group. The study statistician will then stratify the randomization of providers to ensure each study arm is balanced across large and small volume providers and across clinics. The study statistician will place the intervention group assignment in sealed envelopes labeled with providers' names. Providers will be given their envelopes at the conclusion of a brief study orientation and informed consent meeting and before completing the baseline assessment.

Setting: Study sites will be an academic medical center (Children's Mercy Hospital Primary Care Clinic - CMH PCC) and both locations of a private practice (Heartland Primary Care - HPC). CMH PCC sees a racially and ethnically diverse group of patients (41% African American/Black, 29% Hispanic, 18% White) from the Kansas City metropolitan area, of which 73% are covered by Medicaid. CMH PCC has 38 providers (28 pediatricians and 10 nurse practitioners) and treats approximately 2100 children with an ARTI that meet study inclusion

criteria yearly. HPC is a community-based private practice with two locations in sub-urban Kansas City serving a diverse patient population (14% African American/Black, 16% Hispanic, 75% White; 42% covered by Medicaid). HPC has 9 pediatric providers (6 pediatricians and 3 nurse practitioners) who care for 2000 children that meet study inclusion criteria annually. Approximately 20% of parents at study sites are Spanish speaking.

Participants: This study involves providers and parent-child dyads. We will attempt to recruit all eligible providers at all study sites (pediatricians, pediatric nurse practitioners; n = 47), defined as those who regularly treat patients that meet our inclusion criteria. Providers primarily assigned to administration, urgent care or specialty clinics that serve complex care patients will not be eligible. We will conduct brief study orientation and informed consent meetings to enroll providers during regularly scheduled clinic meetings or individual contacts.

We will recruit up to 1600 parent-child dyads (See Figure 1). Dyads will be eligible if the patient is between ages 1-5 years (i.e., before sixth birthday), presents with ARTI symptoms (e.g., cough, congestion, difficulty breathing, sore throat, ear ache) and his/her parent is fluent in English or Spanish. Children will not be eligible if they have received an antibiotic in the last 30 days, have a concurrent probable bacterial infection (e.g., urinary tract infection, soft tissue infections), known immunocompromising conditions (e.g., HIV, malignancy, solid-organ transplant, chronic corticosteroid use), or factors that make shared decision-making around prescribing an antibiotic extremely complex, like children with complex chronic care conditions (e.g., cystic fibrosis),[24] or who require hospitalization during the visit. We will include patients with penicillin allergy as shared decision-making with this group is especially important given more limited treatment options. Parents or children who have previously participated in the study will not be eligible to participate again. Potentially eligible dyads will be identified through prescreening all appointments and parents will be given a study flyer upon check-in. Potential eligible dyads will be greeted in the exam room before the provider arrives, given a short

synopsis of the study, and offered eligibility screening. If more than one caregiver is with the child, they will be asked to designate one person who will complete the informed consent and all assessments. Providers will have no role in identifying potentially eligible dyads, screening, consenting or data collection.

Trial Interventions

Higher Intensity Intervention. With attention to the feasibility in the US healthcare system, this intervention will be informed by a series of evidence-based interventions conducted in the UK and Europe: Enhancing the Quality of Information-sharing in Primary care (EQUIP),[23,25] Improving the Management of Patients with Acute Cough Trial (IMPACT),[26,27] Stemming the Tide of Antibiotic Resistance (STAR)[28,29] and Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe (GRACE).[30]

Higher Intensity Arm Provider Training: Providers in this arm will receive two trainings. First, a 20-minute, in-person general education training provided by a study physician (ALM, JGN) will cover the pros and cons of antibiotics, the impact of inappropriate use, Centers for Disease Control and Prevention antibiotic prescribing guidelines, common reasons for antibiotic misuse, and viewing/discussion of the parent educational cartoon (described below). Didactic and interactive learning strategies will be employed to review the appropriate diagnostic criteria to help distinguish a viral ARTI from a bacterial ARTI, as well as, the recommended narrow spectrum antibiotic for bacterial ARTI. Second, providers will receive a 50-minute, in-person training on parent-centered communication skills provided by a behavioral psychologist (KG). The training will use a variety of educational strategies including viewing/discussion of motivational and role model videos, lecture, and group discussion. The goal is to enhance providers' confidence in use of parent-centered communication strategies (e.g., open ended

questions, affirming and elicit-provide-elicit) and the study tri-fold brochure to conduct key aspects of the EQUIP/IMPACT/STAR/ GRACE interventions during consultations. Specifically, they will learn to: 1) elicit parents' expectations, 2) affirm parents' concerns, 3) provide an evidence-based estimate of likely illness duration, 4) provide gain-framed antibiotic information, 5) recommend options for symptom relief, 6) identify triggers for re-consult and contingency plans, and 7) elicit parents thoughts on the plan. Providers will also learn to use the study tri-fold brochure to ensure that they complete all necessary aspects of the intervention and provide written notes for parents to refer to after the visit. The inside of the study tri-fold brochure provides gain-framed information about when antibiotics are and are not necessary and what risks are involved in taking antibiotics. Research has shown that people react to the same tradeoff in different ways depending on whether the possible outcomes are presented as losses or gains.[31] In this study, we will train providers and tailor our parent materials to highlight the gains of not using antibiotics (e.g., staying safe from side effects, making sure that effective cures are available in the future, knowing that their child's body will fight off most ARTI on its own) that may increase parents' comfort with not getting an antibiotic prescription for their child. Drawing from the EQUIP study,[25] the outside of the brochure includes a place to write the child's first name; check boxes to indicate the diagnosis, recommended home care treatments, and reasons for re-consultation; expected recovery time, if antibiotics are needed, and tips for communicating with providers.

To reduce their reliance on guessing what parents want, providers will also be trained to rely on parents' antibiotic desire ratings taken from their baseline survey and provided at the start of each visit via a sticky note on the exam room door where parent-child dyads will be waiting. To assess fidelity to the communication skills, we will audio record a subsample of visits (10%) in both Higher and Lower Intensity arms and objectively code use of key communication strategies using established methods that we have successfully employed in other studies.[32,33] We will deliver in-person provider training as studies have shown the value of an active

approach over more passive web-based versions,[34] but we will also develop web-based refresher trainings.

Higher Intensity Arm Parent Training: In exam rooms prior to the consultation, parents will complete the baseline survey, view a 90 second educational cartoon video with accompanying educational tri-fold brochure and rate their desire for antibiotics via a tablet computer. The educational video uses gain-framed messages[31,35] to explain when antibiotics are and are not indicated while emphasizing the risk of side effects and the creation of resistant organisms. It also highlights what information should be provided during the consultation (e.g., an estimate of illness duration, recommendations for system relief, and triggers for re-consult and contingency plans). Parents in this arm will receive a hard copy of the study tri-fold brochure.

Lower Intensity Intervention: This intervention will be modeled on proven parent and provider focused educational interventions used in previous studies.[19,34,36–44] Providers will complete the same 20 minute, in-person general education training described above. Parents will receive the same parent training described above except that parents will not receive a hard copy of the study tri-fold brochure and their antibiotic desire ratings will not be shared with providers.

Several measures will be taken to reduce the likelihood of contamination between arms. Specifically, we will: 1) train study team members to ensure that all of our communications (written or in person) with providers in the Lower Intensity arm do not reveal any of the strategies from the Higher Intensity training, 2) review the importance of keeping intervention arms distinct in RCT designs during training, 3) directly ask providers to pledge not to share any details of the additional communication skills training with their colleagues randomized to the Lower Intensity arm, 4) control the dissemination of the tri-fold brochure to ensure that only parents who are consulted by providers in the Higher Intensity arm receive them, and 5) offer communication strategies for dealing with colleagues who ask for more information.

Data Collection

Providers/Administrators: At baseline, providers will complete a brief survey collecting demographic data, and providers' views on parent interest in antibiotics for viral illness, their comfort with telling parents that antibiotics are not necessary, and their concern about parents' responses. Once parent-child dyad recruitment is complete, a brief survey mirroring the baseline provider assessment and a brief (<10 min) semi-structured individual interview will be conducted with providers and administrators to learn about their experience of being in the study, suggestions for improvement and ideas about disseminating to other settings. Providers/Administrators will not receive incentives for study participation.

Parents: At baseline, immediately before their scheduled visit with a provider, parents will complete a brief tablet computer administered Research Electronic Data Capture (REDCap) survey about their antibiotic knowledge and interest in antibiotics for their child's current condition. They will then view the educational video and indicate their interest in antibiotics for their child's current condition again and rate the likelihood of actually receiving antibiotics during their visit. After meeting with their provider, parents will complete a brief survey about their experience of the visit including their rating of shared decision making, satisfaction with parent-provider communication and overall satisfaction with the visit. Two weeks later, parents will be contacted via phone to complete a follow-up survey to assess: resolution of child's illness, any additional healthcare visits and/or treatment, if contingency or "back-up" prescriptions were filled, presence and severity of side effects from any antibiotics administered, use of home care treatment suggested by provider, assessment of the educational video and brochure, and satisfaction with study participation. EMR data will be abstracted using a standardized data collection form and evaluated by study physicians to determine the appropriateness of antibiotic

prescribing. Parents will be provided with $10 per completed survey in recognition of their time and effort.

Measures

Interest in assessing patient/parent-provider communication has garnered significant attention, but measurement challenges remain. Despite a large number of published instruments, availability of valid, reliable, and scalable measures is a recognized barrier to progress in research and implementation of patient-centered care.[45] Lack of patient involvement in scale development has been cited as a contributing factor, so we have engaged parent and provider stakeholders in the selection of measures for this study. All measures have been adapted based on their feedback, pilot testing including cognitive debriefing was performed to ensure the briefest possible assessment of study outcomes. All measures were translated into Spanish using standard methods and appropriate pilot testing.

Primary Outcome

Antibiotic Prescribing: Our primary research question is which of the two interventions leads to a lower rate of inappropriate antibiotic prescribing. We hypothesize that the rate among providers in the Higher Intensity arm will be lower than the rate produced by providers in the Lower Intensity arm. If the rates do not significantly differ, we will recommend the Lower Intensity intervention as preferable for dissemination, as its implementation requires less time and resources. Inappropriate prescribing will be assessed on a weekly basis by study physicians, blinded to study arm, who will review the medical record documentation for each enrolled patient's visit to determine if inappropriate antibiotic prescribing occurred. Prescriptions will be considered inappropriate if they meet any of the following criteria: 1) antibiotic prescribed for a viral ARTI, 2) antibiotic prescribed for a presumed bacterial ARTI that does not meet Table 1 criteria, 3) broad-spectrum antibiotic prescribed for a bacterial ARTI in a child without a penicillin allergy, or 4) non-recommended alternative antibiotic prescribed for a bacterial ARTI

(see Table 2) in a child with a penicillin allergy.

Table 1. Diagnostic criteria for ARTIs [19,36,34,46,47]

Bacterial ARTI	Diagnostic criteria
Acute Otitis Media (either criteria)	1. Fever ≥38.3°C (101°F) with either a or b: a. Moderate to severe bulging of tympanic membrane on exam, or b. Mild bulging of TM and recent (<48hrs) onset of ear pain 2. New onset of otorrhea not due to acute otitis externa
Sinusitis (any of the 3 criteria)	1. Daytime cough or nasal discharge for greater than 10 days 2. High fever (>39°C) with purulent nasal discharge or facial pain lasting 3 consecutive days at the beginning of the illness 3. Worsening signs or symptoms characterized by the new onset of fever, headache, or increase in nasal discharge following a typical viral URI
Community acquired Pneumonia (either criteria)	1. Fever, tachypnea, and focal findings on pulmonary exam 2. a) Fever, b) Tachypnea, cough, or retractions AND c) Chest radiograph consistent with a focal consolidation
Streptococcal pharyngitis (both criteria)	1. Fever, pharyngitis, & positive rapid streptococcal antigen test or culture 2. Lack of viral signs and symptoms

Table 2. Appropriate Antibiotic Selection[19,36,46,47]

Bacterial ARTI	Primary Antibiotic	Secondary Antibiotics for Penicillin Allergy
Acute Otitis Media	amoxicillin	cefdinir, cefpodoxime, ceftriaxone, cefuroxime, clindamycin
Community-acquired Pneumonia	amoxicillin	cefpodoxime, cefprozil, cefuroxime, clindamycin
Sinusitis	amoxicillin	cefdinir, cefpodoxime, cefuroxime, clindamycin
Streptococcal pharyngitis	amoxicillin	cephalexin (preferred unless previous type I hypersensitivity reaction to penicillin) clindamycin, azithromycin

Instead of relying on diagnostic codes as has been done in previous studies,[46,48] the study physicians will assess the appropriateness of the patient's diagnosis by reviewing detailed symptoms, physical examination findings, and diagnostic tests in the EMR. This will guard against the potential bias of relying on diagnostic codes alone, as clinicians sometimes match diagnostic codes to support their antibiotic prescribing.[12] Children determined to have a bacterial infection will need documentation of the specific diagnoses and the clinical criteria confirming that diagnosis (listed in Table 1). Ten percent of all chart reviews will be verified by the other study physician blinded to the initial coding and study group. Overall antibiotic prescription rate

for different ARTI diagnoses by arm will also be reported.

Secondary Outcomes

Re-visits and Adverse Drug Reactions: We will determine if children seen by providers in the two study arms differ in terms of re-visits and/or adverse drug reactions. Data on these clinical outcomes will be collected via follow-up phone calls with parents conducted two weeks after the visit. Parents will be asked if any additional healthcare visits and/or treatment occurred and, if antibiotics were given to the child, if any side effects or adverse drug reactions occurred. Parents will also be asked to report on when their child's symptoms improved, if contingency prescriptions were filled, use of home care treatment suggested by the provider, assessment of the educational video and brochure, and satisfaction with study participation.

Shared Decision-Making: We will assess parent ratings of shared decision-making using an adapted version of the 3-item CollaboRATE questionnaire.[49] This very brief (< 30 seconds) scale was developed with input of end-users and assesses the "effort" that providers put forward to initiate shared decision-making. Members of our community advisory board and participants in several studies have strongly preferred the CollaboRATE scale to other measures of shared decision-making, especially for more routine health care issues.[50] Items are: "How much effort was made to… (1) help you understand your child's health issue?; (2) listen to the things that matter most to you about your child's health issues?; and (3) include what matters most to you in choosing what to do next?" Items are scored on a 10-point response scale ranging from 0 "No effort was made" to 9 "Every effort was made." In a simulation study the CollaboRATE scale demonstrated discriminative validity between 6 standardized patient-provider encounters that included varied amounts of shared decision making, concurrent validity with other measures of SDM, excellent test-retest reliability, and sensitivity to change.[51]

Quality of Parent-Provider Communication: We will use a single item: "How satisfied were you with the communication between you and your child's health care provider?" with a five point Likert type response format ranging from "Very dissatisfied" to "Very satisfied."

Overall Satisfaction with the Visit: We will use a single item: "Overall, how satisfied were you with the visit?" with a five point Likert type response format ranging from "Very dissatisfied" to "Very satisfied."

Data Analyses

Power and sample size: Prior research examining our primary outcome has shown that 30% of the antibiotics prescribed in the outpatient ARTI visits are inappropriate.[5] Prior behavioral intervention studies have produced 20% to 81% reductions in inappropriate prescribing,[46,47] with statistically significant differences between intervention and control arms (effect sizes: 8.3%[46] and 13.1%[47]). Based on the ICC observed in the Meeker et al. study which is most similar to our study, we assume an ICC of .04. Assuming 30% inappropriate prescribing at baseline and a 20% decrease in the Lower Intensity arm and a conservative 50% decrease in the Higher Intensity arm following intervention, with 40 providers (clusters), α of .05, and 80% power, we will need a sample size of 760 per arm to detect a 9% difference between arms (inappropriate antibiotic 24% in Lower Intensity arm vs. 15% in Higher Intensity arm after intervention). Consistent with our historical retention rates in similar studies in the same setting, we will protect against an attrition rate of 5% and aim to recruit 1,600 participants to ensure adequate power to assess our primary outcome and secondary outcomes.

Planned analytic strategy*:* All analyses will be conducted using an intent-to-treat strategy with available data. Initial analyses will examine the underlying distributions of the primary and secondary outcomes. “Ceiling effects” on these measures of parent satisfaction are not uncommon and depending on the level of skewness, we may elect to dichotomize specific scales. We will construct an analytic model to assess the impact of intervention type on our primary outcome of inappropriate antibiotic prescribing. This is a 2-stage nested design, with parents nested within providers (Level-1 units) and study site (Level-2 units). Consequently, ordinary least squares (OLS) and logistic regression models are not appropriate since the data violate the independently and identically distributed (IID) assumption. We will use generalized linear mixed-effect regression models (GLMM) using Stata[52] which allow for easy specification of both fixed and random effects, including accommodating ≥1 cluster variables. Alternative covariance structures will be investigated; though we hypothesize the exchangeable (or compound symmetry) structure will suffice. We will employ robust standard errors to help minimize misspecification and examine time as a potential random effect. The data will be analyzed using a post-test only approach. Next, we will examine the effects of the potential covariates (e.g., parent/patient’s gender, insurance type, parent’s self-reported race and ethnicity, parent’s educational attainment and provider’s years of clinical experience) on the primary and secondary outcomes. Our goal is to identify parsimonious final models with the fewest covariates that best describe the outcomes.

Additionally, we will explore the heterogeneity of treatment effect, or the possibility that one or both of the interventions work better for specific groups. Variables for consideration include: language spoken at home, language the visit was conducted in, and age of child. We will create a binary indicator for each variable and include each as an interaction term in the regression models. We will examine these interaction terms across intervention arms and explore within-arm differential trends in our primary and secondary outcomes over time.

Missing Data: All analyses will be conducted with available data. We do not anticipate important amounts of missing data, as all data for primary outcomes are collected in a single visit before incentives are offered and we will require responses in the REDCap form.

Ethics and dissemination

Ethical approval was obtained from the Children's Mercy Hospital Pediatric Institutional Review Board (#16060466). All participants will provide written informed consent prior to participating in the study. We will employ multiple strategies to protect confidentiality of personal information about potential and enrolled participants. Pre-screening of patients will be conducted exclusively by trained study staff on password protected computers and REDCap data collection tool. Appointments with potential participants will be flagged in electronic clinic scheduling systems accessible only to clinic and study staff. Enrolled parent and patient participants will complete all measures in REDCap projects, which will only be accessible to study staff who must use multiple passwords to access REDCap through the Children's Mercy network. Personal identifying information, namely medical record number and contact information, is marked as an identifier in REDCap and is then censored when the database is downloaded for analysis. All identifying information will be removed with the deletion of the REDCap project at the end of the study. Audio files of clinic visits will be stored in a password protected file on the Children's Mercy server that is only accessible to members of the study staff. Consent forms and signature logs for reimbursements will be secured in a locked file cabinet within a locked office on a secured floor.

A full data package will be maintained by the investigators at Children's Mercy Hospital for at least seven years after data collection is complete. Third-party access to the full data package will be addressed by Children's Mercy Hospital on a case-by-case basis.

Results will be disseminated through publication in peer-reviewed journals and conference presentations. Study progress and findings will also be updated on clinicaltrails.gov (#NCT03037112).

Discussion

Effective parent-provider communication facilitates rapport-building, exchange of critical information, and shared decision-making which ultimately has the potential to reduce inappropriate antibiotic prescribing and use. Nevertheless, efficacious and feasible training interventions that enhance effective parent-provider communication, shared decision making and antibiotic prescribing are lacking. This study will be the first to compare the efficacy of two interventions directly targeting parent-provider communication about antibiotics in the US outpatient pediatric setting. It will also provide novel insights about parental expectations for antibiotics following the receipt of gain-framed information and providers' experience of the interventions. If successful, the superior intervention could be widely disseminated and potentially lead to reduced health care costs through more appropriate antibiotic use, decreased additional visits by parents who may not have felt satisfied with their initial visit and ultimately less antibiotic resistance.

Figure Legends

Figure 1: Schematic diagram of parent-patient dyad participant flow

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Competing Interests

The authors declare no competing interests.

Author Contributions

All authors made substantial contributions to the design of the study. KG, ABE, ALM, BRL, EAH and JGN contributed to drafting the protocol and revising it critically for important intellectual content. KBD SS AR KP DY KW SL CCB contributed critical revisions to the draft for important intellectual content. All authors reviewed and approved of the final version submitted for publication and agree to be accountable for all aspects of the work in ensuing that questions related to accuracy and integrity are appropriately investigated and resolved.

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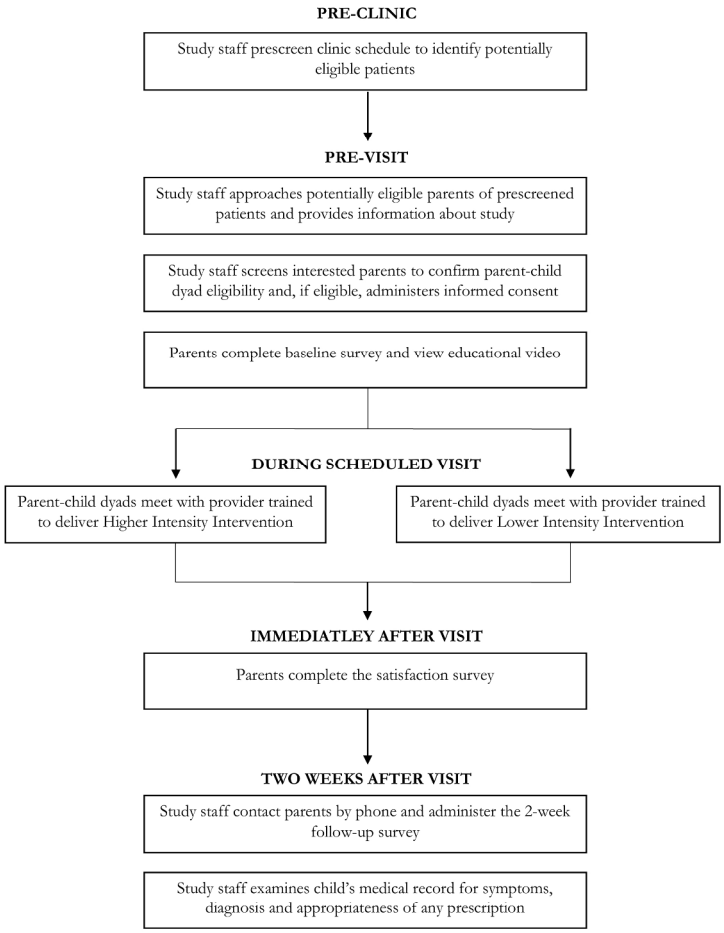

Figure 1: Schematic diagram of parent-patient dyad participant flow

215x279mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___3_____
	2b	All items from the World Health Organization Trial Registration Data Set	throughout document and NCT trial registry
Protocol version	3	Date and version identifier	__1_____
Funding	4	Sources and types of financial, material, and other support	__21_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1_____
	5b	Name and contact information for the trial sponsor	__21_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None (see p. 21)

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__N/A_____
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__5-7_____
	6b	Explanation for choice of comparators	__6-7_____
Objectives	7	Specific objectives or hypotheses	___7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__8-9_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__9-10_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__10-13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__9_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_11-12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_9-10_____

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__14-17_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_9-13 and Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___17_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___9-10, 14____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___8_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___8,14,15____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___N/A_____
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_13-17_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_13-16_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13, 17_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_17-18_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__18_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__17_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__8_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__8_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__8_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__8_____
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___8_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___8_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__8-10_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___19_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___21_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__20_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___2_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	Authorship contributions detailed in BMJ submission system
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_20_____

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_N/A_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.