

**STEPStools: Developing Web Services for Safe Pediatric Dosing**

**Kevin B. Johnson, MD, MS (PI)**  
Professor, Biomedical Informatics  
Professor, Pediatrics  
Vanderbilt University Medical Center  
Nashville, TN

**Cynthia S. Gadd, PhD (Co-Investigator)**  
Associate Professor of Biomedical Informatics  
Department of Biomedical Informatics  
Vanderbilt University Medical Center

**Stuart T. Weinberg, MD (Co-Investigator)**  
Assistant Professor of Biomedical Informatics  
Department of Biomedical Informatics  
Assistant Professor of Pediatrics  
Department of Pediatrics  
Vanderbilt University Medical Center

**Coda Davison (Program Coordinator)**  
Vanderbilt University Medical Center

**Marvin Palmer (Programmer)**  
Vanderbilt University Medical Center

**Jill Helmke (Clinical Research Pharmacist)**  
Vanderbilt University Medical Center

**Yun-Xian Ho (Research Analyst)**  
Vanderbilt University Medical Center

**Carlton Lee, Pharm.D., MPH (Co-Investigator)**  
Associate Professor of Pediatrics  
Johns Hopkins Hospital

**S. Andrew Spooner, MD (Co-Investigator)**  
Associate Professor of Clinical Pediatrics  
Cincinnati Children's Hospital Medical Center

**Project Dates:** 09/30/2007 – 02/28/2011

**Federal Project Officer:** Erin Grace

**This project was supported by the Agency for Healthcare Research and Quality**

**Award Number: 5 R18 HS017216-03**

---

**Abstract**

**Purpose:** The project's goals are to construct, test, and evaluate dose rounding and compound formulation tools in a pediatric e-prescribing system.

**Scope:** Pediatric e-prescribing systems contain gaps in functionality, especially in applying compounded medication and rounding tolerance knowledge. We hypothesized that web-service based tools would improve e-prescribing.

**Methods:** We developed a compounded medication knowledgebase and rounding algorithm by obtaining data from three large children's hospitals in addition to expert consensus, literature review, and interviews. We implemented a rounding system and assessed it with a test set of pediatric e-prescriptions. Discrepant test cases were evaluated by 44/139 eligible pediatric prescribers (32% response). We integrated STEPStools into an e-prescribing system and assessed ease of implementation and frequency of use.

**Results:** STEPStools achieved 84% accuracy for its recommendations. Web services implementation was hampered initially by RxNorm knowledgebase gaps affecting term mapping. The service was called 268 times daily on average. 39% of responses contained a dosing suggestion. Results confirm that web services are a feasible knowledge and tool distribution method. Additional work should improve the performance of the rounding algorithm and the number of medications it is able to round.

**Key Words:** web services; e-prescribing; decision support systems; pediatrics; computers; meaningful use

## Purpose

The goal of this project, creating Safety Through E-Prescribing System Tools (STEPSTools), is to build and evaluate a suite of tools that can be used **nationally** to provide a compounded formulation knowledgebase and to provide information about dose-rounding.

## Scope

Medication errors are a leading cause of iatrogenic morbidity and mortality in children. The process of prescribing for children has added complexity over adult prescribing. Challenges for safe and effective pediatric prescribing are caused primarily by the wide variation in developmental stage and physical ability, coupled with the accelerating and decelerating rate of growth during the first 16-18 years of life. The table below summarizes some of those issues, based on an early report from the American Academy of Pediatrics.

Requirement	Example
Data representation	Weight in tenths of a kilogram in first months of life (e.g., 3.4 kg) Age in days, weeks, months, or years depending on age of child
Age-based dosing recommendations	Digoxin mg/kg/day dosing changes as child grows
Need for easily administered dosage forms	Digoxin example above
Need to adjust dose with age	Self explanatory

According to a recent eHealth Initiative report, electronic prescribing (e-prescribing) “refers to the use of computing devices to enter, modify, review, and output or communicate drug prescriptions.” E-prescribing tools come in a variety of levels of sophistication, with the most advanced tools providing legible orders, alerts and reminders, integration with medical record data that affects prescribing decisions, and enhancements to improve integration within existing clinic workflows. Data about the benefits of this technology have been persuasive enough to catalyze federal incentives for the use of this technology.

While many of the benefits of e-prescribing occur with equal probability in pediatric and adult medicine, some of the unique needs of young infants are as yet unaddressed impediments to safe pediatric prescribing. For example, typical e-prescribing systems that are able to calculate doses rely on medication knowledge bases that provide weight-based dosing recommendations. Before that dose can be prescribed, however, the dose is generally adjusted by rounding it to the nearest measurable and easily administered amount. Currently this step is performed manually by the prescriber, which can lead to confusing or possibly over/underdosing, based on the properties of the medication. Another challenge is that extemporaneous formulations (compounded or diluted formulations) are generally not characterized in existing drug knowledge bases, even though many of the active ingredients are potentially toxic medications. Without the availability of these data, e-prescribing in pediatrics will continue to have a knowledge gap that will impact both safety and adoption.

For this knowledge gap to be solved in the short term, developers will need to produce knowledge that has been created by and endorsed by pediatricians, as well as tools with high reliability and widespread availability. One approach to the development of these tools employs the use of service-oriented architectures and distributed knowledge management. These so-called “web services” represent a new and easily integrated way to disseminate knowledge that offers reusability, efficient distribution,

rigorous testing, and centralized maintenance. We hypothesize that this model can be used to encapsulate and distribute pediatric clinical decision support. The goals of this project were to construct this medical knowledge and to test our ability to deliver it using web services to disparate e-prescribing systems.

To accomplish the goals above, we constructed three aims for this project:

**Aim 1:** Convene an expert panel to construct a knowledgebase of actionable data to guide e-prescribing systems in the appropriate rounding of calculated doses and selection of extemporaneous medication formulations.

**Aim 2:** Using established service-oriented architecture models, construct web services and a web-based client to allow browsing of the knowledge and access to it from disparate e-prescribing systems.

**Aim 3:** Evaluate the usability and content validity of these STEPSTools web services, using a series of pediatric prescribing use cases, site visits to two pilot sites, and through an examination of the acceptance rate of prescriptions generated with these web services.

## Aim 1- Methods

To address the project goals, our study relied on information from interviews and literature review. We also used a consensus-based process to validate proposed rounding tolerances.

### *Interviews*

We conducted semi-structured interviews to assess the overall considerations used in rounding prescribed medications. We used a purposive sampling plan to recruit subjects who included local and national experts in general pediatrics, subspecialty pediatrics, pediatric pharmacy, biomedical informatics, and pharmacology. The sampling plan focused primarily on ambulatory locations affiliated with academic medical centers, where medication dosing takes into account the needs of home caregivers who must measure and administer the medication.

A member of the project team provided a brief project overview to each domain expert prior to the interview. Each interview started with a recapitulation of the project goals, and then focused the interview around 3 framing questions: “Please describe how you create a prescription where the effects, both intentional and unintentional, are related to the dose”; “Please describe the process for prescribing a compound medication”; and “What is your process for rounding?” All interviews were transcribed and posted to a project wiki site ([www.dokuwiki.org](http://www.dokuwiki.org)) with restricted access for review and discussion among project team members. An iterative process based on discussion and revision of rounding techniques was used to focus and refine subsequent interviews. Results from the interviews were used to help define practical approaches to rounding and to develop a framework for categorizing medications according to the usual rounding philosophy as described by our experts.

### *Literature Review*

We reviewed pharmacologic information for 120 medications that comprised over 95% of the most common outpatient pediatric medications in two academic medical centers. We collected weight-based dosing guidelines, minimum and maximum dosing amounts, and drug toxicity or side effect information from a series of commonly cited articles and texts. Of note, we did not discover any published literature

providing specific rounding tolerances in either the pediatric or geriatric population. We also consulted the adult and pediatric gray literature, including web resources and the Food and Drug Administration web site, for information about some medications. Using the framework developed in the interview phase, we evaluated dosing knowledge for each medication and assigned it to a category within this framework. We used the properties of the assigned rounding category, along with dosing information from domain experts and information about the drug's therapeutic intent and potential adverse reactions obtained from the literature review to propose an initial rounding percentage.

### ***Extemporaneous Formulation Knowledge***

We obtained lists of commonly prescribed compounds from three major children's hospitals in Maryland, Pennsylvania, and Massachusetts. We categorized these compounds into two forms: admixtures and extemporaneous forms. Admixtures were composed of two or more dispensable medications combined into a single medication. Extemporaneous forms were typically composed of a single dispensable medication that was mixed with an inert ingredient to create a suspension with a specific concentration of the active ingredient.

We entered these admixtures and extemporaneous forms into a database that replaced each active ingredient with an RxNorm-encoded representation of that term.

### ***Rounding Percentage Validation***

We used a Delphi approach aimed at generating consensus about each rounding recommendation. This technique works well "to correlate informed judgments on a topic spanning a wide range of disciplines." In our project, this model for consensus building was ideal for a primarily online group of pharmacists, primary care providers and hospitalists to discuss the degree to which medications should be rounded automatically.

We began by entering proposed rounding percentages into an electronic survey instrument familiar to the expert reviewers, called REDCap. Each question presented the recommended rounding percentage, and allowed each group member to agree or disagree with the recommendation. A sample question is shown in Figure 1, below. Each expert completed the survey anonymously. After experts completed the first round of surveys, a facilitator (KBJ/JH) tabulated all responses and provided feedback to the expert group as a whole. All medications for which there was less than 80% consensus about the proposed rounding percentage were discussed among the participants. Based on this discussion, we modified the rounding percentages for these medications, and completed a second round of the survey. We included two pediatric neurologists later in this process to review and agree on rounding tolerances for set of medications typically prescribed by members of that specialty. Finally, there were 16 medications that the group unanimously agreed were out of scope for this effort, either because the group was unfamiliar with their use (e.g., ziprasidone), or because it was determined that dosing in pediatric offices typically did not employ existing weight-based guidelines (e.g., ursadiol). Group consensus for all other medications was achieved after 4 rounds of discussion.

Pretend you have a patient who is being prescribed a dose of each medication below. You've calculated this dose using standard mg/kg/day formulae, and arrive at 5.82 ml per dose, and there's only one formulation to choose from. The e-prescribing system you use returns a rounded dose, based on ease of home administration.

- If the medication allows 0% rounding, the dose will be 5.8 mL.
- If the medication allows 1% rounding, the dose will be between 5.7 and 5.9 mL. You would likely pick 5.9 mL.
- If the medication allows 5% rounding, the dose will be between 5.5 and 5.9 mL. You would likely pick 5.9 mL.
- If the medication allows 10% rounding, the dose will be between 5.2 and 6.4ml. You would likely pick 6mL.
- If the medication allows 15% rounding, the dose will be between 4.9 and 6.7 ML. You would likely pick 6 mL.

Given these choices, for each drug below, do you agree or disagree with the maximum amount we would suggest to allow rounding?

<b>calcitriol Do not round further, OK?</b> <small>* must provide value</small>	<input type="text"/>
<b>Digoxin, do not round further, OK?</b> <small>* must provide value</small>	<input type="text"/>
<b>ondansetron (zofran) do not round further, OK?</b> <small>* must provide value</small>	<input type="text"/>
<b>morphine, do not round further, OK?</b> <small>* must provide value</small>	<input type="text"/>
<b>Tylenol with codeine--round by 5%, OK?</b> <small>* must provide value</small>	<input type="text"/>
<b>clarithromycin (biaxin), round by 5%, OK?</b> <small>* must provide value</small>	<input type="text"/>
<b>diphenhydramine, round by 5%, OK</b> <small>* must provide value</small>	<input type="text"/>
<b>griseofulvin, round by 10%, OK</b> <small>* must provide value</small>	<input type="text"/>
<b>penicillin, round by 15%, OK?</b> <small>* must provide value</small>	<input type="text"/>
<b>guaifenesin/ dextromethorphan, round by 15%, OK?</b> <small>* must provide value</small>	<input type="text"/>

## Aim 1 - Results

### Rounding Framework Development

Table 1 describes the experience and the roles played by each member of the advisory group. Some members participated in interviews or rounding knowledge validation, or both, as designated below.

**Table 1 Expert Working Group Specialties and Activities**

Pediatric Specialty	Total Participants	Median years in specialty	Interviewed	Validated Knowledge (Delphi Process)
Generalist	7	25	4	6
Hospitalist	2	13	2	1
Cardiologist	1	24	1	1
Nephrologist	1	22	1	0

Pharmacist (PharmD)	5	22	3	3
Hematology	1	8	1	0
Neurologist*	2	15	0	2

\*involved in second and third rounds of consensus.

Based on these interviews, we discovered that domain experts approach medication dosing and rounding by balancing the goals of therapy with the potential for side effects related to dosing. Three philosophical approaches emerged. We also created an additional category for medications with insufficient data available to assess the risk of automated rounding.

### Dose-dependent Intended Effects

The first approach was relevant when the intended effect was itself dose-dependent. The iconic active ingredient for this approach was furosemide, which produces diuresis in rough proportion to the amount of the medication given per dose. In this case, domain experts typically start low and titrate the drug upward, typically in small (10%) increments. Medications in this group may be automatically rounded up or down in increments smaller than 10% to reach a more easily administered dose with the same intended effect.

### Dose-dependent Unintended Effects

The second approach had as a goal avoiding unintentional side effects. This approach is typically used for medications such as antibiotics or systemic steroids, where dose-dependent side effects may be avoided by lowering the dose. For most medications in this group, dosing tends to begin at the highest well-tolerated dosage for the indication, and then rounded down to an easily administered dose, bearing in mind the maximum dosing recommendation guidelines.

### Narrow Therapeutic Range

The third approach recognized the potential for drugs to have a narrow therapeutic index and a high risk for toxicity. Drugs such as digoxin and insulin are in this category, and typically are not rounded, or are rounded to the nearest 100<sup>th</sup> of a milliliter from the originally calculated dose in neonates, or 10<sup>ths</sup> of a milliliter in larger infants. Pharmacies are able to provide devices specifically designed to measure and administer these small doses.

### Insufficient Data Available

We included a fourth category for medications, such as mesalamine, where insufficient data exist about the proper dosing model for children, and toxicity is likely with even a slight overdose based on adult data. In these cases, no rounding is typically performed. For many of these medications, there is no manufactured liquid formulation, further complicating the automated process by requiring the pharmacist to construct a compounded form of the medication. Because the final formulation may not be known, it is not possible to create an easy to administer dose during the e-prescribing process.

Based on conversations with domain experts, we assigned tolerable rounding ranges to each category above. These data are summarized in Table 2, below.

Table 2 Summary of Rounding Tolerance Categories

Category	Unintended Side Effects Dependent Upon Dose	Impact of Effect Dependent Upon Dose	Narrow Therapeutic Index	Rounding Tolerance
Avoiding Unintentional Side Effects	Yes	No	No	10-15%
Controlling Intended Effects	No	Yes	No	5-10%
Avoiding Toxicity	No	No	Yes	1-5%
Insufficient Data	n/a	n/a	Usually	0-1%

Table 3 summarizes the medications, rounding categories, and rounding percentages for each of the 120 medications in our database along with degree of agreement among all members of the advisory group. Medications such as amitriptyline and digoxin were sufficiently toxic that our team recommended 0% rounding. For medications in this group, dosing should be rounded to the most readily administrable dose, or changed to a formulation that is more precisely administered. In most cases, these drugs can be safely rounded to the nearest 10<sup>th</sup> of a milliliter, or, in neonates down to as precise as increments of 0.02mL.

In most cases, expert review resulted in a widening, rather than a narrowing of the rounding tolerance. For example, despite the risk of dose-dependent tardive dyskinesia associated with using metoclopramide, in practice, this drug is often rounded more aggressively. Therefore the rounding percent was increased from 5% as initially proposed to 10%. We achieved unanimous agreement for 39% of the proposed medication rounding tolerances in the first round of voting. There were medications that the group agreed were rarely used in practice and were therefore out of scope for this initial project. These drugs included anti-retroviral medications (ritonavir, oseltamivir, lamivudine) and some rarely used neurologic medications. After discussion at a face-to-face meeting, two subsequent rounds resulted in all but 7 medication rounding percentages being acceptable to the group. This final group of medications, typically started by pediatric neurologists, required extensive discussion between the expert group and two guest neurologists before consensus was reached.

Table 3 Summary of Medication Rounding Tolerances. Category refers to the general dosing philosophy used by practitioners for this medication. Consensus Round refers to the number of times this medication was discussed before consensus was achieved. KEY: UI = unintended effect, EI = excess intended effect.

Medication (rounding tolerance)	Category	Consensus Round	Medication (rounding tolerance)	Category	Consensus Round
Amitriptyline (0%)	UI	2	Ketoconazole (10%)	UI	1
Acetaminophen (10%)	Toxicity	1	Lamotrigine (10%)	UI	1
Amlodipine (10%)	UI	1	Levetiracetam (2%)	Toxicity	2
Amoxicillin/Clavulanic Acid (15%)	UI	1	Levofloxacin (1%)	UI	2
Amoxicillin (15%)	UI	1	Levothyroxine (0%)	Toxicity	2
N-acetyl-para-aminophenol (APAP)/Codeine (5%)	UI	3	Lithium(0%)	Toxicity	3
Aspirin (10%)	UI	1	Lorazepam (2%)	Toxicity	3
Atenolol (5%)	EI	2	Mercaptopurine(0%)	Toxicity	2
				Insufficient	
Methotrexate (0%)	Toxicity	1	Mesalamine(0%)	evidence	4
Azathioprine (5%)	UI	2	Methadone(0%)	Toxicity	2
Azithromycin (15%)	UI	2	Methimazole (5%)	UI	1
			Methylprednisolone (10%)	UI	1
Budesonide (10%)	UI	1	Metoclopramide (10%)	UI	1
Carbamazepine (2%)	UI	4	Metronidazole (5%)	UI	2
Cefdinir (10%)	UI	1	Minocycline (10%)	UI	1
Cefixime (10%)	UI	1	Morphine (0%)	Toxicity	2
Cefuroxime (10%)	UI	1	Moxifloxacin (1%)	UI	2
Cephalexin (15%)	UI	1	Mycophenolate (5%)	UI	1
Chlorothiazide (10%)	EI	1	Naproxen(10%)	UI	1
Cimetidine (10%)	UI	1		Insufficient	
			Nortriptyline (0%)	evidence	2
Ciprofloxacin(1%)	UI	2	Omeprazole (10%)	UI	2
Clarithromycin (10%)	UI	2	Ondansetron (10%)	UI	2
Clindamycin (10%)	UI	2	Oxcarbazepine (5%)	UI	4
Clonazepam(0%)	Toxicity	4	Oxycodone(5%)	UI	2
Clonidine(0%)	Toxicity	2	Oxycodone/ N-acetyl- para- aminophenol(APAP) (5%)	UI	2
			Pancreatin (15%)	UI	3
Cyproheptadine (5%)	UI	3	Pancrelipase (15%)	UI	3
Dexamethasone (5%)	UI	2	Polyethylene glycol (15%)	UI	3
Dextroamphetamine (10%)	UI	1	Penicillin V (15%)	UI	2
			Permethrin (15%)	UI	3
Diazepam(2%)	Toxicity	4	Phenobarbital (2%)	Toxicity	4
Digoxin(0%)	Toxicity	2	Pimozide (15%)	UI	4
Diphenhydramine (10%)	EI	3	Prednisolone (10%)	UI	1
Docusate Sodium(10%)	UI	2	Prednisone(10%)	UI	1
Doxycycline(10%)	UI	2	Pregabalin (2%)	UI	3
Enalapril Maleate (10%)	UI	1	Propranolol (5%)	EI	2
Erythromycin(10%)	UI	2			
Ethosuximide (2%)	Toxicity	3			
Famotidine (15%)	UI	1			

Felbamate (0% )	UI	3	Pyridoxine (15%)	UI	1
Fluconazole (10%)	UI	1	Ranitidine (15%)	UI	1
Fluoxetine (5%)	UI	3	Risperidone (5%)	Toxicity	3
Folic Acid (10%)	UI	1	Rizatriptan (5%)	Toxicity	3
Furosemide (5%)	EI	2	Sertraline (15%)	UI	3
Gabapentin (10%)	UI	1	Spironolactone (10%)	EI	1
Glycopyrrolate (5%)	UI	3	Sucralfate (15%)	UI	1
Griseofulvin (10%)	UI	2	Sumatriptan (5%)	Toxicity	1
Guaifenesin (15%)	UI	1	Tizanidine (5%)	Toxicity	3
Hydrocodone/ N-acetyl-para-aminophenol (APAP)(5%)	UI	3	Topiramate (2% )	EI	4
Hydroxychloroquine(0% )	Toxicity	2	Trazadone (15%)	EI	4
			Trimethoprim/ sulfamethoxazole (10%)	UI	2
Hydroxyzine (10%)	UI	1	Valproic Acid (2%)	Toxicity	4
Ibuprofen(15%)	UI	1	Warfarin (0% )	Toxicity	1
Iron Supplements(10%)	UI	3	Zolmitriptan (15%)	EI	1
			Zonisamide (2%)	UI	4

## Aim 2

The overall goal for this aim was to construct tools that could generate an appropriately weight-based and rounded medication dose, using the knowledge completed during Aim 1.

### This aim required three components: rounding algorithm development, web service design, and web service validation. Rounding Algorithm and Web Service Development

The algorithm to determine an appropriate dose was developed after two meetings with the STEPSTools Working and Advisory Group (SWAG) and with a sample of commercial vendors helping to craft the ideal approach to send and receive pediatric-specific knowledge. During these meetings, in which we discussed sending knowledge about extemporaneous formulations and rounded doses, the group made several key observations:

1. Rounding knowledge should be a “just in time” delivery model, and ideally should not only provide the rounding percentage, but should provide a recommended dose given the child’s weight and reason for therapy.
2. Less ideal, though in scope for this study, the rounding web service should accept from the vendor system the child’s weight in kilograms, proposed daily medication frequency, and mg/kg/day dosing strategy to be used. STEPSTools should then return XML corresponding to the calculated doses, rounded doses, recommended dose, reasons for recommending the dose, and any other text explaining the work done within the STEPSTools system.

Given the scope of this project, we elected to implement based on observation 2. The SWAG had additional recommendations that emerged during our discussions:

1. If the age of the patient is less than 7 years, and the dose is in liquid or suppository form, boost the score.

2. If the form is liquid and the dose is a whole milliliter amount, boost the score.
3. If the form is liquid, and the dose is greater than 1 milliliter but less than 10 milliliters, boost the score.

The final algorithm was designed to use the following inputs:

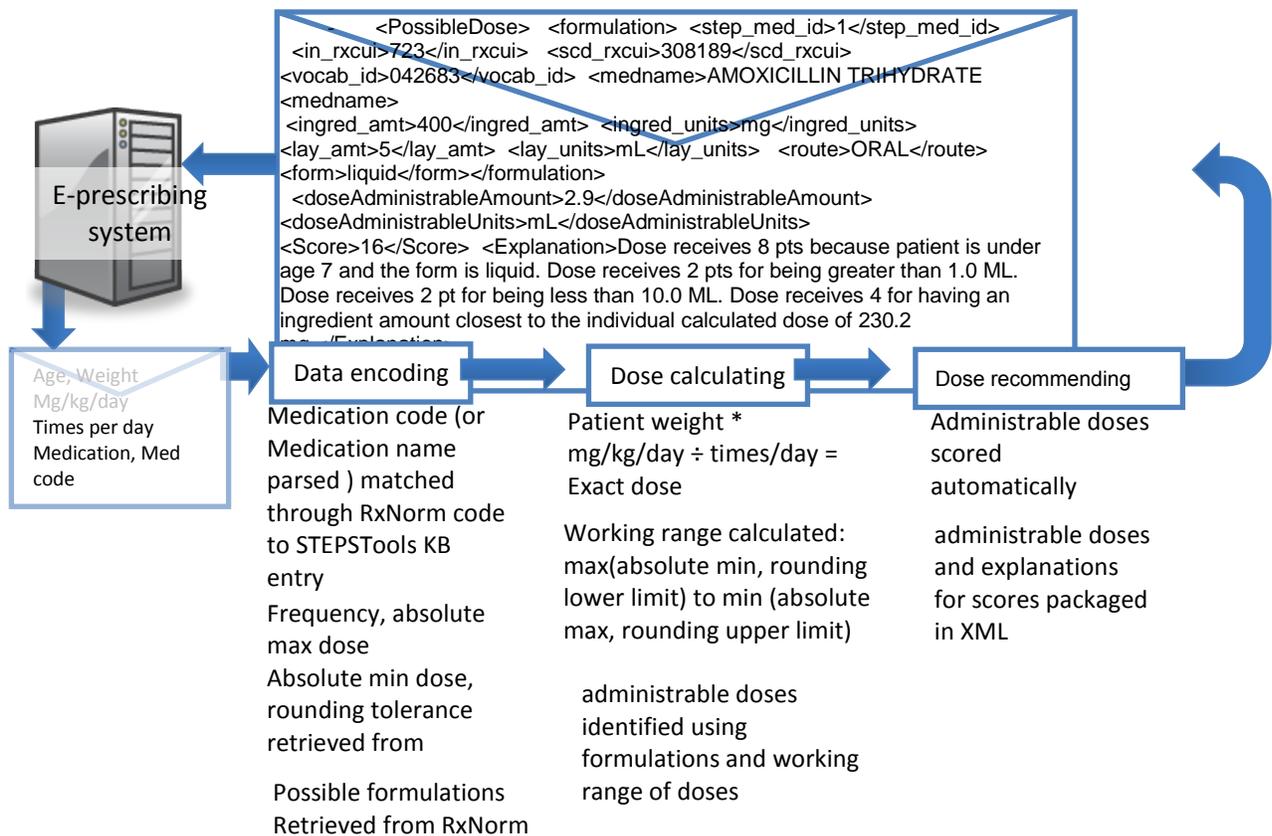
Patient weight (kg)	Patient age (months)	Medication name ( )
Encoding scheme (e.g. NDDF)	Mg/kg/day (or dose)	Number of doses per day

The figure below is a sample HTTP Get message used to send data to the web service.

```
GET http://dev.pedstep.org/Rounding/GetRoundedDosesForMedByFrequency.aspx?_
authToken=0c849415-5f3d-4005-af0e-fa631b893804&
weightInKg=10.23&_
ageInMonths=15&_
dosingFormula=40%20mg/kg/day&_
vocab=NDDF&_
vocabId=003675&_
medicationString=Amoxicillin HTTP/1.1
Host: www.pedstep.org
```

Figure 1 Example HTTP Get message for STEPSTools Rounding recommendation

The algorithm as developed followed the basic steps below.



XML-encoded data about the patient, but including no patient identifiers, are sent to the STEPSTools server. These data are encoded using a combination of RxNorm data and data created during Aim 1. In

addition, we have extracted key dosing information from the Harriet Lane Handbook. These data are used to ensure that calculated doses do not exceed recommended minimum and maximum doses. The algorithm we created relies on a list of available formulations, which is combined with a calculated working range for allowable doses, and heuristics about commonly available dosing tools to deduce administrable doses. These doses are scored using the heuristics identified by the SWAG. We then create a large XML-encoded file containing all recommended doses, scores, and reasons for these scores, and send this back to the calling e-prescribing system.

### Extemporaneous Formulation Web Service Development

The approach for distributing extemporaneous formulations underwent significant evolution through SWAG meetings. During these meetings the group observed that extemporaneous formulation knowledge changes infrequently and may not be worth the performance compromises required to use ad hoc requests for updated knowledge in this domain. Rather, it was considered better to use a method whereby a commercial vendor could request the knowledgebase and receive it, inspect its contents, and then update the local copy of this knowledge.

Our architecture for extemporaneous formulations uses a schema derived from the RxNorm schema and semantic relationships among items. For example, because our research uncovered a recipe for Acetazolamide based on the crushing of a 250 mg tablet, to link this new formulation into RxNorm, we reuse the ingredient term Acetazolamide, but create a new entry called Acetazolamide Oral Suspension Compounded, with a new compounded formulation called Acetazolamide 25 mg/ ml. A similar method is used to integrate admixtures (compounds comprised of multiple ingredients) into RxNorm. This tie is critical to allow e-prescribing systems to link each ingredient to a term that is recognized by their medication knowledgebase, which allows the compounds to trigger drug interaction or other warnings.

We took these data and created a database schema that could be used by two e-prescribing vendors. One challenge in this process was that RxNorm, while able to provide a link from one medication knowledgebase to another, does not provide to the public sufficient information to map at an arbitrary level of granularity. For example, RxNorm has a combination of GCNSeqNo's (dispensable level) and HICSeqNo's (ingredient level) for one database. However, the ideal form to represent the actual medication being compounded is the routable form. Therefore, to communicate with e-prescribing systems, we needed to provide them with a mapping from our routable form (Amoxicillin Oral) to their ingredient form (Amoxicillin trihydrate.) In some cases, the vendor then needed to map back to their local routable form for decision support to work. While this is a relatively small step, it was an unanticipated hurdle that RxNorm could not overcome for us.

### ***Aim 3 – Concordance Analysis***

To assess the validity of the rounding tolerances and the degree to which STEPSTools recommendations were in agreement with the prescribing practices of practitioners, we began by conducting a concordance analysis.

#### Setting

The analysis relied on prescribers from primary care, neurology and cardiology practices at two academic medical centers. These sites were chosen because of the frequency with which medications prescribed by these specialists were found in STEPSTools.

### Study Design

The study used a 6-month sample of electronically-generated prescriptions from one academic center. For each prescription, we saved data that would serve as input parameters (weight, age in months, medication, medication code, coding scheme, frequency, and mg/kg/day dosing) and data that would serve as the output validation (formulation, dose, frequency.) Prescriptions were excluded if they were not in the STEPSTools knowledge base, or if the mg/kg/day rationale for the medication was unable to be located among the data we received. The final set of prescriptions were divided randomly into two groups. We used 60% of the sample chosen at random as the training set, and the remaining 40% as the test set. The training set was used to improve the capabilities of the rounding algorithm and to identify any performance issues in the web services. For example, initially, the rounding algorithm would select as an optimal dose an arbitrarily high number of tablets, if that dosing instruction would generate a precise, though unadministerable dose. We used the training set to improve these issues. Once all issues were resolved, we entered all test cases into our testing suite. Any test cases that were not in agreement with the sample prescription were flagged as discrepant. Discrepant cases were then stratified by medication name, so that there was one case on the survey for each medication name, ensuring that the survey would include the minimum number of questions to address the discrepancy. The draft survey underwent face validity and pilot testing by three physicians prior to its distribution. An example question from the survey is shown below.

A child who is 5 years old and weighs 15.5 kg will be receiving 103.2mg/kg/day of Amoxicillin (or Amoxil) 2 times a day (799.8mg/dose). What dose would you recommend?

- 10 ml of 400 mg/5 ml per dose
- 15 ml of 250 mg/5 ml per dose
- None of the above
- I do not prescribe this medication

What is your preferred recommendation?

\_\_\_\_\_  
 (Please provide your preferred dose and/or dosage form)

Reason for preferred recommendation:

- Better dose amount for age
  - Better dose amount for weight
  - Better dosage form for age
  - Better dosage form for weight
  - Other
- (Please choose your best reason)

Please briefly describe your reason:

\_\_\_\_\_

How confident are you about your recommendation?

not at all confident completely confident



(Place a mark on the scale above)

**Amoxicillin Trihydrate/Potassium Clavulanate for a 23.65 kg, 63-month-old child.**

- Oral liquid, 90 mg/kg/day (or 630 mg/day), BID, 3 days
- Oral liquid, 300 mg/day (or 400 mg/5 mL), BID, 3 days
- Either recommendation would be fine
- None of the above

## Reason(s):

- Better method of administering medication
- Better dose amount
- Better dosing schedule
- Better choice for age
- Better choice for weight
- Other: \_\_

How confident are you in your preferred choice?

1 (unsure) 2 3 4 5 (extremely confident)

**Data Analysis**

Exploratory analyses were conducted using R statistical software. Our unit of analysis was the survey question (corresponding to the medication)

**Results**

There were a total of 80 test cases compared. Of these, there was complete concordance between the recommended dose/formulation and the prescribed dose/formulation for 31, or 39% of the cases. There were 28 cases, representing 25 medications, where STEPSTools recommended a different formulation or dose than was in the test case. These cases became the entries in the survey.

Of note, for 20 cases, STEPSTools was unable to generate a rounded dose. The most common reason for this was medications for which a small dose was being recommended. For example, one case was for a 5.86 kg, 6 month old infant, to receive lorazepam at a recommended dose of 0.03 mg/kg/day. STEPSTools returned the following explanation,

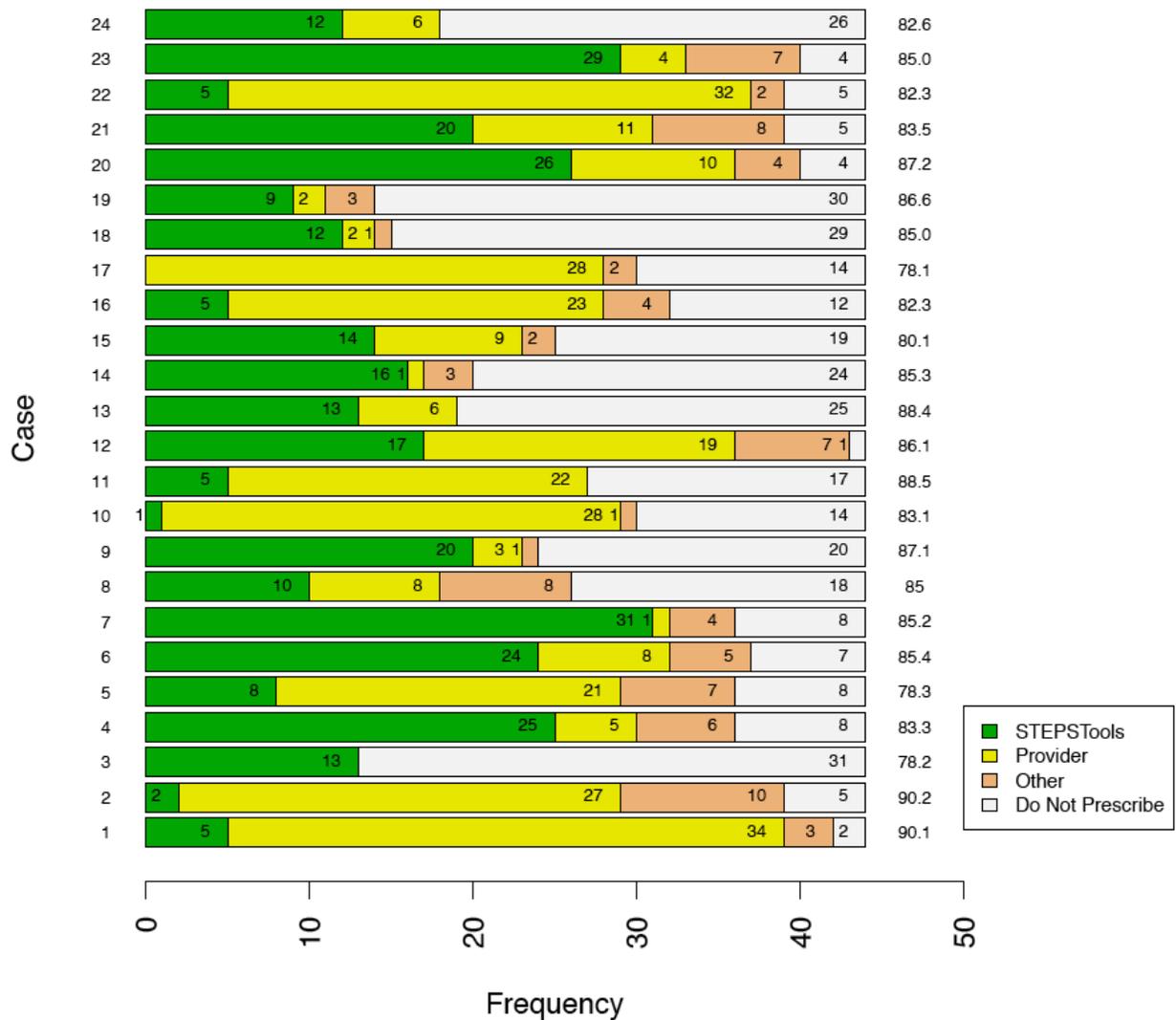
The rounding range low calculated by STEPSTools (0.19 mg) is below the absolute minimum dose (0.293 mg/dose) for Lorazepam, so the working range low was set to equal the minimum dose. The rounding range high calculated by STEPSTools (0.21 mg) is also below the absolute minimum dose. When this occurs, STEPSTools sets the working range high to a dose equal either to the absolute maximum or to the rounding range percentage above the absolute minimum, whichever is less. This yields a range consistent with STEPSTools relative dose rounding recommendations but within absolute dose range recommendations. In this case, the rounding range percentage above the absolute minimum is less, so STEPSTools has used the recommended rounding percentage for lorazepam of 0.05 to calculate a new working range from 0.293 mg to 0.30765 mg.

It then encounters a problem, because our data suggest that dosing should be in increments no smaller than tenths of a milliliter. Although lorazepam is available in a concentration of 2mg /1 ml (or 0.2 mg for each 0.1 ml) STEPSTools calculates a dose of 0.15 ml, which it cannot resolve into an administerable dose within this working range, and returns no value, along with this explanation, "<Explanation>STEPSTools was unable to round the dose, so there are no possible doses returned by the service.</Explanation>"

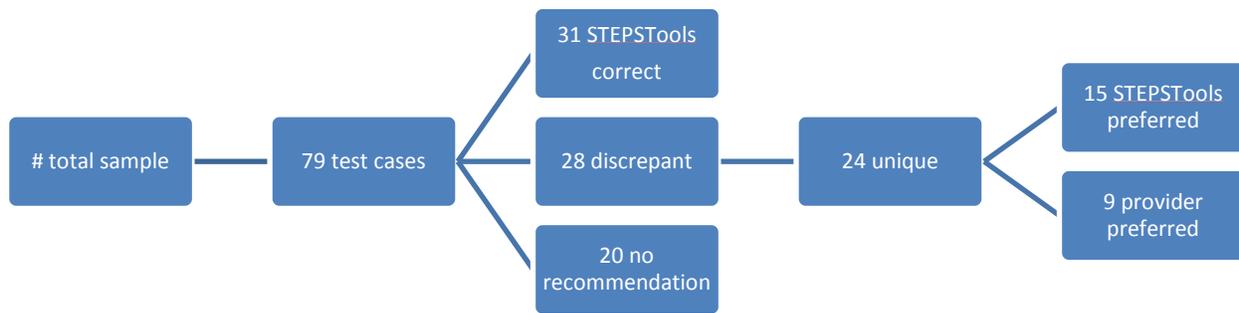
The 24-item survey was piloted with 10 subjects and then distributed to a total of 172 pediatricians. We received 44 complete responses after 6 reminders over the course of three months, for an overall response rate of 26%.

1. What if we exclude the questions for which STEPSTools had virtually NO selections?
2. Overall score given initial fitness results and discrepancies.

Overall, the answer proposed by STEPSTools was chosen significantly more often than either the provider-furnished answer or a respondent-provided alternative choice (44.7 %;  $p < 0.001$ ). However, there were medications where the STEPSTools recommendation was virtually never selected. The figure below summarizes these data for each question in the survey.



In the Figure above, each number to left of the stacked bar corresponds to a survey question on the survey. The number on the right corresponds to the average confidence level of the respondents (ranging from 0 (not at all confident) to 100 (completely confident)). STEPSTools recommendations were preferred for 15 of the 24 questions, with a > 80 score of confidence for all but one (question 3, azathioprine). When combined with the data from all test cases, STEPSTools either matched or exceeded the performance of the test cases in 46 (84%) of the cases where it was able to provide a recommendation. These overall results are summarized below.



In many cases where STEPSTools was not preferred over the test case, the STEPSTools algorithm performed correctly, and might have been chosen had we provided the explanation for the selected dose. For example, in case #10, STEPSTools did not recommend the dose amount of 80 mg that was provided by our test data set, because according to its algorithm, the minimum dose for age should have been 148 mg/dose.

Medication	Respondent Reason for Preferred Recommendation (Modes)
1 (Acetaminophen)	Better dose amount for weight; better dosage form for weight
2 (Amoxicillin)	Better dose amount for weight (5 thought 100 mg/kg/day dosing formula was too high)
5 (Azithromycin)	Better dosage form for age (wanted the liquid formulation for a 9 year old)
10 (Fluconazole)	Better dose amount for age; better dosage form for age
11 (Furosemide)	Better dosage form for weight ; better dose amount for weight
12 (Ibuprofen)	Better dosage form for age (did not prefer capsule for 9 year old)
16 (Naproxen)	Preferred twice daily dosing over once a day dosing.
17 (Ondansetron)	Better dose amount for weight
22 (Prednisolone)	Better dosage form for age

### Implications and Next Steps

Based on this analysis, we believe that this initial version of STEPSTools is performing at a sufficiently high level that its recommendations provide value to pediatric prescribers. The conservative nature of the STEPSTools algorithm ensures a level of safety at this early juncture. Next steps will need to include additional work on the algorithm to handle very small doses, to include compound formulations in the list of formulations that STEPSTools applies to the algorithm, and to appropriately dose medications with more than one active ingredient. Once these steps are completed, we will continue to add medications to the STEPSTools rounding knowledgebase.

## Web Services Utilization

We conducted an interview before STEPSTools' implementation (environmental scan) and an interview after implementation (summative evaluation) with each of our 11 subjects (1 subject did not complete the summative evaluation interview). (See *Table 1*.) Our sample of prescribers and prescribing agents consisted of physicians and nurses representing general pediatrics and 3 different pediatric specialties who regularly use the e-prescribing system, RxStar, to generate prescriptions. We conducted 12+ hours of observation during regular clinic hours and also asked interviewees to demonstrate their use of the e-prescribing system when prescribing some of the drugs in the STEPSTools knowledgebase for a test patient. We interviewed two pediatric outpatient pharmacists to collect impressions of STEPSTools' impact on the dispensing of prescriptions and also interviewed two e-prescribing vendor representatives to gather impressions about the implementation of STEPSTools into RxStar.

*Table 1.* Interview subjects and their prescribing activity.

ID	Professional Role	Estimated number of Rxs per month <sup>◆</sup>
ANPr1	Neurology Attending Physician	12
ANPr2	Neurology Attending Physician	50 <sup>◆</sup>
ANPr3	Neurology Chief Resident	80
ACNu1	Cardiology Nurse, Case Manager	100
ACNu2	Cardiology Nurse Practitioner*	
AGPr1	General Pediatrics Attending Physician	250 <sup>◆</sup>
AGPr2	General Pediatrics Attending Physician	125 <sup>◆</sup>
APh1	Outpatient Pharmacist	3000
APh2	Outpatient Pharmacist	3240
AV1	e-Prescribing System Software Developer	N/A
AV2	e-Prescribing System Project Manager	N/A

<sup>◆</sup>Based on self-report in summative evaluation interview.

<sup>◆</sup>Includes prescriptions that providers generate directly and oversee (e.g., residents prescribe).

\*This subject only participated in the environmental scan interview.

We used a grounded theory approach to analyze our qualitative data. Relationships in our data were determined via axial coding.

## Preliminary Results

Users' perceptions of the practice of rounding and compounding remained fairly consistent between feedback collected in the environmental scan and the summative evaluation. All users were not aware of explicit changes in the e-prescribing system as a result of the implementation of STEPSTools. The e-prescribing vendor representatives corroborated this by noting that the implementation strategy was designed so that STEPSTools would be fully integrated into the prescriber's existing workflow. AV1 commented that, "all the people who do not know about STEPSTools' existence may not even notice [the change]." AV2 added that STEPSTools "is well-integrated into the RxStar workflow, so it's not necessarily an extra step that the users have to take."

### *Impressions of rounding*

The following themes emerged from our data about STEPSTools' rounding web service:

- **Users see potential for a tool to assist with rounding.**
  - "you are always going to have the potential to mess up and do the math incorrectly and to round wrong. I think there is always that potential. I honestly think Rx Star has helped us because it makes us at least think through it. It does the math for us too, so, but as long as you have your brain on and don't just accept everything it says, then I think you are probably okay." (AGPr1, Environ)
- **Users would like more flexibility in recommendations, e.g., specific medication schedules, high-dose Amoxicillin.**
  - (See Table 2, Cases1,6, & 8)

### *Impressions of compounding*

Each of the themes that emerged from our data about STEPSTools compounding component is supported below by quotes from the environmental scan (Environ) and summative evaluation (Summ).

- **Certain subspecialties prescribe compounded medications more frequently than others; these prescribers found the added compounded medications in the list to be useful.**
  - "since we had talked originally, a lot of those compounded ones have come in and are now on there, so I don't have to free-text as much as I did before." (ACNu1, Summ)
  - "According to a lot of the physicians, they say they can't find a compound so they end up free-texting it or they type it for the tablets and tell us to make it for the liquid...[but now] I have noticed that it seems to be more that they're selecting the actual compounded product, like they're finding it now...and the correct concentration." (Aph2, Summ)

*Table 2.* Examples of observed cases of new prescriptions generated for medications in the STEPSTools knowledgebase and the prescriber's resulting actions.

Case	Pediatric Specialty	Medication	Prescriber's actions
1	General	Amoxicillin 400mg/5mL oral	Edits dose amount
2	General	Azithromycin	Adds 2 <sup>nd</sup> dose

3	General	Amoxicillin 400mg/5mL oral	No changes
4	General	Azithromycin 200mg/5mL	Adds 2 <sup>nd</sup> dose
5	General	Orapred 15mg/5mL oral	Changes dose amount and frequency
6	General	Amoxicillin 400mg/5mL oral	Changes dose amount
7	General	Cefdinir	Changes frequency of BID to daily
8	General	Amoxicillin 400mg/5mL oral	Enters all values manually
9	General	Ibuprofen 100mg/5mL oral	Changes dose amount
10	General	Cefdinir 125mg/5mL oral	Changes frequency of BID to daily
11	Cardiology	Furosemide 10mg/mL oral	Enters all values manually
12	Neurology	Celontin 300mg cap	No changes

---

### ***Impressions of implementation process***

Feedback from the e-prescribing system software developer suggested that the implementation of STEPSTools was average in level of difficulty and mostly followed “regular procedure.” They did not identify any challenges that would be barriers to software developers familiar with web services architectures.

## **Conclusions**

We have been able to create two knowledge sources using AHRQ funding and with active participation from an expert panel of pediatricians and pharmacists. Using these knowledge sources, in addition to a heuristic-based algorithm to round calculated doses, we were able to create a web service infrastructure and to demonstrate the capability of these services to deliver recommendations in real time to a software system in use by a pediatric community.

## **List of Publications**

1. Helmke, JS, **Johnson, KB**, Weinberg ST, Davison C, Palmer M. Development of a Knowledge Base for Pediatric Medication Dose e-Rounding. Accepted for platform presentation, AAP National Conference and Exhibition, 2010.
2. **Johnson KB**, Lee CKK, Spooner SA, Davison CL, Helmke JS, Weinberg ST. Automated Dose Rounding Recommendations for Pediatric Medications. *Pediatrics*, in press, 2011.
3. **Johnson KB**, Lehmann CU, Kashefipour, I. Electronic Prescribing in Pediatrics: Towards Safer and More Effective Medication Management. *Pediatrics*, in press, 2011.
4. **Johnson KB**, Ho YX, Weinberg ST, Palmer M, Davison C. Development and Evaluation of Web Service for Pediatric Dose Rounding. Manuscript in preparation, 2011.