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Standardizing ED-based migraine clinical research: a data-driven analysis of commonly-used trial outcome measures

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Abstract

Introduction—Although many high quality migraine clinical trials have been performed in the emergency department (ED) setting, almost as many different primary outcome measures have been used, making data aggregation and meta-analysis difficult. We assessed commonly used migraine trial outcomes in two ways. First, we examined the association of each commonly used outcome versus the following patient-centered variable: the research subject's wish, when asked 24 hours after investigational medication administration, to receive the same medication the next time they presented to an ED with migraine ("would take again"). We chose this variable as the criterion standard because it provides a simple, dichotomous, clinically sensible outcome, which allows migraineurs to factor important intangibles of efficacy and adverse effects of treatment into an overall assessment of care. The second part of our analysis assessed how sensitive to true efficacy each outcome measure was by calculating sample size requirements based on results observed in previously conducted clinical trials.

Methods—Secondary analysis of data previously collected in four ED-based migraine randomized trials performed between 2003 and 2007. In each of these trials, subjects were asked 24 hours after administration of an investigational medication whether or not they would want to receive the same medication the next time they came to the ED with a migraine. Odds ratios (ORs) with 95%CI, adjusted for gender and medication received, were calculated as measures of association between the most commonly used outcome measures and "would take again". The sensitivity of each outcome measure to treatment efficacy was determined by calculating the sample size that would be required to detect a statistically significant result using estimates of that outcome obtained in two clinical trials.

Results—Data from 378 subjects were used for this analysis. Adjusted ORs for association of "would take again" and other commonly used primary headache outcomes are as follows: achieving a pain-free state by two hours, OR = 3.1 (95% CI 1.8, 5.4); sustained pain-free status, OR=4.5 (95% CI 1.9, 11.0); no need for rescue medication, OR = 3.7 (95% CI 2.1, 6.6). An improvement on a standardized 11-point pain scale of ≥33% had an adjusted OR = 5.2 (95% CI, 2.2, 12.4). The best performing alternate outcome, ≥33% improvement, correctly classified 288 subjects and

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misclassified 77 subjects when compared to "would take again". ≥33% improvement and pain free by two hours required the smallest sample sizes, while sustained pain free and "would take again" required many more subjects.

Conclusions—"Would take again' was associated with all migraine outcome measures we examined. No individual outcome was more closely associated with "would take again" than any other. Even the best performing alternate outcome misclassified more than twenty percent of subjects. However, sample sizes based on "would take again" tended to be larger than other outcome measures. On the basis of these findings and this outcome measure's inherent patient-centered focus, we propose "would take again" be included as a secondary outcome in all ED migraine trials.

Introduction

Many high quality migraine clinical trials have been performed in the ED setting [1-19], yet a standardized ED-based migraine clinical trial outcome does not exist. Studies performed to date utilize different primary outcomes and inconsistently report various secondary outcomes. The International Headache Society's Clinical Trials Subcommittee has developed a methodology for outpatient clinical trials[20], but its relevance to ED patients is unknown. When choosing a primary outcome for ED-based migraine clinical trials, multiple options exist: headache intensity levels, change in pain scores, functional disability outcomes, and need for rescue medications have all been used. In addition, adverse medication reactions, nausea, and pain status after ED discharge are important considerations. In outpatient surveys, migraine patients have endorsed the importance of complete relief of pain, no recurrence of headache and rapidity of onset of relief[21].

As with all clinical research, it is important to choose outcomes for migraine trials that are patient-centered. It is not clear, for example, if headache patients prioritize a 50% change in visual analog score, no requirement of rescue medication, or a validated minimum clinically significant difference. The International Headache Society has endorsed the importance of an assessment of patient preference [20].

In this manuscript, we analyze summary data we previously collected in four ED-based migraine clinical trials to determine the degree to which commonly used outcomes in migraine trials are associated with a proposed criterion standard endpoint, i.e., the patient's desire to receive the same medication the next time they present to an ED with an acute migraine ("would take again"). We then use data from two of these clinical trials to estimate how sensitive each of these outcome measures is to true differences in efficacy, thus determining the efficiency of the outcome measure.

Methods

Overview

This is a secondary analysis of data we previously collected in four randomized migraine clinical trials performed between 2003 and 2007[8-10,19] (Table 1). In each of these trials, subjects were asked 24 hours after medication administration whether or not they would want to receive the same medication the next time they came to the ED with a migraine. The goal of this analysis is first, to determine the strength of association between commonly-used migraine outcome measures and "would take again". "Would take again" was chosen as a proposed criterion standard because it allows patients to weigh for themselves the relative efficacy and tolerability of the investigational medication. Also, allowing 24 hours to elapse after medication administration allows the patient sufficient time to reflect upon and assess their experience. The second goal of the analysis is to determine how sensitive to true differences in efficacy each outcome measure was by calculating sample size requirements

based on observed estimates of each outcome measure. This study was reviewed administratively by the Montefiore Medical Center IRB and determined to be exempt from full committee review.

Patient population

These four studies were conducted in four different EDs in New York City. Patients were included in the studies if they met criteria for acute migraine or acute probable migraine, as defined by the International Classification of Headache Disorders, 2nd edition[22]. Patient assessments were performed one hour, two hours, and 24 hours after medication administration.

Criterion standard

The proposed criterion standard for this analysis is the subject's response to the question, "Do you want to receive the same medication the next time you come to the ER with a migraine?"

Outcome measures (predictor variables)

Descriptions of headache intensity and functional limitations were assessed at baseline and then one, two, and 24 hours after medication administration. Headache intensity was assessed on a four point ordinal scale. Headaches could be described as severe, moderate, mild, or none. Functional disability was characterized as: 1) I've been doing my normal daily activities;2) I've had a little bit of difficulty doing what I usually do; 3) I've had a great deal of difficulty doing what I usually do and can only do very minor activities; or 4) I've been unable to get out of bed. The following dichotomous variables were computed based on the outcome measures just described.

-Pain-free: a headache of any intensity becoming "no pain".

-Headache relief: a headache of moderate or severe intensity becoming "mild" or "no pain"

-No functional disability: Able to perform all usual activities without limitations

No need for rescue medication was defined as no administration of any additional analgesic medication or migraine specific medication at any time in the ED after administration of the investigational medication

The following sustained outcomes are recommended for use in migraine clinical trials by the International Headache Society's Clinical Trials Subcommittee. These too are based on the four point scales described above. The sustained outcomes encompass initial relief and recurrence. To achieve a sustained outcome, a patient must experience relief from the acute headache and the headache cannot recur.

-Sustained pain-free: Achieving a pain-free state within two hours of medication administration and maintaining it for 24 hours

-Sustained headache-relief: Achieving a headache level of "mild" or "none" within two hours of medication administration and maintaining it for 24 hours

-Sustained disability free: Achieving a normal functional status within two hours of medication administration and maintaining it for 24 hours.

Finally, using a validated and reproducible eleven point verbal pain intensity scale, on which ten represented the worst imaginable pain and zero represented no pain, the percent change in pain intensity was calculated by dividing the difference in pain intensity (calculated as the two hour pain intensity score subtracted from the baseline score) by the baseline score: percent change= (baseline pain intensity-two hour pain intensity)/ baseline pain intensity. We chose

cut-points of ≥33% improvement, ≥50% improvement, ≥66% improvement, and ≥90% improvement as relevant cut-points to examine.

Primary analysis

Frequencies are presented with 95%CI. Associations between each of the dichotomous outcome measures were calculated using the phi coefficient and presented in a matrix. Adjusted ORs with 95%CI were calculated for each outcome measure by entering gender and medication received into a logistic model, along with the individual outcome measure and the criterion standard. Multivariate logistic regression could not be used to identify the best outcome measure because of substantial collinearity among the various measures of headache improvement.

In order to determine efficiency of the individual outcome measures, we determined the sample size that would be required to detect a statistically significant result if that individual outcome measure were the primary outcome of the RCTs included in this analysis. In two of the four trials, one of the investigational medications consistently beat the other across all outcome measures. In the other two trials included in this analysis, neither of the investigational medications was consistently better. To determine efficiency of the outcome measures, we performed the following analysis on data collected from the two trials in which one agent was consistently superior: we performed sample size calculations based on the observed point estimates for each outcome measure for each trial. Sample size calculations were performed using α=0.05, β=0.20, and two tails. Sample size calculations were performed with Power and Precision 2.1 (Biostat, Englewood, New Jersey). All other statistical analyses were performed using SPSS 13.0 (SPSS Inc.,Chicago, Illinois).

Power calculation

The sample size is fixed based on data gathered in previous studies. 378 subjects allow a power of 90% to discover a statistically significant odds ratio, assuming 1:1 distribution between groups (those that attained the outcome of interest versus those that did not attain the outcome of interest), alpha=0.05, and “would take again” rates of 80% in those that attained the outcome of interest versus 65% in those that did not. We assumed that 80% of subjects who attained the outcome of interest would want to receive the same medication again if the outcome measure were a useful one; similarly we assumed that not more than 65% of subjects who did not attain the outcome measure would want to receive the medication again if the outcome measure were useful.

Results

Data from 378 subjects, enrolled in four migraine clinical trials were used for this analysis. Overall, there was a high level of approval of the various investigational medications as measured by our proposed criterion standard: 79% (95%CI: 75, 83%) of subjects wished to receive the same medication again.

An association matrix based on the phi coefficient is presented in Table 2. All commonly used outcomes are associated with all others. Of all outcomes analyzed, “would take again” is the most independent in that it has only modest associations ($0.1<\varphi<0.3$) with all other variables.

Association of individual outcome measures with “would take again” are presented in Table 3. Two hour outcome measures tended to have stronger associations than their one hour counterparts, but these ORs were not statistically significantly different (confidence intervals overlap substantially). For each of the “sustained” outcomes, patients achieved some level of headache improvement within two hours of medication administration, such as headache relief,

pain-free status, or normal functioning, and maintained this outcome for 24 hours. In general, the sustained outcomes were more closely associated with the criterion standard than the one and two hour outcomes, although the ORs were not statistically significantly different (confidence intervals overlap substantially). Of 75 patients who required rescue medication, only 59% (95%CI: 48, 69%) would want the same investigational medication the next time, versus 84% (95%CI: 79, 88%) of the 294 who did not.

Sensitivity and specificity of ≥33% improvement and ≥50% improvement are presented in Tables 4a and 4b. ≥33% improvement, the best performing individual outcome correctly classified 288 of 365 subjects (79% [95%CI: 75, 83%]).

Table 5 depicts sample sizes calculated for each outcome measure in each of two clinical trials. In general, short term outcome measures required fewer subjects than outcomes incorporating 24 hour follow-up.

Discussion

To the best of our knowledge this represents the first data-driven assessment of the association between commonly used outcome measures in ED migraine clinical trials. We selected "would take again" as the criterion standard outcome because it provided a simple, dichotomous clinically sensible, patient-centered endpoint, which allows migraineurs to factor important intangibles of efficacy and adverse effects of treatment into an overall assessment of care. Our findings can be used as a reference point for emergency medicine headache researchers.

The desire to receive the same medication at the next ED visit had only modest associations with more traditional pain outcomes. These data support our central hypothesis: measuring pain alone, functionality alone, and certainly other migraine symptoms or adverse effects alone, does not adequately summarize a patient's experience with the migraine medication. Relatively small improvements in pain intensity scores at two hours were no less closely associated with "would take again" than substantial improvements in pain intensity scores. Therefore, clinical variables other than improvement in pain are contributing to a migraineur's desire to receive the same medication again. Migraine clinical trials that focus exclusively on improvement in a pain intensity scale may not be measuring the most clinically relevant outcome.

Alternatively, it may be that asking patients whether they wish to receive the same medication again is of little value. Pain research is hampered by lack of objective measurements and is forced to rely on sensible and reproducible outcome measures. Attempts to link pain intensity measures to clinically relevant outcomes are limited by the validity of the chosen criterion standard.

Overall, measures which incorporated 24 hour pain assessments and functional assessments showed the highest correlation with the criterion standard. Recurrent or persistent migraine after ED discharge is common and difficult to predict. Up to 2/3rd of discharged ED headache patients experience headache the day after ED discharge [23,24]. Although obtaining 24 hour follow-up requires additional effort on the part of the investigator, failure to obtain this information seems likely to over-estimate the efficacy of the intervention because at two hours, many of the events which determine a patient's willingness to take a medication again may not have occurred yet.

Adverse events were relatively unimportant to patients. This is probably because minor or short-lived adverse events, such as dizziness, weakness, and drowsiness, dominate the adverse event reporting, which may have lessened the importance of adverse events as an outcome measure by the time the criterion standard was assessed 24 hours later. Patients may also be willing to tolerate some side effects in exchange for headache relief. Our anecdotal experience

is that some patients have very unpleasant reactions to certain investigational medications: for example, akathisia after one of the dopamine-antagonist anti-emetics, or chest pain, flushing and palpitations after subcutaneous sumatriptan. When queried, these patients ask to never receive the same medication again. However, these extreme events are relatively rare. Usually adverse events do not influence a patient's decision to receive the same medication again. Therefore, occurrence of adverse events is not useful as a primary outcome measure.

Surprisingly, rescue medication use did not help discriminate between those who did and did not want the same medication again. Perhaps this is because patients confused the efficacy of the rescue medication with the efficacy of the investigational medication. Need for rescue medication tended to have moderate correlation with one and two hour pain and functional outcomes and was less closely associated with post-ED outcomes. Rescue medication use may be quite relevant from an ED throughput perspective—more medication equals more nursing time—and is inherently appealing because it signifies failure of the investigational medication. However, it may not be sufficiently sensitive to patients who did not like the investigational medication and does not account for the post ED period.

There are several possible explanations for the homogeneity and relative modesty of adjusted ORs among all outcomes. The first is variability in patient expectation. Patients expecting complete and persistent relief after investigational medication administration would have been disappointed by anything less, whereas patients suffering unremitting headache despite multiple oral medications may have been happier with less relief. A second explanation is heterogeneity in how individual patients value the benefits and side effects of the medications. For some patients, relief of pain may be the most important feature, but for others it may be relief of nausea or photophobia. Some patients may be sensitive to side effects, and value a minimum of side effects over relief of headache. Rapidity of onset of headache relief and headache recurrence may also be of variable importance to different patients. Thus, there may not be one outcome that is ideal for every patient.

≥33% improvement had the strongest association with the criterion standard and required relatively small sample sizes to demonstrate statistical significant in the RCTs we analyzed. Part of its success has to do with its consistent positioning much closer to the margins than the center of the range of frequencies. It is easier to demonstrate significantly significant differences in rates if the rates are, for example, 98% and 88% than if they are 88% and 78%. Similarly, odds ratios based on sensitivities in the nineties will be greater than odds ratios based on more balanced distribution in a two by two table.

"Would take again" proved to be a conservative outcome in that it required larger sample sizes in the two trials we analyzed. This should be understood within the context in which it was analyzed: these were comparative clinical trials testing first-line migraine medications. The reasons for these relatively large sample sizes are likely related to the multiple domains in which this outcome operates—to outperform another medication on this endpoint a medication would have to be both more efficacious, better tolerated, and diminish the recurrence of headache after ED discharge. A strong argument can be made for choosing conservative outcomes in the context of acute pain research. However, this outcome may miss an important difference in efficacy. "Would take again" is not recommended as a primary endpoint in smaller clinical trials because it is not sensitive to treatment effects. It is none-the- less helpful because it provides a patient-centered summary of aggregate benefits over 24 hours.

When choosing a primary outcome for ED-based headache clinical trials, other factors to consider include logistical barriers to obtaining target endpoints. For example, we have found that patients at times request discharge as soon as they have experienced relief. Thus primary outcomes based solely on a two-hour assessment of relief, pain-free status, or normal

functionality may result in a high level of missing data. Finally, the majority of ED-based migraine research has been unfunded, investigator-initiated work. Thus, a premium is placed on smaller sample sizes that can be readily obtained without the vast resources of the pharmaceutical industry. “Would take again” may require a great deal of research subjects.

Limitations

Though driven by an a priori hypothesis generated prior to data analysis, this was a retrospective analysis of previously collected data. As with any study of clinical outcome measures, validation is essential. This is best left to a prospective study.

The calculated adjusted ORs were modest, reflecting variation in the responses of our patients. This is not unexpected in pain research, though does speak to the need for validation of these findings.

Because the criterion standard was ascertained 24 hours after medication administration, this may have inflated the importance of the post-ED course. On the other hand, because of the frequency of short-term recurrence of migraine, assessment at 24 hours provides some prophylaxis against overestimation of medication efficacy.

Most of the patients in this analysis received metoclopramide. It is not clear if the results would have been comparable if some patients had received placebo, or if more had received one of the other medications, such as prochlorperazine or sumatriptan. This too can be addressed in a prospective validation study.

Finally, this study is underpowered for the differences discovered. For example, to demonstrate a statistically significant difference between the point estimate of the OR for a 33% improvement, 5.2, and that of a 50% improvement, 3.1, would require 2000 subjects or six times as many as we included. The difficulty of assembling a cohort of migraineurs of this size in preparation for a randomized clinical trial speaks directly to the need for a uniform endpoint to facilitate meaningful aggregation and meta-analysis of reasonably homogeneous data from multiple trials. We chose not to compare the pain measures as repeated measures, as doing this would have widened the confidence intervals and resulted in the need for an even larger sample size to demonstrate statistically significant differences. Because our analysis did not report any statistically significant differences, this choice did not influence our conclusions. Measuring multiple pain outcomes and accounting for these in the sample size calculation and analysis is an issue for migraine clinical trials as well.

Conclusions

Although the optimal primary outcome for ED based migraine clinical trials is not yet known, a patient’s wish, when queried 24-hours post-medication administration, to receive the same medication for headache in the future, appears to be a conservative, patient-centered outcome measure, that allows a complete picture of the patient’s experience. In the interest of facilitating homogeneity of meta-analyses and other forms of data aggregation and subject to validation of our findings in prospective studies, we propose this outcome measure be included as a secondary outcome in all ED-based migraine trials.

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Table 1

Summary of the four RCTs included in this analysis

Year of publication	N	Comparator 1	Comparator 2	Results	Conclusion
2005	78	MCP 20mg IV drip every 30 minutes PRN persistent pain (up to 80mg),with 25 or 50mg of DPH	Suma 6mg SQ injection	Primary (Change in NRS): Favors MCP by 0.9 (-0.3, 2.0) • >33% improvement: Favors MCP by 13% (1, 25%) • Pain free by 2 hours: Favors MCP by 23% (3, 45%) • Sustained pain free: Favors MCP by 9% (-7, 29%) • Would take again: Favors MCP by 14% (-3, 31%)	No difference between treatments
2006	40	TMB 200mg IM injection +DPH 25mg IM injection	Suma 6mg SQ injection	Primary (Change in NRS): Favors Suma by 2.2 (0.6, 3.7) • >33% improvement: Favors Suma by 25% (5, 45%) • Pain free by 2 hours: Favors Suma by 17% (-13, 47) • Sustained pain free: Favors Suma by 6% (-20, 32%) • Would take again: Favors TMB by 10% (-19, 39%)	Suma superior*
2007	205	MCP 20mg IV drip+ DPH 25mg IV drip+ placebo	MCP 20mg IV drip+ DPH 25mg IV drip+ Dex 10mg IV push	Primary(Sustained pain free): Favors Dex by 6% (-5, 17%) • >33% improvement: Favors Dex by 7% (0, 14%) • Pain free by two hours: Favors Dex by 8% (-6, 22%) • Would take again: Favors Placebo by 1% (-10, 12%)	No difference between treatments
2008	77	MCP 20mg IV drip+ DPH 25mg IV drip	PCZ 10mg IV drip+ DPH 25mg IV drip	Primary (Change in NRS): Favors PCZ by 0.6 (-0.6, 1.9) • >33% improvement: Favors PCZ by 11% (-1, 23%) • Pain free by two hours: Favors PCZ by 19% (-3,41%) • Sustained pain free: Favors PCZ by 11% (-7, 29%) • Would take again: Favors PCZ by 4% (-16, 24%)	No difference between treatments

MCP=metoclopramide; DPH=diphenhydramine; Suma= sumatriptan; TMB= trimethobenzamide; Dex=dexamethasone; PCZ= prochlorperazine; SQ= subcutaneous injection; IM= intramuscular

*This study was designed as a one-tailed study so the conclusion in the original publication was different.

The following outcome variables were assessed in all four of these trials: 1hr pain free; 1hr headache relief; 2hr pain free; 2hr headache relief; 2hr normal functionality; sustained headache relief; sustained pain free; sustained relief + no side effects; sustained normal functionality; adverse medication effects; nausea at 1 hr; rescue medication use; improvement on NRS scale at 2 hours; would take again

Table 2

Association among various outcome measures, reported as phi coefficient

	1hr pain free	2hr pain free	2hr relief	2hr normal functioning	Sustained pain free	Sustained normal functioning	No rescue medication	≥33% improve	≥50% improve
2hr pain free	0.66								
2hr relief	0.22	0.35							
2 hr normal functioning	0.26	0.38	0.54						
Sustained pain free	0.38	0.55	0.19	0.24					
Sustained normal functioning	0.17	0.28	0.32	0.61	0.40				
No rescue medication	0.30	0.36	0.40	0.33	0.23	0.27			
≥33%improve	0.18	0.28	0.70	0.40	0.16	0.23	0.32		
≥50%improve	0.26	0.38	0.71	0.52	0.21	0.33	0.34	0.74	
“Would take again”	0.13	0.22	0.20	0.27	0.18	0.29	0.25	0.22	0.19

All values in this tables have p≤0.01

Table 3

Association of outcome measures with criterion standard, wish to receive the same medication again.

Variable	Adjusted OR (95%CI)
One hour pain free	2.3 (1.2, 4.2)
One hour headache relief	2.9 (1.7, 5.0)
Two hour pain free	3.1 (1.8, 5.4)
Two hour headache relief	3.6 (1.8, 7.4)
Two hour normal functionality	3.9 (2.2, 7.0)
Sustained outcomes	
Sustained headache relief	4.0 (2.4, 6.8)
Sustained pain free	4.5 (1.9, 11.0)
Sustained relief + no side effects	4.6 (2.4, 8.8)
Sustained normal functionality	5.0 (2.7, 9.3)
Undesirable characteristics and adverse events	
No adverse medication effects	1.4 (0.83, 2.4)
No nausea at one hour	2.6 (1.1, 6.0)
Did not require rescue medication	3.7 (2.1, 6.6)
Improvement on an 11 point pain intensity scale	
≥33% improvement in NRS at 2 hours	5.2 (2.2, 12.4)
≥50% improvement in NRS at 2 hours	3.1 (1.6, 6.0)
≥66% improvement in NRS at 2 hours	3.2 (1.9, 5.6)
≥90% improvement in NRS at 2 hours	3.5 (1.9, 6.2)

Adjusted ORs account for medication received and gender.

Headache relief= pain of mild or none

Sustained= achieving outcome within two hours and maintaining it for 24 hours

Table 4

a. Test characteristics of ≥33% improvement versus the criterion standard			
	“Would take again”, Yes	**“Would take again”, No**	
Achieved ≥33% improvement	274	65	339
Did not achieve 33% improvement	12	14	26
	286	79	365
Sensitivity: 96% (95%CI: 93, 98%)			
False Negatives: 4% (95%CI: 2, 7%)			
Specificity: 18% (95%CI: 11, 28%)			
False Positives: 82% (95%CI: 72, 89%)			
b. Test characteristics of ≥50% improvement versus the criterion standard			
	“Would take again”, Yes	“Would take again”, No	
Achieved ≥50% improvement	260	60	320
Did not achieve 50% improvement	26	19	45
	286	79	365
Sensitivity: 91% (95%CI: 87, 94%)			
False Negatives: 9% (95%CI: 6, 13%)			
Specificity: 24% (95%CI: 16, 34%)			
False Positives: 76% (95%CI: 66, 84%)			

Table 5

Frequencies (with 95%CI) for all outcomes obtained in two migraine clinical trials and the sample size required to demonstrate a statistically significant difference between the two comparators, based on the actual point estimates.

	"Would take again"	**Pain free by 1hr**	**Pain free by 2hr**	**Normal functioning 2 hrs**	**Did not need rescue meds**	**≥33% improvement by 2 hours**	**Sustained pain free**	**Sustained normal functioning**
Sumatriptan 6mgSQ (n=38)	74% (58, 85%)	21% (11, 36%)	34% (21, 50%)	69% (53, 81%)	74% (58, 85%)	85% (71, 93%)	18% (9, 33%)	34% (21, 50%)
High dose metoclopramide IVSS (n=40)	88% (74,95%)	34% (21,49%)	58% (43,72%)	83% (69,92%)	95% (83,99%)	98% (88, 100%)	29% (17,44%)	58% (43,72%)
Sample size required	246	370	144	340	90	142	460	144
Metoclopramide 20mg IVSS (n=38)	73% (57, 85%)	29% (17, 45%)	41% (27, 57%)	58% (42, 72%)	83% (68, 92%)	87% (73, 94%)	14% (6, 29%)	37% (23, 53%)
Prochlorperazine 10mg IVSS (n=34)	76% (59, 87%)	39% (25,56%)	59% (42,74%)	74% (57,86%)	92% (78,97%)	97% (85,99%)	24% (13,41%)	50% (34,66%)
Sample size required	6560	700	240	310	520	200	388	460

Sample size calculations performed with Power and Precision 2.1, (Biostat, Englewood, NJ) and assume two tails and alpha=0.05, and 80% power. SQ= subcutaneous; IVSS= IV drip