OBJECTIVE MEASUREMENT OF COUGH IN OTHERWISE HEALTHY VOLUNTEERS WITH ACUTE COUGH

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Word Count: 2750

Funding: GlaxoSmithKline and the Medical Research Council
ABSTRACT (words 200)

Cough is one of the commonest reasons for medical consultation and acute cough associated with upper respiratory tract infections (URTIs) a global problem. In otherwise healthy volunteers complaining of cough associated with symptoms of URTI, we aimed to assess objective and subjective measures of cough, their repeatability and perform power calculations for the design of future studies to test therapies.

We studied 54 otherwise healthy volunteers with acute cough (<3 weeks) [median age 22yrs (IQR 21-26), 64% female, mean FEV₁ 97.6% (±10.5) predicted]. All subjects performed 24hr ambulatory cough monitoring and reported cough frequency and severity using VAS scales on two consecutive days. Sample size calculations were performed for crossover and parallel group study designs.

Objective cough frequency was high [session 1: geometric mean 12.1 c/h (95% CI 9.7-15.2)] and fell significantly [session 2: 9.0 c/h (95% CI 6.9-11.6)], (p<0.001). Repeatability was higher for objective cough frequency [intra-class correlation coefficient ICC=0.94 (p<0.001)] than reported cough frequency [day VAS ICC=0.784 (p<0.001)]. For crossover/parallel studies <15 and <41 subjects per arm, are required to detect a 50% reduction in cough frequency with 90% power.

Acute cough frequency is highly repeatable over any 48hrs allowing small sample sizes to be used when investigating the effectiveness of novel anti-tussives.

Key words: colds; cough monitoring; viral infections; URTI
INTRODUCTION

Acute cough (<3 weeks duration) is generally caused by viral upper respiratory tract infections (URTIs)[1], and cough is the commonest reason for which people seek medical attention[2-4]. On average URTIs affect adults 2-4 times a year[5-7] and evidence suggests that 93% of cases have an associated cough[8]. Acute cough is a global problem costing the UK economy an estimated £979 million annually due to loss of productivity, healthcare costs and the purchase of over-the-counter (OTC) medications[9].

The mean duration of cough due to an URTI is 2.4 weeks [8, 10], however such studies rely upon patient reporting of cough, a potential limitation when these measures often poorly correlate with objective quantification of coughing in several other conditions[11-14]. Although acute cough is usually self-limiting and transient, like chronic cough it significantly impairs quality of life[15], and may even precipitate chronic coughing[16].

Despite the magnitude of the problem of acute cough, few studies have assessed the effectiveness of available OTC cough medicines. Most studies performed suggest current therapies are no more effective than placebo, hence cannot be recommended[17]. This together with increasing concerns about the safety of anti-tussives in children has led the MHRA and FDA to introduce restrictions in their use.[18-20].

The testing of existing and novel anti-tussive therapies has, until recently, been constrained by the lack of validated tools for the assessment of coughing. However, we have found, using custom-built digital recording equipment, it is possible to record and objectively quantify cough sounds over 24hr periods in ambulatory patients[21]. The study of treatments for acute cough associated with URTI is often considered particularly difficult due to its transient nature, the requirement for large parallel designed studies and significant placebo effects[22].
but the studies upon which these perceptions are based have only measured cough over
periods of up to 3 hours[23, 24]. The objective measurement of acute cough over longer time
periods in ambulatory patients may overcome some of these difficulties. Therefore the aims
of this study were i) to measure objective ambulatory cough frequency in otherwise healthy
adults with acute cough and symptoms suggesting a URTI, ii) to establish the short-term
variability of acute cough associated with URTI symptoms, iii) to understand the
relationships between objective and subjective measures of cough and iv) to perform power
calculations for the design of future studies of novel anti-tussive agents.

MATERIALS AND METHODS

Subjects

Otherwise healthy adults complaining of a cough <3 weeks duration and with a history of
current or preceding symptoms suggestive of a viral URTI (i.e. at least one of rhinorrhoea,
sneezing, post-nasal drip, nasal congestion, sore throat, hoarse voice, fever and headache)
were recruited using poster advertisements. Current smokers and ex-smokers with a smoking
history of >20pack years were excluded, as were those with abnormal spirometry
(FEV$_1$<80% predicted or FEV$_1$/FVC ratio <0.7). Subjects taking ACE inhibitors, codeine or
other anti-tussive medicines (including OTC treatments) were also excluded. All subjects
provided written informed consent and the study was approved by the local ethics committee
(Tameside and Glossop 08/H1013/81).

Study Design

Subjects attended on three consecutive days. At the first attendance a medical history was
collected, spirometry performed (to ATS/ERS standards[25]) and assuming the inclusion and
exclusion criteria were met, subjects were fitted with an ambulatory cough monitor and
provided with a symptom diary (session 1). Subjects attended again 24hrs later; the cough
monitor batteries and memory card were replaced and another symptom diary provided (session 2). The final visit occurred a further 24hrs later, when the cough monitor was removed and symptom diaries collected. OTC medicines were not permitted during the study period.

**Methods**

**URTI Symptoms**

At the initial visit the presence and onset of rhinorrhoea, sneezing, post nasal drip, nasal congestion, sore throat, hoarse voice, fever and headache was documented. Subjects also reported when the cough started and the colour, frequency and volume of any sputum.

**Objective Cough Frequency**

Two 24hr ambulatory cough sound recordings were performed using a custom-built device with lapel and chest wall microphones (Vitalojak, Vitalograph Ltd, Buckinghamshire, UK). The numbers of explosive cough sounds per hour[26] were counted by a single trained person (KS) using an audio editing package (Adobe Audition 3.0, Adobe, CA, USA). We have validated this technique against cough counting from video recordings[27], and found excellent agreement between trained observers[14, 28, 29]. To facilitate manual counting, silences and low level background noises were removed by validated, custom-written software[30]. Subjects documented the times they went to bed and got up for each recording session; these defined the periods for the day and night cough rates.

**Subjective Cough Measures**

Visual analogue scales (VAS, 100mm) were used to assess each subject’s perception of their cough. For each 24hr session subjects recorded i) cough frequency (0mm=no cough, 100mm=worst cough), ii) severity (0mm=no cough, 100mm=severe cough) and iii) difficulty falling asleep due to coughing (0mm= not at all, 100mm=couldn’t sleep).
Analysis

Analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, IL) and SAS version 9.2 (SAS Institute Inc., Cary, NC). The primary endpoint, 24hr cough frequency was positively skewed and therefore log transformed to allow parametric analysis; for other variables non-parametric tests were applied. Repeatability between sessions was assessed using intra-class correlation coefficients (two-way, random effects). Spearman’s correlation coefficients were calculated for the relationships between cough measures.

As day cough frequency was highly repeatable and greater than at night, the daytime cough frequency data were used to estimate variance parameters corresponding to parallel group and crossover designs. Two Generalised Linear Mixed Models were fitted to the total daytime cough count using PROC GLIMMIX. Each model had a fixed effect for recording session, used length of daytime recording as a log offset term and assumed the responses followed a Negative Binomial distribution (log link function). The cross-over design model had an additional random subject effect term fitted on the linear predictor. The corresponding variance parameter estimates were used to obtain the standard error of a treatment effect under simple future parallel and crossover study designs. This standard error was used to compute the power of detecting a 50% reduction in cough rate on active treatment relative to the cough rate on placebo (2-sided test, 5% alpha). Since the standard error of the treatment effect (and hence power) also depends upon the placebo response, several power curves were derived to cover a range of plausible future placebo response rates. For further details see the online supplement.
RESULTS

Subject Characteristics

Fifty-four subjects completed the study (see Figure 1). Subjects had a median age of 22.0yrs (IQR 21.0-25.8), median BMI 23.2kg/m² (IQR 21.0-27.4) and 64% were female. Spirometry showed a mean FEV₁ of 97.6% predicted (SD±10.5) and FEV₁/FVC ratio 0.85 (SD±0.08). Two subjects were excluded with airflow obstruction, although we acknowledge that the FEV₁/FVC ratio may underdiagnose airflow obstruction in a small percentage of young adults[31].

Reported URTI Symptoms

Of the reported coryzal symptoms; 79.3% had rhinorrhoea, 72.4% sneezing, 70.0% post-nasal drip, 84.5% nasal congestion, 72.4% sore throat, 44.8% fever and 55.2% headache. The median reported duration of coughing at study entry was 4.0 days (IQR 3.0-7.0) and coughing started a mean 1.4 days after the cold started (+/-SD 2.2). 63.8% of subjects described a productive cough and of these, 97.3% coughed up sputum daily and 2.7% weekly. 71.1% coughed up a teaspoon, 24.3% a tablespoon and 2.7% a cupful of sputum daily. 35.1% described the sputum as green, 27% yellow, 8.1% clear, 5.4% white and 24.3% did not know the colour.

Measures of Acute Cough

Objective Cough Frequency

A comparison of the measures of cough on both study sessions are summarised in Table 1. Objective cough frequencies fell significantly from study session 1 to 2, a median of -2.4c/h (IQR -7.8 to -0.1) and -28.2% (IQR -42.6 to -1.2) from baseline, see Figure E1 for Bland Altman plot. Considering daytime and night separately, only daytime cough frequency fell significantly; a median of -3.8c/h (IQR -11.2 to -0.2) and -28.0% (IQR -44.3 to -2.7) from
baseline. There were no significant correlations between the 24hr cough rate on either session 1 or 2 and the reported time since the cough or cold started. The difference in daytime cough rates between study sessions was also unrelated to the reported time since the cough started (r=0.05, p=0.72) or the cold started (r=0.18, p=0.18) see Figure 2.

Cough rates in females were not significantly different from those in males for 24hr cough frequency [geometric mean 13.7c/h (95%CI10.2-18.4) vs. 9.8c/h (6.8-14.1), p=0.15] or day (p=0.17) or night (p=0.21). Also there was no apparent effect of age on cough frequency (r=0.4, p=0.79).

There was a marked diurnal variation in cough with frequency substantially higher during the day than over night for both sessions (p<0.001 and p<0.001, respectively). Figure 3 shows the median cough frequency across all subjects at each time point during the first 24hr recording period. It is notable that cough frequency in individuals was quite variable from hour to hour although interestingly the profiles of these variations tended to be similar for the two sessions, see examples in Figure 4.

**Subjective Cough Measures**

Daytime cough frequency VAS followed a similar pattern to objective cough frequency but also showed a significant change at night, see Figure E2 and E3 for Bland Altman plots. In contrast, VAS measures of cough severity and sleep latency did not significantly change between sessions.

**Relationships between Cough Measures**

There were significant weak-moderate positive correlations (r=0.28-0.59) between objective cough rates and VAS measures for each study session (see online supplement Table E2 for details).
Repeatability of Cough Measures between Study Sessions

The intra-class correlation coefficients for the measures of cough are shown in Table 2, suggesting that objective measures of cough are highly repeatable between the study sessions, especially daytime and 24hr cough frequency.

Relationships between Changes in Cough Measures

Figure 5 shows the relationships between the differences in objective cough counts and cough frequency VAS from session 1 to session 2. For daytime (Figure 5A), there was only a very weak linear relationship between objective and subjective estimates of change in cough (r=0.29, p=0.03), although the majority of subjects do appear in the left lower quadrant, i.e. both measures recorded an improvement in cough. Overnight however, most individuals cluster around the centre of the plot with little change in either measure (Figure 5B), suggesting very poor concordance between the subjective and objective changes, and no linear relationship (r=0.02, p=0.90).

Sample Sizes for Future Study Design in Acute Cough

The relationships between sample sizes and power to detect a 50% reduction in daytime cough frequency (over placebo) for both crossover and parallel group studies are shown in Figures 6A and 6B respectively. The influence of different placebo effects are also shown; for example, if the placebo response rate was mean 5c/h, the green line displays the power to detect a 2.5c/h reduction against the total number of subjects, whereas if the placebo cough rate was 25c/h, the orange line displays the power to detect a 12.5c/h reduction.

DISCUSSION

This is the first study to investigate 24hr objective cough frequency and its repeatability in otherwise healthy subjects complaining of an acute cough associated with URTI symptoms. Cough frequency was high and demonstrated significant variability between subjects.
Although objective cough frequency fell significantly from session 1 to 2, it was highly repeatable, especially compared with VAS ratings of cough frequency, severity and sleep latency. Furthermore changes in objective cough frequency were poorly predicted by changes in the cough frequency VAS ratings. Power calculations based on this data suggested that even considering sizeable placebo effects, anti-tussive efficacy could be observed in small numbers of subjects, especially if the characteristics of the medicine being tested allows for cross-over design studies.

It is interesting to note that the average cough frequency in acute cough was comparable to that we have previously reported in patients presenting to a specialist clinic with chronic cough (>8 weeks duration)[11, 26] and in excess of rates observed in conditions such as chronic obstructive pulmonary disease[12], asthma[13] and cystic fibrosis[14]. This raises the possibility that the similar mechanisms drive both acute and chronic coughing and indeed one study has suggested that a third of chronic cough patients report an URTI initiating their cough[16]. Unlike in chronic cough[32] we did not observe any significant influence of age or gender on objective cough frequency in this study population, but the sample size may have been insufficient to detect these effects. This is however consistent with the finding that men and women with an acute cough have similar cough-specific quality of life scores, in contrast with chronic cough, where women have worse scores than men.[15]

As might be anticipated for a viral illness, cough rates significantly dropped from session 1 to session 2, in keeping with cough resolving rapidly[8]. Whilst it is not possible to determine the mechanisms underlying the fall in cough frequency from this study, it is important to appreciate that objective cough frequency was still highly repeatable. This may seem contradictory, but the drop in cough rate was consistent across the range of cough frequencies at session 1, and the rank order of the patients (in terms of cough rates) remained very similar.
for session 2. Therefore although the absolute cough rates fell, the variability in cough frequency within-subjects (between sessions 1 and 2) was much less than the variability between subjects (within each session), resulting in high intra-class correlation coefficients and repeatability. This finding has important implications for future trial design, suggesting that cross-over studies utilising objective cough frequency measures are feasible over a 48-hour period. Such a study design would however only be appropriate for short-acting agents with rapid onset/offset and equal efficacy in patients, irrespective of their baseline cough rates; such characteristics are however likely to be desirable in a therapy for acute cough. It is also noteworthy that the reported onset date of the cough or cold symptoms did not predict the objective cough frequency, suggesting that the trajectory of objective cough counts in viral illness is highly variable. Within the 3 week time window for acute cough, it is therefore unnecessary to target patients with any particular reported symptom duration for recruitment.

The importance of the placebo effect in the treatment of acute cough has been frequently highlighted, and may be responsible for up to 85% of the efficacy of some cough medicines[24]. These large effects have generally been found under laboratory conditions, monitoring cough over just 15-minute periods. Such conditions might be expected to exaggerate placebo effects compared with monitoring over 24 hours in a subject’s own environment. Nonetheless, when performing power calculations from this data we included a wide range of placebo means (representing potential outcomes of small and large placebo effects) and still found sample sizes to be relatively small.

For our power calculations, we estimated that an improvement of 50% in objective cough frequency may be required for patients to appreciate an improvement in their cough. Studies with effective medicines are needed to clarify this issue, however, in chronic cough patients
undergoing reflux monitoring with a naso-gastric catheter, a fall of one third in objective
cough frequency was accompanied by a significant improvement in cough VAS, suggesting
this change was perceived as an improvement[36]. In the absence of data specific to acute
cough, we estimated that a slightly larger change (i.e. 50% fall) might be necessary for an
improvement in coughing to be appreciated, however this figure may differ significantly
across conditions.

This study has some limitations, firstly our study population were mainly young adults, and
therefore it remains to be determined whether cough frequencies may be different in older
adults with URTI symptoms. Epidemiological data would suggest that the incidence of URTI
tends to be inversely correlated with age and that the sample we studied (adults in their early
twenties) are representative of the age group most frequently affected by URTI episodes
(apart from children)[37, 38]. Secondly, our sample contained more women than men. It is
known that more women present to general practice with coughs secondary to URTI[37],
which may also explain the excess of females presenting for inclusion in this study. Indeed
other studies of treatments for acute cough have often recruited a similar proportion of
women[39-41]. Finally it remains to be seen whether limiting recruitment to patients earlier
in the natural history of colds has any significant impact on the variability and repeatability of
cough frequency.

In summary, this study shows that acute cough rates are comparable to those found in chronic
cough and highly repeatable over any 48hr period. These findings have significant
implications for the testing of novel anti-tussive agents, demonstrating that objective cough
frequency monitoring is a more powerful tool than subjective measures of acute cough,
reducing the number of subjects required and making cross-over designs possible.
ACKNOWLEDGEMENTS

We wish to acknowledge the contribution of all the volunteers who took part and also the funding provided by GlaxoSmithKline. Also Dr Jacky Smith is funded by a Clinician Scientist Fellowship from the Medical Research Council.
REFERENCES


19. Codeine-containing liquid over-the-counter medicines: should not be used for cough under 18 years: MHRA; 2010.


TABLES

Table 1: Summary of measures of cough on first and second study sessions; data are median (interquartile ranges) compared by Wilcoxon test, except for 24hr cough frequency (*geometric mean and 95% confidence interval), log transformed cough frequency compared by paired t-test. Note for some VAS scales session 1 scores were zero, so percentage change could not be calculated (\(\text{n}=52 \ \text{†n}=46\)).

<table>
<thead>
<tr>
<th></th>
<th>Study Session 1</th>
<th>Study Session 2</th>
<th>Change</th>
<th>p</th>
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<tr>
<td><strong>Objective Cough Frequency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24hour</td>
<td>12.1c/h* (9.7-15.2)</td>
<td>9.0c/h* (6.9-11.6)</td>
<td>-28% (-43 to -1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime</td>
<td>19.0 (9.2-31.7)</td>
<td>13.2 (5.6-26.3)</td>
<td>-28% (-44 to -3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Night</td>
<td>1.7 (0.3-4.2)</td>
<td>1.3 (0.2-5.1)</td>
<td>-32% (-64 to 77)</td>
<td>0.51</td>
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<td><strong>Cough Frequency VAS</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Daytime</td>
<td>34.0mm (24-54.8)</td>
<td>28.5mm (15.3-44.8)</td>
<td>-23% (-48 to 4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Night</td>
<td>11.0mm (6.0-27.5)</td>
<td>11.0mm (3.3-30.0)</td>
<td>-17%(^{\text{¥}}) (-50 to 29)</td>
<td>0.001</td>
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<td><strong>Cough Severity VAS</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Daytime</td>
<td>36.0mm (24.3-54.0)</td>
<td>28.5mm (15.5-45.0)</td>
<td>-25% (-49 to 8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Night</td>
<td>21.0mm (8.0-43.8)</td>
<td>17.5mm (4.0-46.3)</td>
<td>-14%(^{\text{¥}}) (-56 to 19)</td>
<td>0.17</td>
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<tr>
<td><strong>Sleep Latency VAS</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11mm (2.3-22.3)</td>
<td>10.5mm (1.0-30.0)</td>
<td>-5%(^{\text{†}}) (-64 to 80)</td>
<td>0.77</td>
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Table 2: Repeatability of cough measures from study session 1 to 2; ICC= Intra-class correlation coefficient.

<table>
<thead>
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<th>Measure</th>
<th>ICC</th>
<th>95% Confidence Interval</th>
<th>p</th>
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<tr>
<td>Objective Cough Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24hour</td>
<td>0.94</td>
<td>0.90-0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daytime</td>
<td>0.93</td>
<td>0.87-0.96</td>
<td>&lt;0.001</td>
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<tr>
<td>Night</td>
<td>0.85</td>
<td>0.74-0.91</td>
<td>&lt;0.001</td>
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<tr>
<td>Cough Frequency VAS</td>
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<tr>
<td>Daytime</td>
<td>0.78</td>
<td>0.63-0.87</td>
<td>&lt;0.001</td>
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<tr>
<td>Night</td>
<td>0.78</td>
<td>0.62-0.87</td>
<td>&lt;0.001</td>
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<td>Cough Severity VAS</td>
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<tr>
<td>Daytime</td>
<td>0.79</td>
<td>0.64-0.88</td>
<td>&lt;0.001</td>
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<tr>
<td>Night</td>
<td>0.81</td>
<td>0.68-0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep Latency VAS</td>
<td>0.71</td>
<td>0.50-0.83</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 1: Summary of recruitment of subjects

Enquires n=89

Recruited n=58
- Inclusion criteria:
  - Cough > 3 weeks
  - Current/past history of URTI symptoms
  - Age < 18 yrs
  - Ex-smoker > 20 pack yrs
  - No current smokers
  - Not on ACE inhibitors/Codams/OTC medication

Not eligible n=31
- Reason for exclusion:
  - Asthma
  - Current smoker
  - > 20 pack yrs
  - Relevant respiratory condition
  - No cough, just cold

Spirometry
- FEV1 & FVC > 80% predicted
- Ratio > 70% predicted

Excluded n=2

Enrolled n=56
- Data collected:
  - Objective cough frequency
  - Subjective cough frequency & severity
  - Demographic data
  - Cough details
  - Cold details

Excluded n=2
- (non-adherence to medication restrictions)

Completed n=54
**Figure 2:** Change in daytime objective cough frequency on first and second study day in relation to reported onset of A) cough symptoms and B) coryzal symptoms. Note log10 scales on both y axes.

![Figure 2](image)

**Figure 3:** Hour to hour variability in cough counts for first 24hr monitoring period averaged across all subjects, median counts are shown and error bars represent the interquartile range (IQR).
**Figure 4:** Examples of hour to hour variability in cough counts over both 24hr monitoring periods in two individual subjects A) with low cough rate and B) with high cough rate.
**Figure 5:** Relationship between differences in objective cough frequency and cough VAS from study session 1 to 2 for day and (A) and night (B).

**Figure 6:** Sample size calculations in acute cough for both A) parallel and B) crossover designed studies. Graphs display balance between power and the total number of subjects required to detect a 50% reduction in cough frequency over placebo, calculated for a range of plausible cough rates on placebo therapy. Note for parallel designs, each treatment arm would require half the number of subjects shown in graph A.