Evaluation of an Adaptive Seamless Design for a Phase II/III Clinical Trial in Recurrent Events Data to Demonstrate Reduction in Number of Acute Exacerbations in Patients With Chronic Obstructive Pulmonary Disease (COPD)

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\section*{ABSTRACT}

The aim of this work is to present an adaptive two-stage seamless design for a Phase II/III clinical trial in chronic obstructive pulmonary disease (COPD). This approach implies sample size re-estimation based on the primary outcome efficacy variable, namely the annual acute exacerbation rate. Patient recruitment in COPD trials can be slow; the proposed statistical approach may allow for a faster completion of the trial by reducing the time between interim analysis (IA) (Phase II) and new recruitment (Phase III). In addition, an adaptive design with re-estimation of the sample size during the study may increase its likelihood of success, especially in cases where estimated interim vaccine efficacy is lower than expected. By applying the proposed approach, at the time of the IA (end of Phase II), a decision can be taken to stop the trial for futility, to continue the trial (by advancing to Phase III) with the planned sample size or to continue the study and increase the sample size. We carried out simulations to evaluate the performance of the method.

\section*{1. Introduction}

Chronic obstructive pulmonary disease (COPD) is characterized by persistent, progressive and only partially reversible airflow obstruction (WHO 2017). Acute exacerbations (AEs) of COPD (AECOPDs) are defined as events that cause worsening of the patient’s respiratory symptoms. The rate at which AECOPDs occurs varies greatly between patients, with severely affected patients experiencing AEs more frequently. Additionally, AECOPDs increase morbidity and mortality, lead to a faster decline in lung function and poorer patients’ functional status, and have a significant impact on healthcare systems worldwide (Sapey and Stockley 2006). Several medications (e.g., inhalers) have been shown to have a positive impact in terms of reducing the rate of AECOPDs, but despite the large panel of products available, AECOPDs still occur frequently. Reducing the frequency and severity of AECOPDs is one of the challenges being pursued in pharmaceutical research, and an investigational vaccine, with the purpose of preventing AECOPDs, is under development at GSK.

In a classical clinical development plan, a Phase IIb vaccine trial aiming at assessing vaccine efficacy (VE), safety, reactogenicity, and immunogenicity, is followed by a larger confirmatory Phase III trial. A clinically relevant endpoint to demonstrate VE could be represented by a reduction in the risk of moderate and severe AECOPDs. Both phases would use placebo as comparator and would assume a constant VE over time.

In the case of the investigational COPD vaccine, there is uncertainty associated to VE, mainly due to the early status of data collection and the still ongoing efforts to understand the vaccine’s mechanism of action, but also due to the bacteriological and/or viral nature of the events (Sapey and Stockley 2006; Wilkinson et al. 2017) not allowing for prediction with a good level of certainty. To account for this, one option is to use a group sequential design, allowing to stop the trial early (with a smaller sample size) if the observed treatment effect is smaller than the smallest clinically meaningful difference. Another approach could be the adaptive design, with the possibility to increase the sample size if the results at the interim analysis (IA) are promising (Fisher 1998; Cui, Hung, and Wang 1999; Muller and Schafer 2004; Gao, Ware, and Mehta 2008; Bretz et al. 2009; Mehta and Pocock 2011; Jennison and Turnbull 2015). Moreover, different approaches of sample size re-estimation for Phase III confirmatory clinical trials have been extensively discussed in the literature by Fisher (1998), Cui, Hung, and Wang (1999), Muller and Schafer (2004), Gao, Ware, and Mehta (2008), Mehta and Pocock (2011), Jennison and Turnbull (2015), and Grayling, Mander, and Wason (2019), among others. The authors illustrate the benefits of the adaptive approach arising from the capability of devoting sample size resources to the clinical trial, based on different statistical approaches. For most of these articles, emphasis has been laid on assessing the operating characteristics of the trial such preserving the overall Type I error, and the expected number of patients at the time of the final analysis (Mehta and Pocock 2011). For example, in the article by Gao, Ware, and Mehta (2008), the properties of Brownian motion were employed to derive a method of sample size re-estimation at the penultimate analysis in a group sequential design. Cui, Hung, and Wang (1999) employed an approach in which the Wald statistics were combined with prespecified weights. However, this method has
faced some criticisms from some authors (Mehta and Pocock 2011) regarding the down-weighting of a certain portion of the data. Mehta and Pocock (2011) employed the promising zone approach which entails partitioning the IA outcomes into unfavorable, promising and favorable zones based on the attained conditional power. In this article, we employ the same approach. As such, we use the two-stage adaptive design and set specific cut-off values for the promising region. We then compare the adaptive strategy against the fixed sample and the group sequential approaches with respect to their operating characteristics.

It is worth mentioning that the promising zone approach has been shown to be advantageous in a sense that the traditional hypothesis tests, p-values and statistical adjustments can still be used without any extra complications/adjustments (Mehta and Pocock; Jennison and Turnbull 2015).

Adaptive trial designs have become more frequent in recent years and regulatory authorities show a greater interest in approaches that could improve the efficiency of current drug development processes (Balser, Chang, and Bliss 2018; U.S. Food and Drug Administration 2019).

Researchers presented different approaches to deal with the upcoming need to speed the development time of drugs/vaccines and reduce the costs. Several clinical trial designs’ adaptations under different scenarios have been proposed, such as: evaluating early endpoints, both long and short terms (Liu and Pledger 2005); facing the multiplicity issue (Glimm et al. 2018; Grayling, Mander, and Wason 2019) when more endpoints are to be considered; proposing a response adaptive randomization (Gajewski, Statland, and Barohn 2019) for selecting a final dosage to carry one or a combination of Bayesian and frequentist approaches (Schmidli, Bretz, and Racine-Poon 2007).

In this article, we evaluate the issues faced in designing a clinical study with a long-term endpoint, taking into consideration the need to shorten the development time (seamless design) and the uncertainty regarding VE (potentially requiring sample size recalculation). We present an adaptive design strategy, according to which a single trial will be conducted, incorporating both exploratory (Phase II) and confirmatory (Phase III) stages. We also describe the statistical methods and rationale used in designing this seamless Phase II/III adaptive study, and we present the results from the simulations carried out to evaluate its power and efficiency. The proposed approach can be applied to any new drugs or vaccines under development; however, this article focuses on the real case of a candidate vaccine aiming at reducing the risk of AECOPDs.

2. Materials and Methods

2.1. Structure of the Article

The article is organized as follows: Section 2.2 introduces the case study and describes its features and assumptions; Section 2.3 presents the statistical methods proposed to handle the simulated recurrent event data, including sample size; Section 2.4 describes the implementation of the adaptive design, starting from evaluation of the fixed design, followed by the introduction of an IA with z boundaries (Hwang and Shih 1990) spending function with $\gamma = -2$ (for $\beta$) and $\gamma = -4$ (for $\alpha$), for approximating the O’Brien and Fleming spending function (O’Brien and Fleming 1979) for futility (group sequential design) and then the inclusion of sample size reassessment (adaptive design); the characteristics of each approach are explored and presented in Section 2.5, using simulated studies.

2.2. Study Design Features

We propose a randomized, observer-blind, Phase II/III seamless (adaptive), placebo-controlled, multi-center study with two parallel groups receiving investigational vaccine or placebo. Patients aged 40–80 years with moderate and severe COPD are to be included; an equal number of participants will be allocated to each treatment group (randomization ratio 1:1). A 0, 2-month vaccine schedule will be applied, assuming that any efficacy effect will occur only one month following the last dose and will be sustainable during the next 12 months. Each enrolled patient will be followed up for 13 months after completion of the vaccine schedule. Thus, the planned duration of the study is approximately 38 months (Figure 1), with 24 months allocated for enrollment. The primary endpoint is represented by the incidence of moderate and severe AECOPDs over a period starting one month after the second dose and lasting for one year.

Enrolled participants will receive a first dose of either vaccine or placebo on Study Day 1, and a second dose on Study Day 61 (two months after the first dose).

An IA is foreseen when approximately half of the planned number of patients is recruited, with the purpose of evaluating futility and safety. The sample size of the trial is re-estimated based on the estimated interim VE.

VE is defined as: $VE = 1 - RR$, where $RR$ denotes the relative rate of having an AECOPD in participants who received the vaccine, compared to those who received the placebo. Superiority is established if the lower limit of the 95% confidence interval of the VE is $>0$.

Aiming for 90% power to detect a 30% VE at a significance level of 0.025 (one side), we assumed an incidence of 0.8 cases of moderate and severe AECOPDs patient per year (Dransfield et al. 2013; Wedzicha et al. 2013; Bourne et al. 2014). For simplicity, we did not consider the drop-out rate, which was expected to be 25% (Bourne et al. 2014), translating into an expected loss of information of 10% at the final analysis.

2.3. Statistical Methods

2.3.1. Test Statistic for the Primary Endpoint

The study’s primary endpoint is the rate of moderate or severe AECOPDs. There are two treatment groups, namely investigational vaccine and placebo (indexed by $Gi$: 1 = vaccinated; 0 = placebo) and a number of patients $N$ (indexed by $i = 1, 2, \ldots, N$) to be followed for a fixed time $t_i$. We model the number of moderate or severe AECOPDs ($Y_i$) using negative binomial regression with mean $\lambda_i$:

$$\log(\lambda_i) = \log (t_i) + \alpha + \beta G_i$$

and dispersion parameter $k(\text{var}(Y_i) = \lambda_i + k\lambda_i^2)$. Note that the negative binomial regression corresponds to a Poisson
regression model with a gamma-distributed random intercept (with mean 1 and variance \(k\)), where the random effect has been integrated out (marginal model).

The VE is estimated as

\[
\hat{VE} = 1 - \exp(\hat{\beta})
\]

and the standardized statistic \(Z\) to test the null hypothesis \(H_0 : \beta = 0\) versus \(H_1 : \beta < 0\) is given by

\[
Z = \frac{\hat{\beta}}{\sqrt{\text{var}(\hat{\beta})}}.
\]

### 2.3.2. Sample Size Calculation

When planning a clinical trial, sample size calculation is an important component, especially for Phase III trials. Keen et al. (2007) have proposed the following formula for comparing two negative binomial rates in COPD, assuming a complete and equal follow-up period (i.e., one year) for both vaccine and placebo. The number of patients \(N\) is computed as

\[
N = 2 \times \left( \frac{z_1 - \beta + z_1 - \alpha/2}{\log(\lambda_1 / \lambda_0)} \right)^2 \times \left( \frac{\lambda_1 + \lambda_0}{\lambda_1 \lambda_0} + 2k \right),
\]

where \(\lambda_1\) and \(\lambda_0\) are the rates in the vaccine and placebo arms, respectively, and \(k\) represents the dispersion parameter for the negative binomial distribution.

### 2.4. Design Implementation

In planning this study, we considered several design options, including fixed design, group sequential design and adaptive design with sample size re-estimation at the IA.

Below, we describe the implementation of the adaptive design, starting with calculation of the sample size based on the fixed design. We consider a two-stage group sequential design with one IA after enrolling 50% of participants.

#### 2.4.1. Fixed Sample Design

We start with a randomized Phase III clinical trial aiming at demonstrating superiority of a vaccine versus placebo in COPD patients, where the primary endpoint is the AECOPD rate after a one-year follow-up.

The incidence rate of AECOPD is assumed to be 0.8 for the placebo group and 0.56 in the treatment group for an expected VE of 30% (Wedzicha et al. 2013). Given a one-sided \(\alpha = 0.025, \beta = 0.1\), and a dispersion parameter of 1.5 (Bourne et al. 2014), we obtain a sample size of about \(N_2 = 1000\) evaluable participants for the fixed Phase III design (see Equation (1)). The sample size of the Phase II trial \(N_1 = 500\) is half of the sample size of the Phase III. The Phase III trial is performed only if the estimated VE from the Phase II trial \(VE_1\) is larger than 10% (futility). The effect size applied in the Phase III design is the same as for the Phase II; no adaptation by design is applied (Wang, Hung, and O’Neill 2006).

#### 2.4.2. Group Sequential Design With One IA

The group sequential design corresponds to the Phase III trial described above with an IA to evaluate nonbinding futility of the investigational vaccine. A stop for strong evidence of efficacy at early stage is not considered to allow for collection of enough samples for safety analyses. The complete enrollment is expected to last for two years and each patient will be followed for one year after vaccination to account for seasonality impact. Having an IA after 50% of participants are enrolled and their follow-up is completed, implies that the IA will be performed close to the final analysis. For this reason, the IA is performed immediately after the enrollment of the last Phase II patient. This means that the Stage 1 \(z\)-statistic \((Z_{1,1})\) is computed on \(N_1 = 500\) patients with partial follow-up. If the VE estimated at IA \((VE_{1,1})\) is smaller than 10%, then the trial is stopped for futility. Otherwise, another \(N_2 = 500\) patients are recruited and the final \(z\)-statistic \((Z_{1,2})\) is computed at the end of the trial based on 1000 patients with complete follow-up. Since we do not stop the trial for efficacy, the full \(\alpha\) is spent for the final analysis (no \(p\)-value adjustment is required).

#### 2.4.3. Adaptive Design With Sample Size Re-Estimation at IA

We include unblinded sample size recalculation at the IA of the group sequential design as described above. This leads to an adaptive design with sample size re-estimation.

The sample size reassessment is based on the VE estimated using partial information \((Z_{1,1})\). The goal is to determine “unfavorable,” “promising,” and “favorable” zones for the interim results. In the spirit of Mehta and Pocock (2011), we considered the “unfavorable” (10% \(\leq VE_{1,1} < 15\%\)), the “promising” (15% \(\leq VE_{1,1} < 20\%\)), and the “favorable” (VE_{1,1} \(> 20\%\)) zones at the
IA. The sample size of Stage 2 is increased in case of promising results at the IA (Mehta and Pocock 2011; Hsiao, Liu, and Mehta 2019). The final statistic is the conventional Wald test for the final data.

The three designs are represented in Figure 2.

2.5. Simulations

2.5.1. Simulation Plan

To assess the characteristics of the different designs (Type I error, power, and probability to stop early), 5000 simulated trials are carried out under different scenarios (10,000 under the null hypothesis).

Recurrent event data are generated using negative binomial distribution with four different values of VE: 0% (null hypothesis), 15%, 22.5%, and 30%; $\lambda_0 = 0.8$ incidence rate of AECOPD in the placebo group, an equal allocation of patients to vaccine and placebo arms (1:1 randomization ratio) and a one-year complete follow-up. In the group sequential and adaptive scenarios, the IA is performed on 500 patients with partial follow-up (i.e., immediately after the enrollment of the last Phase II patient).

3. Results

Both Type I error and power from different designs are computed as the proportion of trials that have $VE_{1,1} > 10\%$ at IA (or end of Phase II for fixed design) and final standardized Wald statistic at the end of the trial $Z_{1,2} < -1.96$. Note that there is no $\alpha$ spent at the IA because the trial is only stopped for futility.

The comparison of the designs is initially performed with respect to maintaining Type I error, as illustrated in the first three rows of Table 1. All approaches are conservative because the non-binding stopping rule for futility is applied. The Type I error of the three designs without stopping for futility is shown between brackets. When futility is not considered, all designs maintain the Type I error rates close to the nominal level of 0.025. The probability to stop for futility is larger in fixed design because the Phase II trial is using more information (full follow-up).

Results under the alternative hypothesis show that the adaptive design yields the highest power and that the group sequential is the design with the smallest average number of patients and the shortest duration. With respect to these two operating characteristics, our findings are similar to what was observed by Mehta and Pocock (2011). However, the adaptive and group sequential designs provide quite similar results. The adaptive design is not providing much benefits compared to the fixed and group sequential designs as it requires much more than 500 additional patients to have a good chance to conclude “a successful trial.”

In comparison with the fixed design, the group sequential and the adaptive design require fewer patients (about 350

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**Figure 2.** Fixed, group sequential and adaptive design for COPD. $VE_{1}$, estimated vaccine efficacy from the Phase II trial; $VE_{1,1}$, estimated vaccine efficacy at interim analysis.

**Table 1.** Simulation results.

| VE % | Design | Probability to stop for futility | Type I error or power (Type I error without futility) | Average sample size (years) |
|------|--------|---------------------------------|----------------------------------------------------|-----------------------------|
| 0    | Fixed  | 0.80                            | 0.004 (0.023)                                      | 694                         | 2.8 |
| 0    | GS     | 0.76                            | 0.015 (0.026)                                      | 618                         | 1.5 |
| 0    | Adaptive | 0.76                           | 0.014 (0.025)                                      | 653                         | 1.6 |
| 15   | Fixed  | 0.32                            | 0.31                                              | 1181                        | 3.9 |
| 15   | GS     | 0.34                            | 0.39                                              | 828                         | 2.0 |
| 15   | Adaptive | 0.34                           | 0.41                                              | 909                         | 2.2 |
| 22.5 | Fixed  | 0.12                            | 0.70                                              | 1375                        | 4.3 |
| 22.5 | GS     | 0.16                            | 0.72                                              | 917                         | 2.2 |
| 22.5 | Adaptive | 0.16                           | 0.74                                              | 993                         | 2.4 |
| 30   | Fixed  | 0.03                            | 0.94                                              | 1473                        | 4.5 |
| 30   | GS     | 0.05                            | 0.93                                              | 975                         | 2.3 |
| 30   | Adaptive | 0.05                           | 0.94                                              | 1025                        | 2.5 |

VE, vaccine efficacy; GS, group sequential design; Average sample size (time) includes the total number of patients (recruitment + follow-up time) in Phase II and the number of patients (recruitment + follow-up time) to be enrolled in Phase III.
patients less) and shorter trial duration (about two years shorter).

4. Discussion

The development of a vaccine against AECOPDs presents several challenges such as: the uncertainty of VE, which strongly depends on epidemiological aspects (the prevalence of the specific pathogens and seasonal variation); and a slow recruitment rate, also a crucial element when there is a high level of uncertainty suggesting a study planner to meet the financial constraints (Gajewski, Statland, and Barohn 2019). Under this context, the proposed adaptive design which includes an IA with incomplete patient follow-up, allows to control for the uncertainty and reduces the time between the IA (Phase II) and new recruitment (Phase III). All the considered designs (fixed, group sequential and adaptive) preserve the Type I error.

An important aspect of our simulations is that we considered the possibility of performing the IA using the information from participants with partial follow-up. We showed that using partial information is clearly an advantage because it permits to speed-up the time of the IA.

The adaptive design has the advantage of increasing the sample size when the VE is lower than expected. The study is initially designed with an assumption of a VE of 30%; however, the vaccine could have a lower effect size that is still clinically relevant (i.e., 20%), and instead of proceeding with an underpowered trial, the sample size is recalculated accordingly.

For simplicity, we showed simulation results with known nuisance parameters ($k$ and $\lambda_0$). As expected, the performance of the designs depends on these parameters. For example, if $VE = 30\%$ and $\lambda_0 = 0.4$ (instead of $\lambda_0 = 0.8$) then the power of the three designs is about 80% (instead of 90%) (data not shown). Different strategies can be used to make the adaptation depending on the nuisance parameters estimated at Stage 1. For example, a futility based on conditional power (not only on VE) will depend on nuisance parameters.

When considering Phase II/III seamless design, it would be of interest to have the IA endpoint (Phase II) different from the final endpoint (Phase III). However, this approach has not been considered for COPD because of the lack of available good surrogate endpoints.

For VE trials on diseases with low incidence rates (e.g., invasive pneumococcal disease) exact methods are often used due to the small number of events (Chan and Bohidar 1998). In the case of COPD, the number of events is not so small (e.g., 0.85–1.30 exacerbation events per patient-year, Sadatsafavi et al. 2016), and therefore, the asymptotic method has been used. A comparison between asymptotic and exacts methods in adaptive designs for vaccines with small number of events would be an interesting topic for future research.

In our simulations, the seasonality component has not been taken into consideration, yet some epidemiological studies have demonstrated that the severity of exacerbation events worsens during certain seasons of the year. Hence, this component should be accounted for in future simulation studies regarding COPD.

Although adaptive designs provide more flexibility than traditional designs, they should always be conducted following guidelines on good clinical practice. In particular, any adaptive design should ensure the validity and integrity of a clinical study (Bretz et al. 2009).

Adaptive designs are beneficial in COPD trials because the recruitment is slow and expensive. The treatment effect is not measured immediately (12 months of follow-up) and this can be a disadvantage for an adaptive trial. To speed-up the trial, we have performed the IA at the end of the recruitment of Stage 1 patients. Simulation results have shown good performance of this approach. However, we recognize that this approach is risky in case of seasonal effect because results at interim can be different from the final results.

In this article, we have evaluated by simulation a design with unblinded sample size adaptation in a realistic COPD vaccine setting. As far as we know, this type of design is not really used/considered/evaluated in the vaccine field.

In conclusion, our simulation results suggest that the group sequential strategies appear to be the most efficient designs, all aspects considered, that is, balancing flexibility, simplicity and uncertainty about design parameters. The adaptive design requires much more than the additional patients considered (larger maximum sample size) to outperform the group sequential trial.

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Author Contributions

Conceived and designed the experiments: AC, AKA, DC, VW. Performed the experiments: AC, DC, PN. Data analysis: AC, DC, PN, VW. Data interpretation and writing: AC, DC, VW. All authors contributed substantially to the development of the article and approved the final version.

Disclosure Statement

All authors are employees of the GSK group of companies and DC, AKA and VW hold shares in the GSK group of companies. VW is also designated inventor on patents owned by the GSK group of companies.

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References

Balser, J., Chang, M., and Bliss, R. (2018), “Interpreting the Regulatory Perspective on Adaptive Designs,” Statistics in Biopharmaceutical Research, 10, 123–129. [274]

Bourne, S., Cohet, C., Kim, Y., Barton, A., Tuck, A., Aris, E., Mesia-Vela, S., Devaster, J. M., Ballou, W. R., Clarke, S. C., and Wilkinson T. (2014), “Acute Exacerbation and Respiratory Infections in COPD (AERIS):
Protocol for a Prospective, Observational Cohort Study,” *BMJ Open*, 4, e004546, DOI: 10.1136/bmjopen-2013-004546. [274,275]

Bretz, F., Koenig, F., Brannath, W., Glimm, E., and Posch, M. (2009), “Tutorial in Biostatistics: Adaptive Designs for Confirmatory Clinical Trials,” *Statistics in Medicine*, 28, 1181–1217. [273,277]

Chan, J. S. F., and Bhuidar, N. R. (1998), “Exact Power and Sample Size for Vaccine Efficacy Studies,” *Communication in Statistics—Theory and Methods*, 27, 1305–1322. [277]

Cui, L., Hung, H. M., and Wang, S. J. (1999), “Modification of Sample Size in Group Sequential Clinical Trials,” *Biometrics*, 55, 853–857. [273]

Dransfield, M. T., Bourbeau, J., Jones, P. W., Hanania, N. A., Mahler, D. A., Vestbo, J., Wachtel, A., Martinez, F. J., Barnhart, F., Sanford, L., Lettis, S., Crim, C., and Calverley, P. M. (2013), “Once-Daily Inhaled Fluticasone Furoate and Vilanterol Versus Vilanterol Only for Prevention of Exacerbations of COPD: Two Replicate Double-Blind, Parallel-Group, a Randomised Controlled Trials,” *The Lancet Respiratory Medicine*, 1, 210–223. [274]

Fisher, L. D. (1998), “Self-Designing Clinical Trials,” *Statistics in Medicine*, 17, 1551–1562. [273]

Gajewski, B. J., Statland, J., and Barohn, R. (2019), “Using Adaptive Designs to Avoid Selecting the Wrong Arms in Multiarm Comparative Effectiveness Trials,” *Statistics in Biopharmaceutical Research*, 11, 375–386. [274,277]

Gao, P., Ware, J. H., and Mehta, C. (2008), “Sample Size Re-Estimation for Adaptive Sequential Design in Clinical Trials,” *Journal of Biopharmaceutical Statistics*, 18, 1184–1196. [273]

Glimm, E., Bezuidenhoudt, M., Caputo, A., and Maurer, W. A. (2018), “Testing Strategy With Adaptive Dose Selection and Two Endpoints,” *Statistics in Biopharmaceutical Research*, 10, 196–203. [274]

Grayling, M. J., Mander, A. P., and Wason, J. M. S. (2019), “Two-Stage Adaptive Designs for Three-Treatment Bioequivalence Studies,” *Statistics in Biopharmaceutical Research*, 11, 360–374. [273,274]

Hsiao, S. T., Liu, L., and Mehta, C. R. (2019), “Optimal Promising Zone Designs,” *Biometrical Journal*, 61, 1175–1186. [276]

Hwang, I. K., and Shih, W. J. (1990), “Group Sequential Designs Using a Family of Type I Error Probability Spending Functions,” *Statistics in Medicine*, 9, 1439–1445. [274]

Jennison, C., and Turnbull B. W. (2015), “Adaptive Sample Size Modification in Clinical Trials: Start Small Then Ask for More?,” *Statistics in Medicine*, 34, 3793–3810. [273,274]

Keen, O. N., Jones, M. R., Lane, P. W., and Anderson, J. (2007), “Analysis of Exacerbation Rates in Asthma and Chronic Obstructive Pulmonary Disease: Example From the TRISTAN Study,” *Pharmaceutical Statistics*, 6, 89–97. [275]

Liu, Q., and Pledger, G. W. (2005), “Phase 2 and 3 Combination Designs to Accelerate Drug Development,” *Journal of the American Statistical Association*, 100, 493–502. [274]

Mehta, C. R., and Pocock, S. J. (2011), “Adaptive Increase in Sample Size When Interim Results are promising: A Practical Guide With Examples,” *Statistics in Medicine*, 30, 3267–3284. [273,274,275,276]

Mulder, H. H., and Schafer H. (2004), “A General Statistical Principle for Changing a Design Any Time During the Course of a Trial,” *Statistics in Medicine*, 23, 2497–2508. [273]

O’Brien, P. C., and Fleming, T. R. (1979), “A Multiple Testing Procedure for Clinical Trials,” *Biometrics*, 35, 549–556. [274]

Sadatsafavi, M., Sin, D. D., Zafari, Z., Criner, G., Connnett, J. E., Lazarus, S., Han, M., Martinez, F., and Albert, R. (2016), “The Association Between Rate and Severity of Exacerbations in Chronic Obstructive Pulmonary Disease: An Application of a Joint Fraility-Logistic Model,” *American Journal of Epidemiology*, 184, 681–689. [277]

Sapey, E., and Stockley R. A. (2006), “COPD Exacerbations 2: Aetiology,” *Thorax*, 61, 250–258. [273]

Schmidth, H., Bretz, F., and Racine-Poon, A. (2007), “Bayesian Predictive Power for Interim Adaptation in Seamless Phase II/III Trials Where the Endpoint Is Survival Up To Some Specified Timepoint,” *Statistics in Medicine*, 26, 4925–4938. [274]

U.S. Food and Drug Administration (2019), “Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry,” available at http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf. [274]

Wang, S. J., Hung, H. M., and O’Neill, R. T. (2006), “Adapting the Sample Size Planning of a Phase III Trial Based on Phase II Data,” *Pharmaceutical Statistics*, 5, 85–97. [275]

Wedzicha, J. A., Decramer, M., Ficker, H. J., Niewoehner, D. E., Sandstrom, T., Taylor, A. F., D’Andrea, P., Arrasate, C., Chen, H., and Banerji, D. (2013), “Analysis of Chronic Obstructive Pulmonary Disease Exacerbations With the Dual Bronchodilator QVA149 Compared With Glycopyrronium and Tiotropium (SPARK): A Randomised, Double-Blind, Parallel-Group Study,” *The Lancet Respiratory Medicine*, 1, 199–209. [274,275]

WHO (2017), “Chronic Obstructive Pulmonary Disease (COPD),” available at http://www.who.int/respiratory/copd/en/. [273]

Wilkinson, T. M. A., Aris, E., Bourne, S., Clarke, S. C., Peeters, M., Pascal, T. G., Schoonbrood, S., Tuck, A. C., Kim, V., Ostridge, K., Staples, K. J., Williams, N., Williams, A., Wootton, S., Devaster, J. M., and on behalf of the AERIS Study Group. (2017), “A Prospective, Observational Cohort Study of the Seasonal Dynamics of Airway Pathogens in the Aetiology of Exacerbations in COPD,” *Thorax*, 72, 919–927. [273]